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Self-harm and suicide during and after opiate agonist treatment: a cohort study of primary care patients in England

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Abstract

Background: The first four weeks after initiation and cessation of opiate agonist treatment (OAT) are associated with an increased risk of all-cause mortality and overdose. We investigate whether the same pattern exists for self-harm and suicide among people prescribed OAT for opioid dependence.

Methods: We used healthcare records from UK Clinical Practice Research Datalink linked to mortality and hospital admission data for adults prescribed OAT at least once in primary care in England between 2nd January 1998 and 30th November 2018. We estimated rates and adjusted rate ratios of hospital admissions for self-harm and death by suicide, comparing time during and after treatment, as well as stable periods of time on treatment with treatment initiation, cessation, and the remaining time off treatment.

Outcomes: 8,070 people (males: n=5,594, 69·3%; females: n=2,476, 30·7%) received 17,004 treatment episodes of OAT over 40,599 person-years. Patients were aged between 18-75 years at cohort entry and mostly of White ethnicity (n=7,006, 86·8%). 807 episodes of self-harm (1·99/100 person-years) and 46 suicides (0·11/100 person-years) occurred. The overall age- and sex-standardised mortality ratio for suicide was 7·5 times (95%CI 5·5-10·0) higher than the general population. There was evidence of an association between OAT and reduced self-harm (adjusted risk ratio out of OAT: 1·50; 95%CI:1·21-1·88), but no evidence of an association with suicide (aRR out of OAT: 1·21; 95% CI: 0·64-2·28), possibly due to limited power. Risk of self-harm (aRR: 2·60; 95%CI: 1·83-3.70) and suicide (aRR: 4·68; 95%CI: 1·63-13·42) were both elevated in the first month after stopping OAT.

Interpretation: Stable periods of OAT are associated with reduced risk of self-harm, emphasising the importance of improving retention in treatment. The first month following cessation of OAT is a period of heightened risk of suicide and self-harm during which additional psychosocial support is required.

Funding: Medical Research Council.

Research in context

Evidence before this study

We searched titles and abstracts in PubMed, without language restrictions, using search terms related to self-harm or suicide ("suicid*", "self-harm*", "self-injury*") and opiate agonist therapy ("methadone", "buprenorphine", "opioid substitution", "opioid agonist") for articles published from database inception to 21st Aug 2020. We also screened publications in a recent systematic review of cause-specific mortality in relation to timing of OAT. The systematic review identified several studies investigating suicide during and after treatment. Overall, the risk of suicide was lower during OAT. In addition, one published study investigated differences in suicide, as well as other causes of death, between the first two weeks of OAT initiation and cessation in an Australian cohort. Crude mortality rates for suicide were elevated during these periods of initiation and cessation compared with overall time on and off treatment, and highest during OAT initiation. We also identified one large-scale Swedish cohort study of suicidal behaviour (including non-fatal suicide attempts), in which periods of methadone treatment were associated with a reduced risk of suicidal behaviours.

Added value of this study

This is the first large-scale study in the UK to investigate the risk of suicide in relation to the timing of OAT (including periods of treatment initiation and cessation), and the first globally to investigate the risk of self-harm. We found that OAT was associated with a substantial reduction in the risk of hospitalisation for self-harm. We did not find evidence of an association between time on and off OAT and death by suicide, although our results do not exclude an association. However, the risk of death by suicide was almost five times higher in the first four weeks after stopping OAT, whilst the risk of hospital admission for self-harm was almost three times higher during this period.

Implications of all the available evidence

Suicide and self-harm are important, yet often overlooked, contributors to mortality and morbidity in people with opioid dependence. The protective effects of stable periods of OAT on suicidal behaviour are notable. This may reflect a range of factors, such as direct protective effects of opiate agonism, indirect effects of increased support provided alongside OAT or selection bias due to lower risk patients taking OAT for longer. Nonetheless, our findings emphasise the importance of increasing retention in treatment and providing enhanced psychosocial support during OAT cessation to address the associated elevated risk of suicidal behaviour.

