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DOI:
10.1111/add.14114

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
SHORT REPORT
doi:10.1111/add.14114

Excess overdose mortality immediately following transfer of patients and their care as well as after cessation of opioid substitution therapy

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ABSTRACT

Aims To investigate clustering of all-cause and overdose deaths after a transfer of patients and their care to alternative treatment provider and after the end of opioid substitution therapy (OST) in opioid-dependent individuals in specialist addiction treatment. **Design, Setting and Participants** Mortality data were identified within a sample of 5335 patients with opioid use disorder who had received OST treatment between 1 April 2008 and 31 December 2013 from a large mental health-care provider in the United Kingdom. We investigated the circumstances and distribution of the 332 deaths identified within the observation window with a specific focus on overdose deaths (n = 103) after a planned discharge, dropout and transfer between services. **Measurements** Crude mortality rates for overdose mortality 14 days, 28 days and more than 1 month after the end of treatment/transfer for overdose mortality. **Findings** Of 47 individuals who died from overdose after having been transferred between services, nine died during the first 2 weeks [crude mortality rate (CMR) = 136.4, 95% confidence interval (CI) = 64.3–243.1] and a further five died during the first month post-transfer (CMR= 79.5, 95% CI = 44.2–129.7). Of the 32 individuals who died from overdose after planned OST cessation, five died during the first 2 weeks (CMR = 151.5, 95% CI = 51.1–319.0) and a further four died during the first month post-discharge (CMR = 82.6, 95% CI = 38.4–151.0). **Conclusions** In the United Kingdom, opioid-dependent people who are transferred to an alternative treatment provider for continuation of their opioid substitution therapy experience high overdose mortality rates, with substantially higher rates during the first month (especially during the first 14 days) following transfer.

Keywords Heroin, mortality, opiates, opioid substitution therapy, overdose, transfer, treatment.

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Submitted 28 November 2016; initial review completed 20 February 2017; final version accepted 15 November 2017
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INTRODUCTION

Research has shown consistently that opioid substitution therapy (OST) is associated with reduced mortality (e.g. [1,2]). More recently, it has also been identified that there is a short-lived substantial excess mortality after termination of OST. In a national primary-care cohort in the United Kingdom, the risk of death was eightfold greater in the month immediately after the end of OST [2]. Similar findings were found internationally [3–5], but none has examined interruptions to continuity of care, such as transfers of patients to alternative services or care providers. Reduced physiological tolerance that occurs with interruption of maintenance therapy is a well-known overdose risk [6]. However, at present very little is known with regard to destabilization that may occur with changes to service delivery, such as those due to cuts in resources or reorganizational changes. These occur frequently, especially currently in the United Kingdom, and is an area of concern [7].

We are currently investigating mortality patterns among patients with opioid use disorder who have received OST treatment using data from a large secondary mental health-care provider [8,9]. Within this work, we have

examined clustering of all-cause and overdose deaths in opioid-dependent individuals in specialist addiction treatment during the period (a) immediately after a transfer of patients and their care to alternative treatment provider and (b) after the end of opioid substitution therapy (OST).

METHODS

Study setting

The South London and Maudsley NHS Foundation Trust (SLaM) is one of the largest specialist mental health-care services in Europe providing, within the framework of the British National Health Service (NHS), comprehensive mental health-care and addiction services to a catchment population of approximately 1.36 million residents throughout seven multi-cultural, ethnically diverse, highly dense boroughs of London. Within the framework of the NHS in the United Kingdom, mental health trusts have close to a 100% monopoly for service provision to their assigned geographic catchment [8]. In 2008, the Clinical Record Interactive Search (CRIS) was developed, and comprises patients' electronic health records in a de-identified format, allowing researchers to search and retrieve complete case records for analysis. There are currently more than 260 000 patients represented on the system. CRIS is approved as a data set for secondary analysis by the Oxfordshire Research Ethics Committee C (reference 08/H0606/71 + 5), and its protocol is described in detail elsewhere [8,9].

