Do interruptions to the continuity of methadone maintenance treatment in specialist addiction settings increase the risk of drug-related poisoning deaths? A retrospective cohort study

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ABSTRACT

Aims To examine the risk of mortality associated with interruptions to the continuity of methadone maintenance treatment (MMT), including transfers between services, in opioid-dependent individuals attending specialist addiction services. **Design** Retrospective cohort study using addiction services and primary care dispensing records, the National Methadone Register and National Drug-Related Death Index (NDRDI). **Setting** Geographically defined population in Dublin, Ireland. **Participants** A total of 2899 people prescribed and dispensed methadone in specialist addiction services between January 2010 and December 2015. There were five exposure groups: weeks 1–4 following transfer between treatment providers; weeks 1–4 out of treatment; weeks 5–52 out of treatment; weeks 1–4 of treatment initiation; and weeks 5 + of continuous treatment (reference category). **Measurements** Primary outcome: drug-related poisoning (DRP) deaths. Secondary outcome: all-cause mortality (ACM). Mortality rates calculated by dividing number of deaths (DRP; ACM) in exposure groups by person-years exposure. Unadjusted and adjusted Poisson regression (covariates age, sex, incarceration, methadone dose and comorbidities) estimated differences in mortality rates. **Findings** There were 154 ACM deaths, 55 (35.7%) identified as DRP deaths. No deaths were observed in the first month following transfer between treatment providers. The risk of DRP mortality was highest in weeks 1–4 out of treatment [adjusted relative risk (aRR = 4.04, 95% confidence interval (CI) = 1.43–11.43, $P = 0.009$] and weeks 1–4 of treatment initiation (ARR = 3.4, 95% CI = 1.2–9.64, $P = 0.02$). Similarly, risk of ACM was highest in weeks 1–4 out of treatment (ARR = 11.78, 95% CI = 7.73–17.94, $P < 0.001$), weeks 1–4 of treatment initiation (aRR = 5.11, 95% CI = 2.95–8.83, $P < 0.001$) and weeks 5–52 off treatment (aRR = 2.04, 95% CI = 1.2–3.47, $P = 0.009$). **Conclusions** Interruptions to the continuity of methadone maintenance treatment by treatment provider do not appear to be periods of risk for drug-related poisoning or all-cause mortality deaths. Risk of drug related poisoning and all-cause mortality deaths appears to be greatest during the first 4 weeks of treatment initiation/re-initiation and after treatment cessation.

Keywords All-cause mortality, drug-related poisoning mortality, heroin, methadone maintenance treatment, opioid substitution treatment, opioid-use disorder, transfer.

INTRODUCTION

Opioid substitution treatment (OST) with methadone has been shown to be safe and effective in suppressing illicit opioid use [1], improving physical and mental health [2] and reducing all cause and overdose mortality [3,4]. However, growing evidence suggests that mortality risk varies during the course of OST. Overdose mortality rates pooled across 11 methadone cohorts estimated 2.6 and 12.7 overdose deaths per 1000 person-years in and out of

methadone treatment, respectively [4]. Furthermore, the first 4 weeks following treatment initiation (11.4 deaths/1000 person-years) and treatment cessation (32.1 deaths/1000 person-years) were identified as the highest risk periods for mortality across cohorts [4]. More recent evidence from a UK study of deaths among patients who had received OST in a large mental-health service between 2008 and 2013 suggests an elevated risk of mortality, particularly overdose deaths, during the month following transfer of patients to an alternative treatment provider for continuation of OST [5]. Almost one-third of all the observed deaths (109/332) occurred following a transfer between services, with deaths following a transfer from secondary to primary care accounting for 38.5% of all such deaths. The remaining deaths following transfer between services occurred following a transfer from secondary to independent/third-sector drug treatment provider (19.3%), community drug treatment services (14.7), general hospital (12.8%) and prison (4.6%). The authors estimated a rate of 136.4 overdose deaths per 1000 person-days during the first 2 weeks following a transfer between services, with a rate of 79.5 overdose deaths per 1000 person-days within the first month following transfer. These findings were unexpected, as transfers involved a planned continuation of OST [5]. Further assessment of the risk of mortality associated with interruptions to continuity of OST using a cohort study design is warranted, as Bogdanowicz and colleagues did not have comparison data on living individuals' exposure to such interruptions.