Introduction:

Suicide is a major public health burden and the second most common cause of death amongst people aged 15-29 years, globally.(1) People with a substance use disorder are at greatly increased risk of suicide.(2) Opioids are the most common substance for which people access drug treatment in England,(3) and the UK is estimated to have the highest level of opioid use in Europe.(4) Although suicidal intent can be difficult to determine in many opioid-related deaths,(5) there is evidence that opioid dependence is associated with a markedly increased risk of suicide.(2)

Opioid agonist treatment (OAT) involves prescription of long-acting opioids such as methadone and buprenorphine alongside other interventions. It has wide-ranging individual, population and societal benefits, particularly in relation to mortality, infectious disease, mental and physical health and criminal activity.(6) A recommended duration of OAT is generally unspecified, although there is evidence that retention in treatment is associated with better treatment outcomes.(6, 7)

Despite the benefits of OAT, in recent years, strong evidence has emerged demonstrating a substantial elevation in overdose and all-cause mortality risk in the first two to four weeks of initiation and cessation of OAT.(8) To date, research investigating suicidal behaviour in relation to OAT has mainly been limited to comparing time on and off treatment.(8) Yet, people often experience significant psychological, social and behavioural change during these transitional periods, which may also be associated with self-harm and suicide. One study that investigated suicide during treatment initiation and cessation in Australia found an elevated risk during these periods.(9)

This study aimed to investigate the overall risk of suicide amongst people with opioid dependence compared with the general population in England, and to determine whether the rate of self-harm and suicide among people with opioid dependence differs during treatment initiation, cessation, and the remainder of time on and off OAT. We hypothesised that self-harm and suicide would be higher in the first four weeks after OAT initiation and cessation, compared with stable periods of OAT.

Methods:

Design

We conducted a cohort study using Clinical Practice Research Datalink (CPRD) Gold data linked with Hospital Episode Statistics (HES) admission data and Office for National (ONS) Statistics mortality data. CPRD Gold contains anonymised primary care records for over 11 million patients from 674 registered general practices in the UK.(10) The sample covers approximately 7% of the UK population and is broadly representative of the general population in terms of age, sex, and ethnicity.(10) Medications are recorded as Product codes, whilst clinical observations are recorded as Read codes. HES is a clinical dataset that includes information on all NHS hospital admissions in England.(11) ONS collates data on specific causes of death in the UK, including suicides.(12) HES and ONS linkage is available for approximately 74% of CPRD Gold practices in England.(13)

Participants

The study population comprised people who were prescribed methadone or buprenorphine as OAT at least once in primary care in England between 2nd January 1998 and 30th November 2018.

Product codes for methadone and buprenorphine and Read codes indicating illicit opioid use were used to define the study population (appendix p.1). These were identified independently and agreed by two authors (P.P. and D.L.).

To avoid inclusion of people prescribed these drugs for other indications, such as analgesia or a cough in palliative care, we: 1) restricted age to at least 18 years at cohort entry, and 65 years or younger at the time of their first OAT prescription; 2) excluded people who were prescribed methadone or buprenorphine but did not have a Read code indicating illicit opioid use if they met the following criteria: a) any prescriptions for an injectable or topical formulation, because these are most commonly used for pain;(14) b) any prescriptions with dosage text stating "for pain"; c) maximum daily dose across all the patient's prescriptions of <4mg buprenorphine and <40mg methadone (Figure 1). These doses were selected to balance sensitivity and specificity, since they are at or above the maximum recommended doses for pain, and at the lower end of prescribed doses for OAT.(14) This criteria was a refinement of those used in previous CPRD studies of people prescribed OAT.(15, 16)

In keeping with standard approaches for CPRD studies,(17, 18) patients entered the cohort at the latest date out of the first recorded OAT prescription, the date the patient registered at their general practice, and 2nd January 1998 (the earliest date for when linked data were available) (appendix p.8). Patients with a first record of OAT prior to their practice registration date were included in the primary analysis to maximise power.

