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J-shaped relationship between supervised methadone consumption and retention in methadone maintenance treatment (MMT) in primary care: National cohort study

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ABSTRACT

Background: Supervised consumption ensures patients take methadone as prescribed and prevents diversion, however, the influence of supervised consumption on retention is unclear. We examined association between supervised consumption and retention across multiple treatment episodes.
Methods: Cohort study of persons experiencing ≥1 MMT episodes in primary care (2004–2010), excluding ongoing episodes at the start of follow-up. Length of treatment episodes based on methadone prescriptions, retention classified as no interruption in prescribed methadone lasting >7 days. When a patient did not receive a new prescription within seven days after the end of coverage of a prescription, they were considered to have ceased treatment. We evaluated the relationship between supervised consumption and time to discontinuation of treatment using proportional hazards gamma frailty models to account for recurrent MMT episodes. Age, gender, median daily methadone dose, and comorbidities included as potential confounders.
Results: 6393 patients experienced 19,715 treatment episodes over the six-year follow-up period. A J-shaped relationship was observed; having between 20 and 60% of methadone scripts supervised (compared to <20%) associated with reduced time to discontinuation (20–39% HR = 0.88, 95% CI 0.81–0.95; 40–59%: HR = 0.87, 95% CI 0.81–0.94). Beyond a threshold of 60%, retention reduced (60–79% of scripts: HR = 1.28, 95% CI 1.20–1.36; >80% of scripts: HR = 3.59, 95% CI 3.38–3.81). Median daily dose between 60 and 120 mg/per day, and multiple treatment episodes also associated with longer time to discontinuation of treatment.
Conclusion: A J-shaped relationship was observed between supervised consumption and retention in treatment. Additionally, patients experiencing multiple treatment episodes tend to stay in treatment for progressively longer periods of time.

1. Introduction

The supervised administration of opioid substitution therapies, where the dose is consumed under the direct supervision of a pharmacist or clinician, is recommended by international guidelines (WHO, 2009) and is standard practice in many countries. Supervised consumption ensures that patients take their medication as prescribed and prevents drug diversion. Diversion poses a risk to others and may result in patients being under-treated, and relapsing to heroin use (Green et al., 2000). A number of observational studies have shown that drug-related deaths are lower in areas with supervised consumption (Weinrich and Stuart, 2000), and that drug-related deaths (Seymour et al., 2003) or deaths due to methadone have fallen following the introduction of super-

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vised consumption, through reducing diversion to the black market (Strang et al., 2010).

Supervised consumption also provides for more regular patient contact which may improve treatment outcomes (McLellan et al., 1993). However, long-term supervised dosing may not always be appropriate as it is labour-intensive, costly, and may impede patients from normalising their lives (Bell et al., 2007; Deering et al., 2011; Notley et al., 2014), which may result in patients dropping out of treatment. Several studies have shown that retention in opioid substitution treatment is associated with a reduced risk of mortality (Davoli et al., 2007; Cornish et al., 2010; Mathers et al., 2013; Cousins et al., 2016). However, few studies have compared the effects of supervised versus unsupervised consumption on retention (Rhoades et al., 1998; Bell et al., 2007; Holland et al., 2012, 2014), with conflicting results. One US RCT comparing supervised methadone consumption twice weekly versus five times weekly found a higher dropout rate in those supervised five times weekly (Rhoades et al., 1998). Similarly, a pilot RCT in Scotland found that retention decreased with increased supervision (Holland et al., 2012). Two RCTs conducted in Australia (Bell et al., 2007) and the UK (Holland et al., 2014) reported conflicting results, showing no difference in retention rates for those in supervised versus unsupervised dosing groups. These studies measured retention in treatment at between 12 and 24 weeks, which does not account for the chronic relapsing nature of opioid addiction and the well documented pattern of patients cycling in and out of treatment (Termorshuizen et al., 2005; Bell et al., 2006; Burns et al., 2009; Degenhardt et al., 2009; Cornish et al., 2010; Cousins et al., 2011; Zhang et al., 2015; Cousins et al., 2016). Furthermore, findings from a large cohort in Canada suggest that patients experiencing multiple treatment episodes tend to stay in treatment for progressively longer periods in later treatment attempts (Nosyk et al., 2009). This is important as findings from a Scottish cohort suggest that survival benefits increase with cumulative exposure to opiate substitution treatment (Kimber et al., 2010). Irish guidelines for prescribing methadone in primary care recommend a maintenance dose of between 60 mg and 120 mg daily, with at least one dose per week supervised in the pharmacy, and prescriptions for supply of methadone are issued for a period of not greater than seven days. The objective of this paper was to assess the effect of supervised methadone consumption on time to discontinuation of methadone maintenance treatment (MMT) across multiple treatment episodes in a national community based study of drug users in Ireland between 2004 and 2010.