Methadone is the most common form of OST in Ireland, and is available free of charge to all persons undergoing OST for opioid dependence [6]. In 1998 the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations were introduced in Ireland, which involved the establishment of a national register, the Central Treatment List (CTL). The Misuse of Drugs Regulations were updated in 2017 to authorize access to buprenorphine or buprenorphine/naloxone for OST on the same statutory basis as methadone. All patients in receipt of OST, including methadone, are listed on the CTL, with each patient linked to one specific prescriber and a single dispensing site. The majority of patients receive treatment in the greater Dublin region (90%), with Dublin Southwest and Kildare representing one of the largest catchment areas in Ireland. OST is provided in specialist outpatient addiction clinics or primary care settings, with approximately 60% of people in treatment in addiction clinics [7]. Daily supervised methadone consumption occurs during the induction and stabilization phase. In the maintenance phase, when a patient is considered to be stable, the level of supervised consumption is often reduced with the possibility of take-home doses. However, no more than 6 days' supply of methadone is dispensed to take home, in both the addiction services and primary care,

except for holidays. For take-home supplies for holidays, multiple prescriptions are required, with a direction to dispense unsupervised on specified dates. Transfers between addiction services and primary care are facilitated by GP Coordinators employed by the addiction services. The GP Coordinator provides all relevant clinical details on the patient being transferred to the new treatment provider. The provision of OST is also available in Irish prisons; if a prisoner is in treatment prior to incarceration their treatment is continued in prison. The prison services contact the patient's previous care provider for clinical details including methadone dosing and when last dose was dispensed. Re-engagement with the OST service provider they attended prior to incarceration is also facilitated as part of the prison discharge policy [7]. Any changes in treatment provider are recorded on the CTL. The aim of this study is to examine the risk of drug-related poisoning (DRP) deaths associated with interruptions to the continuity of MMT, including transfers between service providers, among opioid-dependent individuals in a specialist addiction treatment setting.

METHODS

Study design and setting

This was an observational cohort study of patients who were registered on the CTL and prescribed and dispensed at least one prescription for methadone in specialist addiction services in Dublin Southwest and Kildare between 1 January 2010 and 31 December 2015, reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [8]. Patients' date of accrual was date of their first methadone prescription within the specialist addiction services during the observation period. All dispensed prescription medication records, methadone and co-prescriptions were extracted from pharmacy dispensing records of the addiction services from their date of accrual to study end. Every person registered on the CTL is assigned a seven-digit unique identifier. This unique identifier is also recorded on all dispensing records in the addiction services, allowing for patients' dispensing records to be linked to the CTL which provides details on the patient's treatment history. This allowed us to identify start- and end-dates for treatment episodes outside the included addiction services, including prison. Treatment episodes in primary care were identified by linking patient records in the addiction services and CTL to the Health Service Executive's (HSE) Methadone Treatment Scheme (MTS), which records methadone prescriptions dispensed for OST in primary care. Patients' dispensing records from addiction services and MTS were also linked to the General Medical Services (GMS) pharmacy claims database, which contains details of all

prescription medications, other than methadone, dispensed to GMS eligible patients in primary care. Eligibility for the GMS prescription scheme is through means-testing. All prescriptions are coded using the World Health Organization (WHO)'s Anatomical Therapeutic Chemical (ATC) classification. Finally, the CTL and dispensing databases were linked to mortality data recorded in the National Drug Related Death Index (NDRDI). The NDRDI follows the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) standard protocol to collect data on DRP deaths which is used in 28 European countries, Norway and Turkey. To ensure completeness, mortality data are collected from multiple sources and cross-checked to avoid duplication. Coronial files are the primary source and include post-mortem toxicology reports. Other data sources include: General Mortality Register through the Central Statistics Office (CSO), acute hospitals data via the HSE Hospital In-Patient Enquiry (HIPE) system and the CTL. The study was approved by the Research Ethics Committee of the Royal College of Surgeons in Ireland (REC1418).