Patients were followed up until the earliest date out of 30th November 2018 (the last date when linked data were available), the last date of data collection from the practice, transfer away from the practice, or death (appendix p.8). For analyses of suicide data, we ended follow up on 30th November 2017, one year before the most recent date for which linked data were available. This accounted for the potential time lags in suicides being included in ONS death registration due to the investigation process required for unnatural deaths.(19)

Exposure

Our exposure categories were selected to reflect the time periods investigated within the OAT literature,(8) and facilitate future comparisons. Time on and after OAT was divided into: (1) the first four weeks on treatment, (2) remainder of time on treatment, (3) first four weeks after treatment, and (4) remaining time after treatment. In-keeping with previous studies,(15, 16) treatment episodes (i.e. time "on treatment") were defined as periods of one or more prescriptions of methadone or

buprenorphine as OAT, where there were 28 days or less between the expiry date of one prescription and the start of the next. A gap of greater than 28 days was considered a new treatment episode. We defined time "off treatment" as beginning from the expiry date of the last prescription in a treatment episode and ending on the first day of a new treatment episode, if it occurred.

Approximately three quarters of all methadone prescriptions and half of all buprenorphine prescriptions had missing daily doses, but almost all prescriptions included the total quantity prescribed. We used the method outlined in the appendix (p.9) to estimate the missing doses, which in turn were used in combination with the total quantity to estimate missing prescription durations and expiry dates. Prescriptions were excluded if the total quantity and duration were missing as this prevented estimation of their expiry dates (Figure 1), and after estimating missing daily doses, people who did not have a daily dose recorded in any of their prescriptions were excluded because we were unable to determine periods on and off treatment. Approximately 2% of recorded prescription durations appeared implausible (<1 day or >70 days), likely due to inaccuracies in prescription data entry. These durations were replaced with the average prescription duration (14 days) and excluded in a post-hoc sensitivity analysis.

Outcomes and co-variates

The outcomes were hospital admissions for non-fatal self-harm (identified using HES admissions data) and suicide (identified using ONS mortality data). Both ONS mortality and HES admission data are coded using ICD-10 (appendix p.1). As suicidal intent can fluctuate and be difficult to determine, and any self-harm including non-suicidal self-injury is an important risk factor for suicide, we included self-harm of undetermined suicidal intent. (20) This is in-keeping with current national guidance for the treatment of self-harm. (21) We also included deaths of undetermined intent as suicides since most of these deaths are probable suicides.(22) Events were included regardless of the position of relevant codes in the diagnostic lists.

We included the following potential confounders: age, sex, socioeconomic status (using postcode-linked Index of Multiple Deprivation score quintiles (13)), number of previous OAT treatment episodes, previous self-harm, previous mental illness and major chronic illness score (using the Charlson Index (23)). Ethnicity was not included as a co-variate due to concerns regarding the completeness and accuracy of the data (24), however the available data on patient ethnicity have been presented as baseline characteristics. To maximise completeness, ethnicity data were obtained from both CPRD and HES admission data. To facilitate comparison between these two sources, the data have been grouped into five broad ethnic categories used by the Office for National Statistics. Methods for defining each co-variate, as well as ethnicity, have been provided in the appendix (p.10).

Analyses

We used indirect standardisation (appendix p.15), using age- and sex-specific general population suicide rates in England for five-year age groups between 1998-2017 as a reference, to calculate a standardised mortality ratio.(25) We estimated a 95% confidence interval assuming a Poisson distribution in the number of observed deaths.

To calculate the crude rates of self-harm and suicide by exposure group, we partitioned the time axis and for each time period we divided the total number of occurrences of the outcome by the total person-years follow-up in that period. We then used these time periods as fixed-effects in a Poisson regression model for suicide and in a multilevel negative binomial model (with random effects) for self-harm to account for some patients having multiple hospital admissions with self-harm. We estimated adjusted rate ratios for each period (with remaining time on OAT as the reference group). For the multilevel model, the different time periods (level 1) were clustered for each patient (level 2). Level 1 covariates were measured at the start of each treatment period and comprised of age, number of previous OAT treatment episodes, previous self-harm, previous mental illness and previous chronic

illness score. Level 2 covariates were sex and socioeconomic status. A sex-specific analysis was performed post-hoc (appendix p.26).

