

Use of other opioids during methadone therapy: a population-based study

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ABSTRACT

Aims To determine the extent to which other opioids are prescribed to patients receiving methadone in Ontario, Canada. **Design** Retrospective cohort study. **Setting** Ontario, Canada from 1 April 2003 to 31 March 2010. **Participants** We studied patients aged 15–64 years with publically funded drug coverage who received at least 30 days of continuous methadone maintenance therapy (MMT). **Measurements** The proportion of patients who received more than 7 days of a non-methadone opioid during MMT. A secondary analysis examined the extent to which non-methadone opioids were prescribed by physicians or dispensed by pharmacies not involved in a patient's MMT. **Findings** Among 18 759 patients treated with methadone, 3456 (18.4%) received at least one prescription for non-methadone opioids of more than 7 days' duration. In this group, the median number of non-methadone opioid prescriptions dispensed per year was 11.9 (interquartile range 4.1–25.0). The most frequently prescribed opioids were codeine and oxycodone. Of the 73 520 non-methadone opioid prescriptions of more than 7 days' duration, nearly half (45.8%) originated from non-MMT prescribers and pharmacies. **Conclusions** Many patients receiving methadone maintenance therapy in Ontario receive overlapping prescriptions for other opioids, often for extended periods. The associated prescribing patterns suggest that many such prescriptions may be duplicitous. The prescribing and dispensing of non-methadone opioids to patients receiving methadone maintenance therapy is likely to be observed in jurisdictions outside Ontario, Canada.

Keywords Addiction, drug monitoring, drug safety, health care delivery, methadone, opioid dependence.

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INTRODUCTION

Methadone is a long-acting opioid used to treat patients with opioid dependence [1,2]. In this context, methadone maintenance therapy (MMT) has been shown to reduce illicit opioid use, criminal behaviour, human immunodeficiency virus (HIV) risk factors [3] and mortality [4–7]. Consequently, MMT is the most widely used form of opioid maintenance therapy in the United States, Canada and elsewhere.

In many jurisdictions, opioid analgesics prescribing has increased dramatically over the past two decades, largely due to the promotion of opioids for the treatment of chronic non-malignant pain [8]. This has been associated with a marked increase in opioid-related deaths in North America, particularly deaths involving oxycodone [9–10]. In most parts of North America, prescription opioid misuse has supplanted heroin abuse as the most common indication for MMT [11–14]. Although MMT reduces mortality among people in treatment compared

with no treatment, deaths from overdose still occur in patients receiving methadone [5,15], with a particularly high risk at the initiation and conclusion of MMT [4]. Moreover, toxicological analysis of methadone-related deaths reveals the involvement of additional drugs, in a large variety of cases including non-methadone opioids [16], suggesting that unsupervised non-methadone opioid during MMT increases the risk of mortality.

We examined how often individuals receiving MMT also received prescriptions for more than a week's supply of non-methadone opioids, and whether these prescriptions originated from physicians or pharmacies different from those involved in MMT.

METHODS

Design and data sources

We conducted a population-based cohort study of methadone recipients in Ontario, Canada. We used the Ontario Drug Benefit (ODB) database to identify prescription records for methadone and other opioids. This database contains a detailed record of all prescriptions issued to Ontario residents aged 65 years of age and older, as well as younger patients meeting eligibility criteria for social assistance, including unemployment, disability, high prescription drug costs relative to net household income, receipt of home care services and residence in a long-term care facility. In 2006, 561 091 (7%) of the Ontario population aged between 15 and 64 of ($n = 8\ 300\ 300$) [17]) Ontario residents between the ages of 15 and 64 were both eligible for ODB coverage and filled prescriptions. We used the Registered Persons Database (RPDB) to identify demographic information, the National Ambulatory Care Reporting System (NACRS) to identify information related to emergency department visits and the Canadian Institute for Health Information's Discharge Abstract Database (DAD) to identify information related to in-patient hospitalizations. Claims for physicians' services were obtained from the Ontario Health Insurance Plan database, which records all in-patient and out-patient physician claims in Ontario. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto.

Study subjects

We identified patients between the ages of 15 and 64 years who received at least 30 days of continuous MMT over a 7-year period (1 April 2003–31 March 2010). We focused on this age group because the majority of patients receiving MMT are younger than 65 years. The early period of MMT is characterized by dosage titration to avoid excessive sedation while an adequate dose

of methadone for opioid withdrawal management is reached [18]. Accordingly, for each patient, we defined a period of observation, with the initial index date defined as 30 days following the first methadone prescription. All analyses were restricted to patients with at least 7 days of continuous methadone use beyond this date because we wished to study patients who continued on methadone monotherapy for at least 1 week after a 30-day dose titration period. We identified continuous use of methadone from prescription data, allowing no more than 10 days to elapse between methadone prescriptions. To exclude methadone prescribed for pain rather than MMT, we restricted the analysis to liquid formulations because methadone tablets are specifically reimbursed for the treatment of pain in Ontario.

We excluded patients with invalid identifying information or missing age or gender variables. Methadone-treated subjects were observed from the index date to the time of methadone discontinuation (see above), death or end of the study period (31 March 2010), whichever occurred first.