Study sample

The study sample comprised patients diagnosed with primary or secondary opioid use disorder (OUD; ICD-10: F11 [9]) between 1 April 2008 and 31 December 2013 who died within the same observation period.

Every death in the United Kingdom is reported to the Office for National Statistics (ONS) General Records Office, which is then conveyed to the NHS Care Records Service and available to all NHS organizations, and consequently in CRIS. This identifies deaths within the observation period for both current and previous SLaM patients. The full procedure for identifying and confirming SLaM patient deaths has been described elsewhere [10]. In addition, a linkage to data derived specifically from death certificates allowed us to establish the recorded underlying cause of each death in those where this information was available.

Diagnoses were derived from their designated SLaM electronic health records (EHR) structured fields and from free-text fields using natural language processing (NLP). The NLP application for 'diagnosis' extracts any text strings associated with a diagnosis statement in order to supplement the structured fields, the performance of which has been reported elsewhere [8].

Measures and calculations

The present study investigated potential clustering of deaths (a) after a clinically planned termination of OST and also (b) after a transfer of patient and their care to another service or care provider, with intention for continuation of OST. The main characteristic of interest in this study was the timing of death, specifically overdose deaths, in OUD patients who were prescribed OST treatment. By searching backwards from the date of death until the latest discharge/transfer/dropout, the study measures proportions of all-cause mortality within the 14/28/29+ days post-discharge/transfer/dropout. For overdose mortality specifically, crude mortality rates were calculated and Kaplan–Meier curves used to visualize the results. Rate ratio for all post-treatment groups combined (planned cessation/transfer/dropout) and overdose mortality within 28 days and 29+ days were also calculated.

Treatment episodes

Using CRIS, we extracted de-identified individual records on all patients with OUD who died between 1 April 2008 and 31 December 2013. Searching backwards from each death date, we looked for the start- and end-dates of the most recent OST treatment episode. This information was derived primarily from treatment care plan notes, with each OST treatment episode starting with the date of the first prescription for substitute opioids relating to most recent treatment episode and ending with the expiry of their last prescription. The specific OST medication last prescribed was also noted.

In all cases, a search through discharge notes and free-text fields, including event notes and correspondence, was also conducted manually for validation purposes and to supplement data not available in the structured fields. Particular attention was given to treatment episodes with a gap of fewer than 28 days between the end of one episode and the start date of the next. In such cases, examination of event and discharge notes was particularly useful, as it allowed us to establish whether a patient genuinely stopped and restarted their treatment during a 4-week period. We adopted the '28-day rule' from Cornish and colleagues [2], where a gap of fewer than 28 days between the end of one treatment and the start of the next is not considered long enough for a patient to genuinely stop and restart treatment, and is considered as continuity of the previous treatment episode.

Categorizing reasons for end of treatment

Reasons for cessation of OST treatment were extracted from patients' treatment care plans, in discharge notes and other free-text fields. By cross-examining these sources, we categorized reasons for end of treatment into the following: (1) 'planned end of treatment' (patients with

a clinically planned discharge following cessation of OST); (2)' transfer' (patients who were transferred to another service or care provider who would then take over patients' care including OST prescribing); (3) 'dropout' (patients with a clinically unplanned OST cessation, such as non-compliance, failure to attend key-working sessions and/or failure to collect prescribed OST medications); and (4) 'died in treatment' (if death occurred during an OST treatment episode). Types of transfer were also noted.

RESULTS

Sample characteristics

The total number of patients with a primary or secondary ICD10 F11 OUD diagnosis within the observation window was 5335, with 385 all-cause deaths identified in this sample. Of the 385 individuals who died, 53 (14%) were never prescribed OST within SLaM and/or their records contained no information with regard to their treatment history, and were therefore excluded from analysis. A further 116 (35%) of the remaining 332 patients died while still in OST treatment in SLaM, and hence were not considered further in this analysis of deaths post-OST treatment and post-transfer.