As an exploratory analysis, we fitted an interaction term to investigate whether differences in the rate of each outcome differed between methadone and buprenorphine (appendix p.12). Treatment episodes during which both buprenorphine and methadone were prescribed were excluded from this analysis, as were the time off treatment periods that directly followed these episodes.

We conducted a series of pre-specified sensitivity analyses (appendix p.16). Key analyses included: 1) Including "accidental" poisoning deaths as many of these may be misclassified suicides;(22) 2) Excluding undetermined intent deaths as these may not all be suicides and the threshold for suicide verdicts by coroners in England has changed over time;(22) 3) Restricting to people with a Read code for illicit opioid use to maximise specificity. We also conducted a post-hoc sensitivity analysis in which we restricted the treatment initiation and cessation windows to two weeks each.

The study was approved by the Independent Scientific Advisory Committee (protocol 19_005). Patient consent was not required as all data were de-identified. Patients can opt out of their information being shared for research. Our protocol is available at: https://osf.io/7esb5. Analyses were conducted using Stata version 15·1.

Role of the funding source

The funders did not have a role in any aspect of this study.

Results

Our study cohort included 8,070 adults prescribed OAT at least once in primary care in England between 2nd January 1998 and 30th November 2018 (Figure 1). Table 1 shows the baseline characteristics of the sample at the start of follow-up. The median age at baseline was 33·3 years (IQR: 27·6-39·9 years). Most patients were male (n=5,594; 69·3%), lived in the most deprived quintile of neighbourhoods (n=3,437; 42·6%), and were of White ethnicity (n=7,006; 86·8%), although ethnicity data were missing for 8·4% (n=677) of patients. Almost a third were documented to have received OAT before the start of follow-up (n=2,331; 28·9%). Previous self-harm, mental illness and alcohol dependence were documented in the records of 11·4% (n=922), 44·5% (n=3,590), and 10·2% (n=820) respectively.

In our analysis of hospital admission for self-harm, patients were followed up for a total of 40,599 person-years, during which 17,004 OAT treatment episodes occurred (Table 2). Median follow up was 3·4 years (IQR: 1·2-7·4 years). Most patients received only one treatment episode during follow-up (n=3,642; 45·1%), and the most frequently prescribed OAT drug was methadone (n=6,295; 78·0% of patients received this drug). The median duration of treatment episodes was 84 days (IQR: 20-318 days).

During the follow-up period there were 807 hospital admissions for self-harm made by 493 people: 351 patients had one hospital admission with self-harm, 89 had two, 27 had three, and 26 had four or more.

The risk of self-harm was increased in periods out of OAT treatment compared with during OAT treatment (adjusted risk ratio:1·50 (95% CI: 1·21-1·88) (Table 3). The risk of self-harm was increased in the first 4 weeks after stopping treatment (aRR: 2·60; 95% CI: 1·83-3·70), and the remaining time off treatment (aRR: 1·47; 95% CI: 1·16-1.86) compared to the remaining time on treatment. There was no evidence of an increased risk of self-harm in the first 4 weeks on treatment, but this does not exclude an important association as the confidence intervals were wide (aRR: 1·43; 95% CI: 0·91-2·23). The same pattern of results was observed for both males and females (appendix p.26).

In our analysis of death by suicide, a total of 8,042 people who received OAT were followed up for 40,098 person-years between 1998-2017. 516 deaths occurred, of which 46 were suicides. The suicide mortality rate among study patients was 114.7 per 100,000 compared with 11.2 per 100,000 in the general population in England over this period.(25) The age- and sex- standardised mortality ratio was 7·5 (95% CI: 5·5-10·0) (appendix p.15).

Of the 46 suicides, 24 occurred by hanging, strangulation or suffocation, 19 by self-poisoning, and three by other methods. Methadone +/- other drugs were involved in eight of the self-poisoning deaths, an additional two deaths involved unspecified opioids, and drugs involved in the remaining nine deaths were unspecified.