Outcomes

The primary outcome was the proportion of methadone recipients who filled at least one prescription for more than 7 days of a non-methadone opioid during the observation period. These prescriptions were classified in two ways. First, we classified by drug (codeine, oxycodone, morphine, fentanyl, hydromorphone and meperidine). In this analysis, we considered long-acting oxycodone as a separate category because previous research indicated markedly increasing use during the study period [9,19]. Secondly, we categorized drugs based on formulation as either single-agent long-acting product, single-agent short-acting product or combination product (e.g. opioid formulations in combination with other drugs such as acetaminophen).

To quantify the amount of non-methadone opioids prescribed, we determined the average daily dose of the first prescription dispensed during the observation period, expressed as morphine equivalents. For this purpose, we determined the daily dose from the total mass of drug dispensed and the number of days supplied; the resulting dose was converted to morphine equivalents using published ratios [8], with fentanyl equivalencies defined as the mid-point of ranges specified in those guidelines.

As a secondary analysis, we examined the source of non-methadone opioid by ascertaining whether they were issued by any of the patient's methadone-prescribing physicians, and also whether they were dispensed by any of the pharmacies at which the patient received methadone.

Table 1 Baseline characteristics of methadone recipients.^a

| Variable | >7 days of non-methadone opioids (n = 3456) |
|---|--|
| Age in years, median (IQR) ^b | 40 (32–46) |
| Male (n; %) | 2066 (59.8%) |
| Johns Hopkins ACG ^c , n (%) | |
| 0–4 | 40 (1.2%) |
| 5–9 | 372 (10.8%) |
| 10–14 | 1018 (29.5%) |
| 15–19 | 1402 (40.6%) |
| 20+ | 624 (18.1%) |
| Income quintile, n (%) | |
| Missing | 15 (0.4%) |
| 1 (low income) | 1383 (40.0%) |
| 2 | 828 (24.0%) |
| 3 | 557 (16.1%) |
| 4 | 421 (12.2%) |
| 5 (high income) | 252 (7.3%) |
| Number of ED visits in past 1 year, median (IQR) ^b | 1 (0 to 4) |
| Number of physician visits in past 1 year, median (IQR) ^b | 35 (22–56) |
| Duration of methadone treatment in days, median (IQR) ^b place near top | 308 (124–712) |

^aThis table describes baseline characteristics for individuals with at least 30 days of continued methadone use who also received at least one non-methadone opioid prescription of >7 days duration. ^bIQR: interquartile range (25th and 75th percentiles). ^cThe Johns Hopkins adjusted clinical groups (ACG) system measures the morbidity burden of patient populations based on disease patterns, age and gender [24]. ED: emergency department.

Table 2 Characteristics of non-methadone opioid prescriptions.^a

| Variable | n = 3456 patients |
|---|-------------------|
| Number of non-methadone opioid prescriptions per year, median (IQR) | 11.9 (4.1–25.0) |
| Number of non-methadone opioid prescriptions of duration >7 days, per year, median (IQR) | 7.6 (2.1–15.7) |
| Number of distinct non-methadone opioid drug types co-prescribed, n (%) | |
| Short-acting oxycodone | 1922 (55.6%) |
| Codeine | 1532 (44.3%) |
| Long-acting oxycodone | 1166 (33.7%) |
| Morphine | 397 (11.5%) |
| Hydromorphone | 349 (10.1%) |
| Fentanyl | 265 (7.7%) |
| Meperidine/pethidine | 58 (1.7%) |
| Opioid drug formulations co-prescribed, n (%) | |
| Long-acting single agent formulations | 1705 (49.3%) |
| Short-acting single agent formulations | 529 (15.3%) |
| Short-acting combination products ^b | 2623 (75.9%) |
| Time to first non-methadone opioid prescription (days), median (IQR) ^c | 18 (6–84) |
| Average daily dose of first non-methadone opioid prescription (morphine or equivalent), median (IQR) ^d | |
| Long-acting formulations | 120 (67.3–240) |
| Short-acting formulations | 60 (22.5–133.3) |
| Combination formulations ^b | 25 (15–37.5) |

^aThis table describes all non-methadone opioid prescriptions prescribed to individuals who received at least one prescription of >7 days duration.

^bCombination formulations are opioids in combination with other drugs such as acetaminophen/paracetamol. ^cTime to first non-methadone opioid prescription is measured from cohort entry date. ^dIQR: interquartile range (25th and 75th percentiles).

Statistical analysis

Because our study sample is a census of all patients with social assistance receiving MMT continuously in a defined jurisdiction, we used descriptive statistical analyses. For dichotomous and categorical variables, we determined proportions of different groups of patients. For other variables of at least ordinal quality, we displayed the median and the inter-quartile range.

RESULTS

During the 7-year study period, we identified 18 759 patients aged 15–64 years who received at least 30 days of MMT and met our inclusion criteria. We identified 3456 patients (18.4%) who received one or more non-methadone opioid prescriptions with more than 7 days' supply. The baseline characteristics of these patients are presented in Table 1.