The remaining sample of 216 deaths comprised 66 patients with a planned termination of OST treatment, 109 who were transferred to another service or care provider and 41 who dropped out of OST treatment.

As presented in Table 1, most patients were male, with mean age of 45 years at the time of their death. The median duration of patients' last OST treatment episode was just below 8 months (235.5 days, interquartile range 52–560 days) and the median interval between end of treatment/transfer and death was almost 1 year (349 days, interquartile range 62–800 days). Most destinations for transfers between services were primary care, followed by independent/third-sector drug treatment providers, transfer to alternative (usually out-of-area) community and drug alcohol services, and to general hospitals.

Table 1 Sample characteristics.

	n (%)
Total study sample	216
Males	151 (69.9)
Age (years)	
≤ 29	17 (7.9)
30–39	55 (25.5)
40–49	73 (33.8)
50–59	49 (22.7)
60+	22 (10.1)
Planned OST end	66 (30.6)
Dropouts	41 (19)
Transfer between services	109 (50.5)
Transfer to primary care	42 (38.5)
Transfer to independent/third-party sector	21 (19.3)
Transfer to alternative community drug treatment service	16 (14.7)
Transfer to general hospital	14 (12.8)
Transfer to prison	5 (4.6)
Other transfers	11 (10.9)
Last prescribed medication	
Methadone	179 (82.9)
Buprenorphine	31 (14.3)
Other (diamorphine, Suboxone, morphine)	6 (2.8)
Last treatment episode duration	
One month or less	37 (17.1)
Between 1 and 6 months	59 (27.3)
Between 6 months and 1 year	43 (19.9)
More than 1 year	77 (35.6)

OST = opioid substitution therapy.

All-cause mortality

Under the assumption that the number of patients under treatment remained constant throughout the observation window, we observed what appears to be a higher concentration of all-cause deaths within a month after a planned end of OST treatment and also high concentrations of deaths during the first month after a transfer between services, even when continuation of OST treatment was arranged. Of the 66 individuals who died after a planned termination of OST treatment, 27 (41%) died within 180 days of treatment cessation, including 12 of those being within the first 28 days and seven within the first fortnight post-termination. Of the 109 who died after transfer between services, 43 (39%) died within 180 days of this transfer, including 26 dying in the first 28 days and 17 within the first fortnight post-transfer. Similarly, of the 41 who died after having dropped out of treatment, 12 (29%) died within 180 days of this transfer, with four of these being within the first fortnight post-dropout (details not shown in the Tables).

Overdose mortality

Our primary interest was in deaths caused by fatal overdose. We were able to ascertain the cause of death in 96% of patients (208 of 216). Overdose fatalities were the most common (103; 49%) followed by hepatic-related deaths (30; 14%) and other natural causes (30; 14%). Other causes of death in this sample were infectious disease (12; 6%), pneumonia and other pulmonary causes (15; 7%), other unnatural causes (15; 7%) and unspecified (3; 1%). To establish whether transfer of care and termination of OST treatment were associated with increased risk of overdose death, we restricted our further analysis to fatal

