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Predictors of Opioid-Related Death During Methadone Therapy

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ABSTRACT

We aimed to examine pharmacologic, demographic and medical comorbidity risk factors for opioid-related mortality among patients currently receiving methadone for an opioid use disorder. We conducted a population-based, nested case-control study linking healthcare and coroner's records in Ontario, Canada, from January 31, 1994 to December 31, 2010. We included social assistance recipients receiving methadone for an opioid use disorder. Within this group, cases were those who died of opioid-related causes. For each case, we identified up to 5 controls matched on calendar quarter. The primary analysis examined the association between use of psychotropic drugs (benzodiazepines, antidepressants or antipsychotics) and opioid-related mortality. Secondary analyses examined the associations between baseline characteristics, health service utilization, comorbidities and opioid-related mortality. Among 43,545 patients receiving methadone for an opioid use disorder, we identified 175 (0.4%) opioid-related deaths, along with 873 matched controls. Psychotropic drug use was associated with a two fold increased risk of opioid-related death (adjusted odds ratio (OR) 2.0; 95% confidence interval (CI) 1.2 to 3.5). Specifically, benzodiazepines (adjusted OR 1.6; 95% CI 1.1 to 2.5) and antipsychotics (adjusted OR 2.3; 95% CI 1.5 to 3.5) were independently associated with opioid-related death. Other associated factors included chronic lung disease (adjusted OR 1.7; 95% CI 1.2 to 2.6), an alcohol use disorder (adjusted OR 1.9; 95% CI 1.2 to 3.2), mood disorders (adjusted OR 1.8; 95% CI 1.0 to 3.2), and a history of heart disease (adjusted OR 5.3; 95% CI 2.0 to 14.0). Psychotropic drug use is associated with opioid-related death in patients receiving methadone. Mindfulness of these factors may reduce the risk of death among methadone recipients.

1. Introduction

In patients undergoing treatment for opioid use disorders, methadone therapy is associated with several improved outcomes, including retention in drug treatment as well as reduced opioid use, and some observational studies have observed reductions in all-cause mortality and risk of death from overdose (Esteban et al., 2003; Gibson et al., 2008; Huang & Lee, 2013; Langendam, van Brussel, Coutinho, & van Ameijden, 2001; Mattick, Breen, Kimber, & Davoli, 2009; Perry et al., 2013; Schwartz et al., 2013). On the basis of its effectiveness, the World Health Organization added methadone

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to its list of essential medicines in 2005. It is included on the complementary list of "essential medicines for priority diseases", for which specialist care is needed (World Health Organization, 2005). As prescription opioid use continues to increase (Dhalla et al., 2009), so has opioid misuse and the demand for treatment (Fischer, Nakamura, Rush, Rehm, & Urbanoski, 2010). Consequently, the number of patients treated with methadone has increased dramatically in North America over the past 10 years (Luce & Strike, 2011; Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics & Quality, 2013).

Many challenges accompany methadone therapy, including multiple drug interactions and the risk of fatal QT prolongation (Chou, Weimer, & Dana, 2014; Kapur, Hutson, Chibber, Luk, & Selby, 2011). Drug-related deaths are common among patients on methadone therapy, as are other medical causes and trauma (Clausen, Waal, Thoresen, & Gossop, 2009; Zador & Sunjic, 2000). Individuals on methadone therapy have a higher risk of death during periods of induction and discontinuation (Caplehorn & Drummer, 1999; Clausen et al., 2009; Degenhardt et al., 2009; Srivastava & Kahan, 2006; Zador & Sunjic, 2000; Zanis & Woody, 1998). Additionally, some evidence suggests an association between drug-related death and psychiatric disorders, during or after cessation of methadone treatment (Cousins et al., 2011; Zanis & Woody, 1998).

Methadone prescribing is highly regulated, and patients are closely monitored due to the associated risks of treatment. Clinical practice guidelines identify factors that may increase the risk of methadone toxicity (Chou et al., 2014; Hillier, 2011). Most methadone-associated deaths involve methadone obtained from non-prescription sources or methadone prescribed for pain (Heinemann, Iwersen-Bergmann, Stein, Schmoldt, & Püschel, 2000; Paulozzi et al., 2009; Weimer, Korthuis, Behonick, & Wunsch, 2011), but safety concerns persist in light of the growing number of methadone-related deaths (US Department of Health and Services, 2010).