2. Methods

2.1. Study design and setting

People registered on the national register for methadone maintenance treatment, the Central Treatment List (CTL), aged between 16 and 65 years of age, who were prescribed and dispensed methadone in primary care between 1st August 2004 and 31st December 2010 were identified. All methadone dispensing records (date of prescription, duration, and quantity of methadone dispensed) in the Health Service Executive's Methadone Treatment Scheme (MTS) were also extracted. To be included in the study a patient must have been dispensed at least three prescriptions over the study period. Following this, the MTS and CTL were 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. Eligibility for the GMS prescription scheme is through means test. All prescriptions are coded using WHO's Anatomical Therapeutic Chemical (ATC) classification. No information on diagnosis or disease condition is available. Finally, for every person registered on the CTL during our observation period, the National Drug Related Death Index (NDRDI), a census of drug-related deaths and deaths among drug users in Ireland was checked to identify those who died during the study period. Further details of the data and data linkage can be found in Cousins et al. (2016).

2.2. Treatment status

We defined a patient as being "on treatment" based on the coverage of their methadone prescriptions. Similar to previous studies, if a patient received a new prescription within seven days of the end of their previous prescription's coverage, they were considered to be in continuous treatment (Bell et al., 2006; Burns et al., 2009; Degenhardt et al., 2009). When a patient did not receive a new methadone prescription within seven 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 information was also used to calculate the episode number and duration of treatment episodes for each patient. We calculated the length of methadone treatment episodes from the number of days between the first and last prescription and the coverage of the last prescription. Only treatment episodes beginning after 1st August 2004 were included, to ensure consistency in the calculation of episode lengths and eliminate left-censored observations. Treatment episodes that were ongoing at the end of the follow-up period were right-censored.

2.3. Supervised consumption (primary exposure) and potential confounders

Prescription refill data was used to quantify the level of supervised methadone consumption for each treatment episode. Prescriptions that represented the dispensing of a single dose were classified as supervised. All other prescriptions, indicating methadone dispensing for a number of days, were classified as non-supervised. The percentage of supervised prescriptions per patient was then calculated and categorised into quintiles: less than 20%, 20–39%, 40–59%, 60–79% and 80% or greater supervised. Potential confounders included median dose of methadone for each episode for each person, which was categorised in accordance with UK prescribing recommendations as below, within, and above the recommended methadone maintenance range of 60 mg to 120 mg daily (Department of Health England, 2007). We also examined prescribing records for other drugs and calculated a comorbidity score as the total number of prescriptions for drugs, other than methadone, during the observation period. We counted the number of unique ATC codes (level three) appearing in the patients' prescription data, so that repeated prescriptions of the same or very similar medicines, including different doses or formulation, were only counted once (Brilleman and Salisbury, 2013). We recorded drugs used for psychoses and related disorders as anti-psychotics, and also recorded the use of benzodiazepines, antidepressants, and opioid analgesics. These four groups were excluded from the comorbidity score.

2.4. Statistical analysis

Cox proportional hazards gamma-frailty models can be fitted to account for the dependence in the length of repeated episodes and have been used in a similar study in Canada looking at the duration of repeated exposure to methadone maintenance treatment (Nosyk et al., 2009). Like standard Cox proportional hazards applications, the outcome is the bivariate pair (duration, censorship). In instances where there are multiple repeated durations of inter-