Exposure: interruptions to continuity of OST

We identified patients' treatment status for each day of the study, by service provider (for on treatment episodes), using the coverage of their methadone prescriptions from the addiction services or primary care and from treatment start- and end-dates recorded in the CTL. Once treatment status (addiction services/primary care/prison/out of treatment) was determined for each day of the study period, treatment episodes were defined as periods of continuous daily supply of methadone by treatment provider (or continuous periods off-treatment), with tolerance for up to 7 days of interrupted supply. When a patient did not receive a new methadone prescription within 7 days after the end of coverage of a prescription, that patient was considered to have ceased treatment. The 'off treatment' period continued until a patient re-entered treatment, as indicated by the presence of a new methadone prescription. This 7-day rule was also applied to transitions between services. We adopted this definition based on previous studies, and following consultation with clinical experts in the addiction services [3,9,10]. This information was used to calculate person-time in the following exposure groups:

- First 4 weeks following transfer between service provider (e.g. from addiction clinic to primary care, or prison to addiction clinic)
- In continuous treatment with the same treatment provider for ≥ 5 weeks
- First 4 weeks out of treatment
- ≥ 5 weeks out of treatment
- Treatment initiation following a period out of treatment (first 4 weeks)

Outcome measures

The primary outcome was DRP mortality, with all-cause mortality (ACM) the secondary outcome. Both mortality measures were taken from the NDRDI. The NDRDI refers to poisoning deaths, which they define as deaths which are directly due to the toxic effect of the presence in the body of one or more drugs [11].

Covariates

We also recorded several covariates that could influence mortality risk, based on previous study findings: age [3,12–16], gender [3,12,13,15–17], history of incarceration during the observation period (yes/no) [13,18,19], median methadone dose [12,15] and comorbidities [12,13,15,20]. We calculated median methadone dose for the last treatment episode for each person, and in accordance with prescribing recommendations we categorized people as below, within and above the recommended methadone maintenance range of 60–120 mg daily. For those alive and on-treatment at the study end, their last treatment episode was used and those who died or were censored their last treatment episode before death or ceasing follow-up was used. Medicines dispensed during the observation period were used to identify medical conditions using the validated Rx-Risk tool [21,22]. We mapped the Rx-Risk tool to the International Classification of Diseases, 10th revision (ICD-10), by matching the disease categories to ICD-10 chapter groupings [22].

Statistical analysis

The analysis plan for this study was not pre-registered, and the findings should be considered exploratory. All analyses were conducted in SAS Enterprise Guide version 7.1 (SAS Institute, Inc., Cary, NC, USA). Individual observation time was censored; patients were followed-up during treatment and for a maximum of 1 year after the expiry of their last methadone prescription. The observation time was terminated at date of death or study end (31 December 2015) for those alive and on treatment or 1 year post-treatment cessation.

Poisson regression was used to estimate mortality rate ratios and 95% confidence intervals (CIs) for the primary exposure variable (interruptions to the continuity of MMT), with continuous treatment with the same provider ≥ 5 weeks set as the reference group. Given the small number of DRP deaths, we adjusted for the following clinically relevant covariates, gender, methadone dose and mental health disorders. Age and history of incarceration were considered for inclusion in the multivariable analysis based on their *P*-value from the univariable analysis; a *P*-value below 0.05 was considered for inclusion. For our secondary analysis on all-cause mortality, we included the

primary exposure variable in a multivariable Poisson regression, adjusting for age and gender. Other variables considered for inclusion, based on a *P*-value below 0.05 in univariable analysis, were history of incarceration and the 10 disease categories.

There is potential bias in our application of the 7-day rule to classify time as on and off treatment, as it may be argued that a patient has not genuinely stopped treatment after 7 days without methadone. We therefore repeated our analyses extending the tolerance level to 14 days. We also conducted a sensitivity check to assess the potential effects of specific drug classes from the disease category mental and behavioural disorders on DRP deaths, specifically benzodiazepines, opioid analgesics, anti-psychotics and antidepressants.