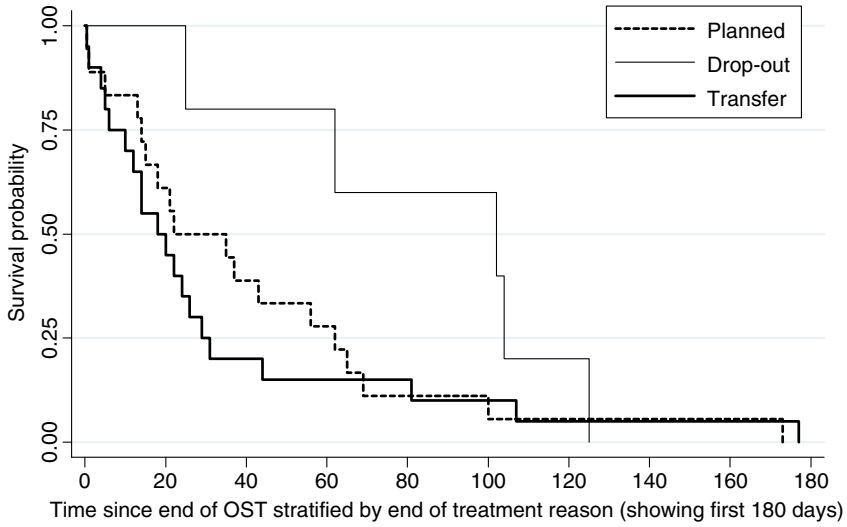

Figure 1 Kaplan–Meier survival curves for time since South London and Maudsley NHS Foundation Trust (SLaM) treatment cessation/transfer (in days) for overdose deaths, stratified by reasons for end of treatment or transfer (showing first 180 days). OST = opioid substitution therapy. [Colour figure can be viewed at wileyonlinelibrary.com]

overdoses only. Of the 103 individuals who died of overdose, 47 were in the post-transfer subgroup and 32 occurred after a planned end of OST, and with high clustering of overdose deaths occurring in both subgroups. The remaining 24 individuals who fatally overdosed had dropped out of treatment.

More specifically, 20 of 47 (43%) of the post-transfer overdose deaths occurred within 180 days, nine of whom died in the first 2 weeks from a total of 14 who died in the first month. Similarly, 18 of 32 (56%)overdose deaths after planned OST cessation occurred within 180 days, five of whom died in the first 2 weeks from a total of nine who died in the first month. Of the 24 overdoses which occurred in the dropout group, five occurred within 180 days but none were recorded within the first fortnight. Figure 1 show the distribution of overdose deaths within 180 days post-transfer with continuation of OST treatment and post-treatment with planned cessation of OST, respectively.

By looking backwards from date of death until the closest discharge date, we were able to calculate person-days in this sample (Details shown in Table 2). First, combining the three reasons for OST treatment end (transfer, planned discharge and dropout), the total follow-up time was 42 716 person-days, with 310 person-days in the group who fatally overdosed in the first 28 days after post-OST

Table 2 Crude mortality rates per 1000 person-days in OUD patients who died of overdose (n = 103).

	n Overdose deaths	*Person-days (time between treatment cessation/transfer and death)*	*Rate per 1000 person-days (95% CI)*
Planned cessation/transfer/dropout			
≤ 14 days	14	99	141.4 (80.0–226.0)
≤ 28 days	24	310	77.4 (50.2–113.0)
29 days+	79	42 405	1.9 (1.5–2.3)
Planned OST cessation			
≤ 14 days	5	33	151.5 (51.1–319.0)
≤ 28 days	9	109	82.6 (38.4–151.0)
29 days+	23	10 184	2.26 (1.43–3.39)
Transfer			
≤ 14 days	9	66	136.4 (64.3–243.1)
≤ 28 days	14	176	79.5 (44.2–129.7)
29 days+	33	17 061	1.9 (1.3–2.7)
Drop-out			
≤ 14 days	0	–	–
≤ 28 days	1	25	40.0 (1.01–203.5)
29 days+	23	15 160	1.52 (0.96–2.28)

OUD = opioid use disorder; OST = opioid substitution therapy; CI = confidence interval.

cessation/transfer, and with a rate of 77.4 deaths per 1000 person-days compared with a rate of 1.9 deaths per 1000 person-days in the group who died of overdose after the first month of treatment cessation/transfer. The rate ratio comparing the two groups was 41.5 (95% confidence interval (CI) = 5.1–66.3, $P < 0.0001$]. Figure 1 displays the survival probabilities for time since end of treatment/transfer and overdose mortality within 180 days after end of treatment, stratified by reasons for end of treatment, showing a reduced survival predominantly in the transferred and planned OST cessation groups.