The characteristics of non-methadone opioid prescriptions with more than 7 days' supply are shown in Table 2. Among the 3456 patients in this group, the median time from cohort entry to first non-methadone opioid prescription was 18 days [interquartile range (IQR) 6–84] (Table 2), indicating use of other opioids early in the course of MMT. The number of opioid prescriptions dispensed each year was 11.9 (IQR 4.1–25.0), and 42.8% of those prescriptions (44 450 of 103 831) were for more than a 7-day supply. As expected, the most frequently prescribed non-methadone opioids were

Table 3 Source^a of non-methadone opioid prescriptions of duration >7 days.

| | |
|--|----------------|
| Non-methadone prescriptions ^b | |
| Total number of all non-methadone opioid prescriptions | 73 520 |
| Non-MMT physician | 49 786 (67.7%) |
| Non-MMT pharmacy | 33 990 (46.2%) |
| Non-MMT prescribing physician and pharmacy | 33 668 (45.8%) |
| Patients receiving non-methadone opioids ^b | |
| Number of patients receiving methadone and another opioid ^c | 3 254 |
| Any non-MMT physician | 3 041 (93.5%) |
| Any non-MMT pharmacy | 2 621 (80.5%) |
| Any non-MMT prescribing physician and pharmacy | 355 (10.9%) |

^aThis table shows results from two analyses. The first analysis describes the prescribing and pharmacy source for all prescriptions. The second analysis describes the prescribing and pharmacy source at the patient level. ^bThe total number of prescriptions for non-methadone opioids of duration 7 days or longer prescribed to patients in methadone maintenance therapy (MMT) programs. ^cThe sample size is smaller than in Table 2 because individuals with missing prescriber identification on non-methadone opioid prescriptions were excluded.

oxycodone and codeine, and half the patients received a long-acting opioid formulation ($n = 1705$, 49.3%).

The median daily dose of the first non-methadone opioid prescription during the observation period was equivalent to 120 mg of morphine (IQR 67.3–240) among patients receiving long-acting opioids and 60 mg (IQR 22.5–13.3) among those receiving short-acting opioids (Table 2).

Sources of non-methadone opioids

The majority of patients received at least one prescription from a physician ($n = 3041$, 93.5%) or pharmacy ($n = 2621$, 80.5%) not involved in their methadone therapy (Table 3). One out of every nine patients ($n = 355$; 10.9%) obtained at least one non-methadone opioid prescription from both a physician and pharmacy that were not involved in their methadone treatment. Of the 73 520 non-methadone opioid prescriptions prescribed for more than 7 days' duration, almost half ($n = 33 668$; 45.8%) were obtained from prescribers and pharmacies not involved with the patients' methadone treatment (Table 3).

DISCUSSION

During this 7-year study, we found that approximately one in five (18.4%) patients treated with methadone received at least one prescription for a non-methadone opioid prescription of greater than 7 days' duration. Importantly, almost half of all such prescriptions during

the study period originated from prescribers and were obtained from pharmacies not involved with the patient's MMT program. Combination therapy of this sort is universally discouraged, and this finding suggests strongly that many such prescriptions reflect duplicitous drug-seeking behavior, either for personal use or for diversion and financial gain.

Many jurisdictions have seen recent, dramatic increases in the rates of prescription opioid abuse and dependence, along with associated increase in mortality [9,13,19–21]. Consequently, there has been an increase in the use of MMT, and prescription opioids have supplanted heroin as the main indication for MMT [11,12,14]. The co-prescription of methadone with other opioids is an unsafe practice, and the large quantities of long-acting oxycodone received by MMT subjects in our study are particularly concerning given the potential for fatal overdose [9]. Previous studies have described the trend of increased use of opioids other than heroin as an indication for MMT at time of enrollment [12,14]. To our knowledge, this is the first study to quantify systematically the co-prescription of opioids among patients who are participating regularly in MMT programs.

Some limitations of our work merit emphasis. First, our prescription data are limited to patients receiving social assistance, and whether these findings apply to more affluent patients is unknown. Secondly, if patients paid cash for opioid prescriptions while covered by ODB, the prescription would not be captured. This limitation would underestimate the extent of opioid co-prescription.

Our findings indicate that co-prescription of other opioids with methadone is common despite current practice guidelines for drug monitoring during MMT. This problem could be mitigated largely by real-time access to prescription data for both physicians and pharmacists prior to writing and filling prescriptions, which exists currently in only a few jurisdictions in Canada, the United States and elsewhere [22,23]. Without preventive measures, the safety and effectiveness of MMT programs is undermined by the diversion of prescription opioids by individuals enrolled in MMT.

In summary, we found that a substantial number of subjects receiving MMT were dispensed large quantities of non-methadone opioids, and that many such prescriptions originated from physicians and pharmacies not involved in the patient's MMT, a finding that suggests purposeful drug-seeking behavior and subversion of accepted MMT guidelines. The corollary of these findings is that comprehensive, real-time access to prescription claims data may curtail the extent to which other opioids are co-prescribed with methadone.

Declarations of interest

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