RESULTS

Description of study population

The cohort included 2960 patients registered on the CTL and receiving at least one methadone prescription in the addiction services of Dublin Southwest and Kildare between January 2010 and December 2015. We excluded 40 patients due to insufficient data to support linkage. We also excluded patients who were prescribed buprenorphine ($n = 21$), as they were considered to be a select group. Buprenorphine was not authorized for OST in Ireland until 2017, and a recent report indicates buprenorphine was prescribed predominantly for patients with codeine dependence or other opiate-based medications [7]. This resulted in 2899 patients (98%).

Characteristics of cohort

A cohort of 2899 people was prescribed and dispensed methadone during the observation period—a total of 13 300 person-years. This cohort represented prevalent OST service users, as 85% entered the study during the first year (January and December 2010; 80% between January and June 2010), with a median follow-up of 5.5 years [interquartile range (IQR = 3.4–5.9]. Table 1 shows the characteristics of the sample. More than one-third of patients were aged greater than 35 years (median age = 33.9 years, (IQR = 30–38), and 68% were men. Almost half the sample experienced transitions between services, with an average of 3 [standard deviation (SD) = 4.2] transitions identified within this subpopulation. The most frequent transitions involved transfers from prison to addiction services (35%), followed by addiction services to prison (32%). This is consistent with the observation that more than one in four patients (28.6%) had a history of incarceration during the observation period. The remaining transitions between services involved transfers from addiction services to primary care (19%), primary care to addiction

services (10%), primary care to prison (2%) and vice versa (1%). More than two-thirds of the sample was identified as having multiple comorbidities. Mental and behavioural disorders (66%), diseases of the digestive system (34%), diseases of the respiratory system (24%) and other conditions (63%) were common. Common conditions in the other category included inflammatory pain ($n = 1591$, 87.4%), pain ($n = 838$, 46.0%) and allergies ($n = 538$, 29.6%). The median methadone dose at last treatment episode was lower than the recommended adequate maintenance dose of 60–120 mg daily for 41% of patients, with 3% exceeding the recommended dose.

Drug-related poisoning mortality

One hundred and fifty-four (5.3%) people died during the observation period, with DRP deaths accounting for 35.7% ($n = 55$) of all deaths (crude DRP mortality rate 0.41 per 100 person-years, 95% CI = 0.30–0.52). Person follow-up time, number of DRP deaths and DRP mortality rates are reported in Table 2, alongside adjusted and unadjusted analysis of exposure to interruptions to continuity of OST and DRP mortality. DRP mortality rates were highest in weeks 1–4 out of treatment, and in the first month of treatment initiation after a period out of treatment. No DRP deaths were observed in the first 4 weeks following transfer between services. After adjusting for covariates, the risk of DRP mortality was highest during the first 4 weeks following treatment cessation and during the first 4 weeks of treatment initiation after a period of being out of treatment. Women and increasing age were also associated with an elevated risk in DRP mortality.

All-cause mortality

The crude ACM rate was 1.14 per 100 person-years (95% CI = 0.96–1.32). Table 3 shows the person follow-up time, number of ACM deaths and ACM rates and the adjusted and unadjusted analyses. None of the ACM deaths was observed in the first month following a transfer between services. The risk of ACM was highest out of treatment, particularly the first month following treatment cessation. There was also a twofold increase in risk of ACM in the remaining weeks off treatment relative to being in continuous treatment. The first 4 weeks of treatment initiation, after a period out of treatment, was also associated with an elevated risk of ACM. Increasing age and diseases of the circulatory system were also associated with an elevated risk of ACM. A history of incarceration during the study period was found to be protective.

Sensitivity analysis

Extending the 7-day rule to 14 days did not alter the overall findings for ACM (Table S2). However, the risk of DRP

Table 1 Characteristics of cohort.