DISCUSSION

This study examined circumstances surrounding the deaths of patients with a diagnosis of opioid use disorder who had received OST treatment in a large mental health-care service, within a nearly 5-year observation period. In addition to substantial clustering of deaths in the early post-OST period, as reported by others [2,3,6], there was also a substantial excess mortality, and especially overdose mortality, in the period immediately following transfer of patients and their care to a different treatment care provider, with this excess mortality pronounced in the first month post-transfer.

Increased risk of death immediately after dropout from treatment may not be surprising [11], and overdose risk post-termination of OST treatment is already recognized [3,5]. However, it is counterintuitive that death rates were higher for patients with planned discontinuations compared to patients who dropped out. Furthermore, our finding of a marked excess of overdose deaths in the period immediately after transfers of patients and their care despite planned continuation of OST treatment is new and unexpected. Large 'transferred' subgroups included patients experiencing transitions from secondary to primary care (i.e. opioid maintenance under the care of a general practitioner) or to large independent care-provider organizations who had secured new NHS contracts after the introduction of competitive tendering procedures [12]. If the purpose of such reorganization is to achieve greater effectiveness and more cost-effective use of resources, then it might have been expected that we would find successful transfer of patients and their treatments, patient stability and stable or lowered risk of mortality [13]; instead, however, our analysis indicated a high number of fatal overdoses, particularity during the first month post-transfer. This needs deeper and wider exploration.

Little is known about the destabilization that may accompany changes to service delivery. The present data did not allow us to ascertain what happened to patients after transfer. Consequently, we were not able to establish whether any failures had occurred during the period of transition itself, or whether any destabilization occurred after a successful transition to the new care provider.

Due to data constraints which prevented from the construction of a cohort, the current analyses were limited to crude associations and included only the most recent OST cessation. Nonetheless, these findings provide important insights into practice, the impact of service organization (including service reorganizational changes) and the associated risks of overdose deaths.

This study urgently needs fuller exploration and replication. Further investigations should establish what happens to patients after transfer. Before any potential explanations are discussed with regard to the mechanisms behind excess deaths post-transfer with continuation of OST, further investigations should focus on exploring these findings using extended data and inferential statistics, as well as service-user and service-provider consultations. If these results are confirmed in subsequent studies, clinicians, care providers and commissioning bodies need to be aware of the marked excess of overdose deaths after transfers of patients and their care, even where continuation of OST is planned. Any transfer of patients whether due to escalation of treatment (e.g. to an in-patient unit) or as part of successful recovery (e.g. from an in-patient unit to rehabilitation care) needs to be undertaken with caution.

Declarations of interests

R.H. and R.S. have received research funding from Roche, Pfizer, J&J, Janssen and Lundbeck and *In Silico* Biosciences. J.S. is a senior NIHR investigator and has conducted a variety of research studies of addictive disorders and treatments and, through the university, has provided consultancy to pharmaceutical companies about new treatments for opioid addiction, including (last 3 years) Martindale, Indivior, MundiPharma and Braeburn/Camurus, for which his employer has received remuneration and specific research grant income. None were the specific subject of study in this work. For further description see: www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. K.M.B. and E.D. have no conflict of interest to declare.

Acknowledgements

This study was supported by the Clinical Records Interactive Search (CRIS) system funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London; a joint infrastructure grant from Guy's and St Thomas' Charity and the Maudsley Charity (grant number BRC-2011-10035); and the National Addiction Centre, King's College London. K.M.B., C.K.C., J.S. and R.S. are part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at

South London and Maudsley NHS Foundation Trust and King's College London. R.D.H. was funded by a Medical Research Council (MRC) Population Health Scientist Fellowship (grant number MR/J01219X/1). J.S. is an NIHR Senior Investigator. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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