There was insufficient evidence of a difference in the risk of suicide comparing periods after treatment with periods on treatment (aRR: 1·21; 95% CI: 0·64-2·28) (Table 4). However, risk of suicide was markedly increased in the first four weeks off treatment (aRR: 4·68; 95%CI: 1·63-13·42)) compared to stable time on OAT. This pattern of results was observed for both males and females during and post-treatment, and males during the first four weeks off treatment. The low number of suicides amongst females did not permit analysis by the four treatment periods (appendix p.26).

We found no evidence of any difference in the adjusted rates of suicide between buprenorphine and methadone when we compared time on and off treatment (χ^2=0·65, df=1, P=0·72). Crude rates of self-harm were slightly higher in patients on buprenorphine compared to methadone during OAT and in the period immediately after OAT (appendix p.14), but there was no evidence for differential effects (interaction comparing on/off methadone and buprenorphine for self-harm: χ^2=3·49, df=1, P=0·17; and between the four time periods: χ^2=4·05, df=3, P=0·40). We did not compare the four

time periods, including treatment initiation and cessation, in relation to suicide due to insufficient power.

In all sensitivity analyses, time off treatment was consistently associated with increased risk of self-harm. When comparing the four time periods, the highest point estimate for the risk of self-harm and suicide occurred during the first four weeks after stopping treatment (appendix p.16).

Discussion:

In this study we found that the risk of self-harm was lower during time on opioid agonist treatment (OAT) compared to time off treatment, and lowest during the stable period on treatment. We did not find evidence of an association between time on and off OAT and death by suicide, although confidence intervals were wide, and an important association could not be excluded. The risk of suicide was, however, almost five times higher in the first four weeks after stopping OAT, whilst the risk of self-harm was almost three times higher during this period. The age- and sex-standardised risk of suicide in our cohort of people with opioid dependence was 7·5 times greater than the general population.

The baseline characteristics of people in our study are comparable to those in previous CPRD studies of people prescribed OAT and people in treatment in drug and alcohol services.(3, 15, 16) The standardised mortality ratio for suicide of 7·5 (95% CI: 5·5-10·0) is similar to the pooled relative risk of 6·9 (95% CI: 4·5-10·5) in a Global Burden of Disease study.(2)

To our knowledge this is the first study investigating non-fatal self-harm in relation to the timing of OAT. Previous studies of non-fatal outcomes in relation to OAT initiation and cessation have mainly focused on infections and non-fatal drug overdoses. (6, 26) Our finding of increased risk of suicidal behaviour during the first four weeks of treatment cessation is in-keeping with a recent meta-analysis of unadjusted mortality rates.(8) The review included suicide data from one published study examining periods of treatment initiation and cessation in Australia, which also identified an increased risk of suicide during cessation as well as initiation.(9) In our study, the point estimates during treatment initiation suggested a heightened risk of suicide and self-harm, which increased further when the initiation window was narrowed to two weeks in a post-hoc sensitivity analysis (appendix p.25). However, in both analyses the confidence intervals included the null hypothesis value. Furthermore, all deaths that occurred during the first four weeks on treatment were of undetermined suicidal intent and, in another sensitivity analysis, there was evidence of an increased risk of self-harm during treatment initiation when the definition of self-harm was broadened further to include accidental poisonings (appendix p.16). In contrast, Degenhardt et al. (2009) did not include deaths of undetermined suicidal intent in their definition of suicide, but the difference in findings could reflect variation between countries in the standard of proof required for a suicide conclusion. (27, 28)

Although the recommended duration of OAT is generally unspecified, our findings support existing studies that demonstrate the potential benefits of increasing retention in treatment.(6) However, in our study the median treatment was 84 days, which is likely to be sub-optimal. Modelling studies indicate that increasing treatment duration to two years would result in a range of population benefits, including a reduction in overdose and HIV-related deaths.(7)

In our study, slight differences in self-harm rates in patients on buprenorphine compared to methadone were neither borne out in statistical tests of an interaction between time period and OAT modality nor observed for suicide. In contrast, there is emerging evidence regarding the protective effects of buprenorphine in relation to suicidal behaviour.(29) Yet, one previous study has investigated suicidal behaviour (including non-fatal suicide attempts) on and off treatment by OAT medication and found that methadone, but not buprenorphine, was associated with a decrease in the rate of suicidal behaviours.(30)