Characteristics	Alive	Dead	Total (%)
Patients	n = 2745	n = 154	n = 2899
Men	1876 (68.3)	105 (68.2)	1981 (68.3)
Age (years) at start of study			
< 28	657 (23.9)	16 (10.4)	673 (23.2)
28–35	1088 (39.6)	56 (36.4)	1144 (39.5)
35–45	795 (29.0)	59 (38.3)	854 (29.5)
> 45	205 (7.5)	23 (14.9)	228 (7.9)
History of incarceration	798 (29.1)	30 (19.5)	828 (28.6)
Median dose last treatment episode			
< 60 mg	1114 (40.6)	60 (39.0)	1174 (40.5)
60–120 mg	1541 (56.1)	85 (55.2)	1626 (56.1)
≥ 120 mg	90 (3.3)	9 (5.8)	99 (3.4)
Transfer between services	1332 (48.5)	50 (32.5)	1382 (47.7)
Number of comorbidities[a]			
0–1	927 (33.8)	34 (22.1)	961 (33.1)
2–5	1117 (40.7)	58 (37.7)	1175 (40.5)
6–10	623 (22.7)	53 (34.4)	676 (23.3)
> 10	78 (2.8)	9 (5.8)	87 (3.0)
Diseases of the circulatory system[a]	446 (16.2)	61 (39.6)	507 (17.5)
Diseases of the digestive system[a]	920 (33.5)	78 (50.6)	998 (34.4)
Mental and behavioural disorders[a]	1788 (65.1)	119 (77.3)	1907 (65.8)
Certain infectious and parasitic diseases[b]	12 (0.4)	0 (0.0)	12 (0.4)
Diseases of the respiratory system[a]	641 (23.4)	49 (31.8)	690 (23.8)
Endocrine, nutritional and metabolic disorders[a]	82 (3.0)	9 (5.8)	91 (3.1)
Diseases of the nervous system[a]	340 (12.4)	24 (15.6)	364 (12.6)
Other[a]	1718 (62.6)	102 (66.2)	1820 (62.8)

Any individual disease category with less than 5 people are not reported in this table to ensure anonymity of patients. [a]Determined by the RxRisk tool mapped to ICD-10 disease categories. [b]Hepatitis C and HIV not included because hepatitis C and HIV medications could not be captured for this study, as they are dispensed in the hospital setting.

deaths during the first month following treatment initiation after a period out of treatment was attenuated, and did not remain significant in the multivariable analysis (Table S1). The addition of specific drug classes, in place of the disease category 'mental and behavioural disorders', did not change the overall findings for DRP mortality (Table S3).

DISCUSSION

Principal findings in context of previous studies

Our findings confirm that the first 4 weeks after treatment initiation and cessation are the highest risk periods for both DRP and ACM deaths [4]. Although similar to estimates from a recent UK study [19], we observed higher rates of DRP and ACM deaths during the first 4 weeks after treatment initiation and cessation compared to previous cohorts of patients in MMT [3,12,15,17,23,24]. The higher mortality rates observed here, and by Hickman and colleagues, may have arisen as both studies involved an ageing and increasingly comorbid population of opioid-dependent patients [19]. We also noted that the effect estimates for DRP deaths increased after adjusting for

methadone dose. The distribution of methadone dose at last treatment was similar for the first 4 weeks of treatment initiation and cessation, with a higher representation of lower doses (≤ 60 mg) for both time-periods. As the lower dose was observed to be protective (albeit not significantly), failure to account for these effects at the univariable level of analysis attenuate risk of interruptions at these specific time-points. The increased risk at treatment initiation could be explained by an accumulation of methadone that exceeds the opioid tolerance level or by the concurrent use of other respiratory depressant drugs or illicit opioid use [4,17,25]. However, unlike Bogdanowicz *et al.* [5], we did not identify any deaths during the first 4 weeks following transfer between services. This may be influenced by the nature of transfers observed in our cohort; the majority of transfers (67%) involved movement between addiction services and prison. As previously described, if a patient is in OST prior to incarceration their treatment is continued in prison, and their community place is held for when they are released. Failure to identify deaths during such transfers is consistent with recent evidence from England and Australia, which shows that OST in prison is associated with a reduction in DRP and ACM deaths during the first

Table 2 Person-years, mortality rates and risk ratios for DRP mortality, by interruptions to continuity of OST adjusted for covariates.