Previous studies have examined various risk factors for overdose-related death among patients in drug treatment programs, including street drug use, demographic, and comorbidities (HIV, hepatitis status, and mental and physical health scores) (Brådvik, Berglund, Frank, Lindgren, & Löwenhielm, 2009; Brugal et al., 2005; Gossop, Stewart, Treacy, & Marsden, 2002; Peles, Schreiber, & Adelson, 2010). Others have examined cardiac mortality among subjects whose methadone levels precluded drug toxicity as the cause of death (Chugh et al., 2008). Still others have explored the role of systemic disease (Darke, Kaye, & Duflou, 2006) and medical and psychiatric comorbidity risk factors for all-cause mortality among individuals who entered methadone maintenance treatment (Huang & Lee, 2013).

However, important gaps remain in the literature related to predictors of opioid-related deaths among patients currently in methadone maintenance treatment. Most studies in this area do not clearly differentiate among people who enter methadone therapy rather than drug treatment more generally (Brådvik et al., 2009; Gossop et al., 2002), those who remain on methadone therapy or those who discontinue (Brugal et al., 2005), those who die while using prescribed or non-prescribed methadone treatment (Chugh et al., 2008; Darke et al., 2006), or those who die of an opioid- or non-opioid overdose (Huang & Lee, 2013; Peles et al., 2010).

Methadone prescribers are advised to use caution when treating patients who use benzodiazepines or alcohol, as well as those who have lung disease. However, the extent to which other co-morbid conditions or concurrent prescriptions influence the risk of opioid-related death during methadone therapy is less well understood (Chan, Stajic, Marker, Hoffman, & Nelson, 2006; Cousins et al., 2011; McCowan, Kidd, & Fahey, 2009; Pilgrim, McDonough, & Drummer, 2013; The DAWN Report, 2004). Previous studies of the extent to which psychotropic drugs increase the risk of drug-related death in methadone recipients used a restrictive case definition of "deaths caused directly by the consumption of one or more illegal drugs" (Cousins et al., 2011; European Monitoring Centre for Drugs and Drug Addiction, 2009; McCowan et al., 2009). We examined the association between psychotropic drug use, among other factors, and opioid-related mortality in patients receiving methadone treatment for an opioid use disorder.

2. Material and methods

2.1. Setting and design

We conducted a nested case-control study of Ontario residents between January 31, 1994 and December 31, 2010. These individuals had universal access to hospital care, physicians' services, and prescription drug coverage. The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

2.2. Sources of data

We identified prescription records using the Ontario Drug Benefit (ODB) Database, which contains comprehensive records of prescription medications dispensed to Ontarians whose prescriptions costs are reimbursed by the provincial government. In 2006 in Ontario, more than 70% of methadone recipients were insured under this program (Hart, 2007). Methadone prescriptions are recorded in the ODB database for each date methadone was dispensed, regardless of whether doses were observed in a pharmacy. In Ontario, methadone prescribing guidelines specify that methadone must be dispensed daily for at least the first 2 months of treatment (Hillier, 2011). Methadone prescribers undergo regular mandatory practice audits by the College of Physicians and Surgeons of Ontario, and compliance with daily dispensing in the first 2 months is extremely high.

Opioid-related deaths were identified using the records of the Chief Coroner for Ontario, as done previously (Dhalla et al., 2009; Dhalla, Mamdani, Gomes, & Juurlink, 2011; Gomes et al., 2011). The investigating coroner classified opioid-related deaths as those with toxicologic findings of opioid concentrations sufficiently high to cause death, or that a combination of drugs (including at least one opioid present at a clinically significant concentration) resulted in death (Dhalla et al., 2009). The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) was used to identify hospitalizations, which contains detailed diagnostic and procedural information regarding all acute care hospital admissions in the province. We used the Ontario Health Insurance Plan (OHIP) Database to determine physician billing claims, including visits to physicians licensed to prescribe methadone and claims for urine drug screens. Comorbidities were identified using the CIHI-DAD, CIHI Same-Day Surgery Database (CIHI-SDS), CIHI National Ambulatory Care Reporting System (CIHI-NACRS) and OHIP databases. The Adjusted Clinical Group (ACG) scoring system was used to measure comorbidity in the preceding year (Weiner, 2003). Demographic information was obtained from the Registered Persons Database (RPDB). These datasets are linked in an anonymous fashion using encrypted health insurance numbers, contain little missing information (Levy, O'Brien, Sellors, Grootendorst, & Willison, 2003), and are routinely used to study drug safety (Juurlink et al., 2004; Juurlink et al., 2009; Park-Wyllie et al., 2011).

2.3. Identification of cases and controls

We defined case patients as those who died of opioid-related causes within 3 days of receiving a prescription for methadone. The date of death served as the index date for all analyses. For each case, we randomly selected up to 5 controls from the population of patients receiving methadone for an opioid use disorder who did not die of opioid-related causes on or before the index date. Control subjects were randomly assigned index dates based on the distribution of case index dates and matched to case patients on calendar quarter of index

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