Periods of elevated suicide and self-harm risk have also been identified immediately post-discharge from mental health services, and policy initiatives, including the requirement to follow up patients within seven days of discharge, have been associated with a reduction in the risk of self-harm. (31, 32)

The large sample size in this study allowed us to investigate suicide (a rare outcome) whilst adjusting for key confounders. Data linkage enabled the examination of hospital-presenting self-harm, a key risk factor for suicide. Although power was limited in our analysis of suicide, there was consistency between the suicide and self-harm analyses regarding increased risk during treatment cessation. We acknowledge some key limitations.

First, there are limitations regarding classification of the exposure, outcome, and co-variates. Misclassification might have occurred due to inaccurate recording of Read, Product, and ICD-10 codes, missing clinical history information, mis-estimation of OAT duration as based on other prescription data, and the complexity of determining suicidal intent. Misclassification is likely to have occurred in a similar way at different stages of OAT, and therefore the most likely direction of bias is towards the null. The baseline characteristics and rate of outcomes are, however, comparable to those in the existing literature, which supports the representativeness of the sample.

Due to the lack of complete prescribing information, we were unable to compare planned and unplanned cessation. Most transitions between time on and off treatment in the UK are, however, likely to be unplanned (33).

OAT delivery varies throughout the UK and some people receive prescriptions directly from drug and alcohol services rather than from primary care. Although differences are generally area-based, people in drug and alcohol services may differ from patients managed solely or in shared care arrangements in primary care. A previous study did not find a difference in the duration of OAT between primary care and drug and alcohol services.(16) Nonetheless, replication of the study in patients managed by drug and alcohol services is required.

Treatment cohorts may not represent all people with harmful drug use if the risk of self-harm in people not in treatment differs to the risk in people who have entered OAT. Furthermore, there may be residual confounding. For example, we did not have details of patients' illicit drug use both during and after follow-up and did not adjust for factors such as homelessness and prison history, which are likely to have been under-recorded in GP records. Replication is therefore also important in other cohorts with more detailed information on clinical history.

Despite these limitations observational studies, such as this study, provide the best available evidence as randomised controlled trials would need unfeasibly large sample sizes to detect differences in suicide rates in people receiving OAT.

To date, research has emphasised the burden of overdose deaths amongst people with opioid dependence. Although suicide is less common, it is an important and often neglected cause of death in this population. People with opioid dependence are at greatly increased risk of suicide compared with the general population, and self-harm is almost twenty times more common than suicide in this patient group. The treatment of hospital-presenting self-harm is estimated to cost the NHS over £150 million per year.(34)

The protective effect of stable periods of OAT on suicidal behaviour is notable. This is likely to be due to a mixture of effects including direct protective effects of opiate agonism, indirect effects of increased support provided alongside OAT and possibly also selection bias due to lower risk patients taking OAT for longer. Nonetheless, the findings provide evidence for the potential benefits of increasing retention in treatment.

The elevated risk of self-harm and suicide in relation to treatment cessation highlights the need for enhanced psychosocial support during these periods. For unplanned treatment cessation this may require integration into advance care planning and assertive outreach and engagement strategies. As acute mental health services may also be required in supporting this patient group, the findings strengthen the case for greater joint working between drug and alcohol services and mental health services.

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Author contributions: PP and MH: conceptualisation; PP, MH, DG, PM and MTR: methodology; PP, HF and MTR: data curation; PP and HF: verification of underlying data; PP: formal analysis; HF, MTR, DG, MH, PM: supervision; PP: writing – original draft; All authors: data interpretation and writing–review & editing

Data sharing statement: This study made use of data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.Data are available from Clinical Practice Research Datalink (www.CPRD.com) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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Table 1: Baseline patient characteristics at start of follow-up (as recorded in primary care records)