DRP	Person-years (py)	Deaths	DRP mortality rate (per 100 py)	Unadjusted analysis			Adjusted analysis		
				RR	95% CI	P-value	aRR	95% CI	P-value
Interruptions to OST continuity[a]									
Weeks 1–4 following transfer between services	248	0	0.00	–	–	–	–	–	–
Weeks 1–4 out of treatment	–	–	1.29	3.29	**1.18–9.16**	0.022	**4.04**	**1.43–11.43**	**0.009**
Weeks 5–52 out of treatment	–	–	0.27	0.69	0.21–2.22	0.530	1.00	0.30–3.34	0.995
Weeks 1–4 of treatment initiation[b]	–	–	1.11	2.85	**1.02–7.92**	0.045	**3.40**	**1.20–9.64**	**0.021**
Weeks 5+ in treatment (same treatment provider)	11 266	44	0.39	1.00	–	–	1.00	–	–
Gender									
Women	4336	25	0.58	1.72	1.01–2.93	0.045	1.89	1.09–3.28	0.023
Men	8964	30	0.33	1.00	–	–	1.00	–	–
Age (in years)				1.04	1.01–1.08	0.023	1.05	1.01–1.09	0.011
Median methadone dose (last treatment)									
< 60 mg	4304	13	0.30	0.70	0.37–1.33	0.280	0.63	0.33–1.23	0.176
61–120 mg	8399	36	0.43	1.00	–	–	1.00	–	–
> 120 mg	597	6	1.01	2.35	0.99–5.57	0.050	2.32	0.97–5.52	0.058
History of incarceration									
No	9595	40	0.42	1.00	–	–			
Yes	3705	15	0.40	0.97	0.54–1.76	0.920			
Mental and behavioural disorders[c]									
No	4194	11	0.26	1.00	–	–	1.00	–	–
Yes	9106	44	0.48	1.84	0.95–3.57	0.070	1.62	0.83–3.16	0.158

[a]Continuous treatment with the same treatment provider for ≥ 5 weeks was set as the reference group; [b]the first 4 weeks of treatment initiation refers to initiation following a period out of treatment; [c]determined by the RxRisk tool mapped to ICD-10 disease categories. OST = opioid substitution treatment; aRR = adjusted relative risk; RR = relative risk; DRP = drug-related poisoning; CI= confidence interval. Bold type highlights results for the primary exposure variable (interruptions to continuity of OST).

Table 3 Person-years, mortality rates and risk ratios for ACM, by interruptions to continuity of OST adjusted for covariates

	Person-years (py)	Deaths	Mortality rate (per 100 py)	Unadjusted analysis			Adjusted analysis		
				RR	95% CI	P-value	aRR	95% CI	P-value
Interruptions to OST continuity									
Weeks 1–4 following transfer between services	248	0	0.00	–	–	–	–	–	–
Weeks 1–4 out of treatment	311	29	9.32	**11.42**	**7.52–17.30**	**<0.0001**	**11.78**	**7.73–17.94**	**<0.001**
Weeks 5–52 out of treatment	1115	16	1.43	1.76	1.03–2.99	0.037	2.04	1.20–3.47	0.009
Weeks 1–4 of treatment initiation[b]	360	15	4.17	**5.11**	**2.96–8.81**	**<0.0001**	**5.11**	**2.95–8.83**	**<0.001**
Weeks 5+ in treatment (same treatment provider)[a]	11 266	92	0.82	1.00	–	–	1.00	–	–
Gender									
Women	4336	49	1.13	0.98	0.70–1.38	0.920	0.98	0.68–1.40	0.890
Men	8964	103	1.15	1.00	–	–	1.00	–	–
Age (in years)				1.05	1.03–1.08	<0.0001	1.04	1.02–1.07	<0.001
Median methadone dose (last treatment)									
< 60 mg	4304	61	1.42	1.45	1.04–2.02	0.027			
61–120 mg	8399	82	0.98	1.00	–	–			
> 120 mg	597	9	1.51	1.55	0.78–3.08	0.220			
History of incarceration									
No	9595	122	1.27	1.00	–	–	1.00	–	–
Yes	3705	30	0.81	0.64	0.43–0.95	0.027	0.64	0.42–0.96	0.033
Diseases of the circulatory system[c]									
No	10 843	93	0.86	1.00	–	–	1.00	–	–
Yes	2457	59	2.40	2.80	2.02–3.88	<0.0001	2.13	1.48–3.06	<0.001
Diseases of the digestive system[c]									
No	8501	75	0.88	1.00	–	–	1.00	–	–
Yes	4799	77	1.60	1.82	1.32–2.50	0.0002	1.20	0.83–1.73	0.326
Certain infectious and parasitic diseases (exc. HIV + HepC)[c]									
No	13 233	152	1.15	1.00	–	–			
Yes	67	0	0.00	–	–	–			
Mental and behavioural disorders[c]									
No	4194	35	0.83	1.00	–	–	1.00	–	–
Yes	9106	117	1.28	1.54	1.06–2.25	0.025	1.21	0.80–1.84	0.372
Endocrine, nutritional and metabolic disorders[c]									
No	12 837	143	1.11	1.00	–	–			
Yes	463	9	1.94	1.75	0.89–3.43	0.100			

(Continues)

Table 3. (Continued)

	Person-years (py)	Deaths	Mortality rate (per 100 py)	Unadjusted analysis			Adjusted analysis		
				RR	95% CI	P-value	aRR	95% CI	P-value
Diseases of the nervous system[c]									
No	11 600	128	1.10	1.00	–	–			
Yes	1700	24	1.41	1.28	0.83–1.98	0.270			
Other condition[c]									
No	4499	51	1.13	1	–	–			
Yes	8800	101	1.15	1.01	0.72–1.42	0.940			
Diseases of the respiratory system[c]									
No	9959	103	1.03	1.00	–	–	1.00	–	–
Yes	3341	49	1.47	1.42	1.01–1.99	0.044	0.97	0.67–1.41	0.875

[a]Continuous treatment with the same treatment provider for ≥ 5 weeks was set as the reference group; [b]the first 4 weeks of treatment initiation refers to initiation following a period out of treatment; [c]determined by the RxRisk tool mapped to ICD-10 disease categories. Note that hepatitis C and HIV medications could not be captured for this study as they are dispensed in the hospital setting. aRR = adjusted relative risk; OST = opioid substitution treatment; ACM = all-cause mortality; RR = relative risk; DRP = drug-related poisoning; HepC = hepatitis C; CI = confidence interval. Bold type highlights results for the primary exposure variable (interruptions to continuity of OST).

month after release [26,27]. Differences between our study and Bogdanowicz *et al.* [5] may also be related to our 7-day rule to classify treatment episodes. Individuals who experienced 8 or more days without methadone between treatment episodes (by different providers) were classified as re-initiating treatment after a period off treatment, as opposed to a transfer. However, when we applied a 14-day threshold, extending the gap to ≥ 15 days before classifying an off period between treatments, the number of deaths following transfer was unchanged. Bogdanowicz *et al* used a 28-day gap, such that a gap of up to 28 days was tolerated between treatments and considered as continuity of the previous treatment episode. In this situation, a transfer between services which included a gap in methadone of up to 28 days would attribute the risk associated with re-initiation to a transfer.

Strength and limitations

The strengths of this study include a large sample of patients in OST in specialist addiction services in Ireland with a long duration of follow-up. The external validity of the study is considered to be high, as our sample of approximately 3000 patients accounts for almost half of all patients in receipt of OST in addiction services in Ireland and registered on the CTL during the study period [7]. The use of administrative databases and dispensing records from the addiction services and primary care allowed us to record OST exposure and interruptions to treatment, including transfers between services and periods out of treatment. Furthermore, the primary outcome of our study, DRP deaths, was obtained from the NDRDI which obtains data from multiple national sources.