Characteristics	Category	No. (%) unless otherwise specified
Patients (n= 8,070)		
Sex	Female	2476 (30·7)
	Male	5594 (69·3)
Age (years)	18-29	2857 (35·4)
	30-39	3212 (39·8)
	40-49	1479 (18·3)
	50+	522 (6·5)
*Ethnicity**	Asian	141 (1·8)
	Black	89 (1·1)
	Mixed	67 (0·8)
	Other	90 (1·1)
	White	7006 (86·8)
	Missing	677 (8·4)
*Previous OAT**	Yes	2331 (28·9)
*Previous self-harm**	Yes	922 (11·4)
*Previous mental illness**	Yes	3590 (44·5)
*Previous alcohol dependence**	Yes	820 (10·2)
Physical health co-morbidity (Charlson score)*	0	5543 (68·7)
	1	1983 (24·6)
	2+	544 (6·7)
*Smoking history**	Yes	5746 (71·2)
Index of Multiple Deprivation score	1 (least)	533 (6·6)
	2	844 (10·5)
	3	1352 (16·8)
	4	1904 (23·6)
	5 (most)	3437 (42·6)

*Methods for defining variables are described in the appendix (p.10)

Table 2: Treatment characteristics

Characteristics	Category	No. (%) unless otherwise specified
Patients (n= 8,070)		
Follow-up time	Total	40,599·2 person-years
	Median (IQR)	3·4 (1·2-7·4) years
Treatment received	Methadone	4844 (60·0)
	Buprenorphine	1775 (22·0)
	Both	1451 (18·0)
No. of treatment episodes during follow-up	0	1242 (15·4)
	1	3642 (45·1)
	2	1379 (17·1)
	3	699 (8·7)
	4+	1108 (13·7)
Treatment episodes during follow-up (n= 17,004)		
Treatment episode duration	Range	1 day - 24·7 years
	Median (IQR)	84 (20-318) days
	Mean (SD)	327 (626) days
Treatment received in each episode	Methadone	11487 (67·6)
	Buprenorphine	4591 (27·0)
	Both	926 (5·4)

Table 3: Crude rate for self-harm by exposure to OAT, and unadjusted and adjusted risk ratios (RR)

	Variable	No. of self-harm admissions	Person-years follow up	Self-harm/100 person years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status	*Overall on treatment*	225	14447·6	1·56 (1·37-1·77)	1·00	1·00
	Overall off treatment	582	26151·6	2·23 (2·05-2·41)	1·55 (1·24-1·94)	1·50 (1·21-1·88)
Treatment period	*Weeks 1-4 on treatment*	27	1035·7	2·61 (1·79-3·80)	1·45 (0·93-2·26)	1·43 (0·91-2·23)
	Remainder of time on treatment	198	13411·9	1·48 (1·28-1·70)	1·00	1·00
	Weeks 1-4 off treatment	54	1156·8	4·67 (3·58-6·09)	2·66 (1·87-3·77)	2·60 (1·83-3·70)
	Remainder of time off treatment	528	24994·8	2·11 (1·94-2·30)	1·54 (1·21-1·95)	1·47 (1·16-1.86)

Table 4: Crude rate for suicide by exposure to OAT and unadjusted and adjusted risk ratios (RR)

	Variable	No. of suicides	Person-years follow up	Suicide rate/100 person years (95% CI)	Risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status	*Overall on treatment*	14	14384·6	0·10 (0·06-0·16)	1·00	1·00
	Overall off treatment	32	25714·0	0·12 (0·09-0·18)	1·24 (0·66-2·34)	1·21 (0·64-2·28)
Treatment period	*Weeks 1-4 on treatment*	2	1032·2	0·19 (0·05-0·77)	2·14 (0·48-9·56)	2·12 (0·47-9·51)
	Remainder of time on treatment	12	13352·3	0·09 (0·05-0·16)	1.00	1.00
	Weeks 1-4 off treatment	5	1151·9	0·43 (0·18-1·04)	4·81 (1.69-13.65)	4·68 (1·63-13·42)
	Remainder of time off treatment	27	24562·0	0·11 (0·08-0·16)	1.18 (0.59-2.34)	1·14 (0.57-2·26)

Figure 1: Patient selection flowchart (N=patients, Px=prescriptions)
*Total figures are not equal to buprenorphine and methadone figures added together as some patients are prescribed both medications.