Our study has several weaknesses and potential biases. First, our study involves a comparison of the same patients throughout follow-up periods in and out of OST, but their movement in and out of treatment is non-random. Consequently, other factors or unrecorded confounders may be associated with interruptions to treatment and mortality. For example, some patients who had left treatment will have stopped their opioid use, which would substantially reduce their risk of mortality relative to patients who relapsed. To account for this potential bias we restricted follow-up to 12 months after treatment cessation, as misclassifying patients at risk is considered to be small as the rate of cessation and long-term abstinence is low [12,28]. Similarly, in relation to periods in treatment, we did not have information on the quality or intensity of care received, which may have influenced patients' risk of mortality when initiating treatment and the likelihood of relapse and treatment cessation [12]. Secondly, methadone prescriptions in the addiction services and primary care cease on hospital admission, and hospitals were not obliged

to inform the CTL of treatment in hospitals during the observation period. Therefore, we were unable to account for transfers to and from hospital. Furthermore, a patient's transition to 'off treatment' prior to mortality may reflect a hospital admission in the period preceding death due to disease, thus leading to an overestimation of mortality off treatment. However, risk of mortality off treatment remained independently significant after adjusting for comorbidities in ACM deaths which accounts, at least partially, for this confounding effect.

Thirdly, the use of dispensing records as our principal source of data, on exposure and covariates, limited our adjustment for potential confounders, such as drug-injecting behaviour, problem alcohol use, HIV and hepatitis C status, all of which may have an impact on mortality [20,28]. Fourthly, our classification of treatment status by treatment provider may have resulted in a misclassification of patients, and person-time, at risk. While the 7-day rule has been used in previous studies [3,9,10] and is considered to reflect clinical practice in addiction clinics, a delayed record of treatment cessation could have led to some deaths that occurred out of treatment being incorrectly classified as occurring in treatment [29]. Fifthly, the generalizability of our findings is limited to OST involving methadone. In light of evidence that the risk of DRP deaths during treatment initiation is lower for buprenorphine than methadone, but with a shorter duration of treatment [19,23], further study is warranted to examine whether a differential risk exists following transfers between services. Finally, although this cohort represents prevalent OST users, and not first-time users, it is considered to be representative of patients in MMT, as our sample experienced repeated periods of treatment initiation and treatment dropout, which is typical of this patient group [4,14,30].

Clinical and policy implications

Our study did not observe transfers between services as periods of high risk, with no DRP or ACM deaths occurring following a transfer. However, any inferences regarding risk must be cautious, as fewer than half our sample experienced a transfer, and among those who did it was most frequently a transition to and from prison. Further investigation of the impact of transfers between services is warranted. For other forms of prescription medicines we have shown that transitions between hospital-based and community-based care providers in Ireland is associated with discontinuity of chronic disease medication [31]. Transition from hospital to community is also associated with enhanced treatment burden and prescription of potentially inappropriate medicines [32]. Therefore, our finding in relation to methadone maintenance treatment and transitions of care should be viewed in this wider context

of system-related interruptions of care that have broader implications for medication safety of prescription drugs. Furthermore, our findings highlight that risk of DRP and ACM deaths is greatest at treatment initiation/re-initiation and treatment cessation. Closer monitoring of opioid tolerance before onset of treatment to establish safe induction, and during the induction period, alongside more effective methods of preventing relapse may attenuate these effects. In addition, increasing patient awareness of DRP risk and increasing the availability of take-home naloxone may mitigate the risk of DRP deaths during these periods of high risk [33].

CONCLUSION

Interruptions to the continuity of MMT by treatment provider were not observed as periods of risk for DRP or ACM deaths. Risk of DRP and ACM deaths was greatest during the first 4 weeks of treatment initiation/re-initiation and treatment cessation.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Sensitivity analysis DRP: Person-years, mortality rates and risk ratios for DRP mortality, by interruptions to

continuity of OST adjusted for covariates using a 14 day threshold

Table S2 Sensitivity analysis ACM: Person-years, mortality rates and risk ratios for ACM, by interruptions to continuity of OST adjusted for covariates using a 14 day threshold

Table S3 Sensitivity analysis DRP (drugs as covariates): Person-years, mortality rates and risk ratios for DRP mortality, by interruptions to continuity of OST adjusted for covariates.