Original Article

Methadone for Pain and the Risk of Adverse Cardiac Outcomes

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Abstract

Context. There are few studies that describe cardiac adverse events in patients prescribed methadone for pain management.

Objectives. To describe incident cardiac adverse events and risk factors for cardiac adverse events in primary care patients prescribed methadone for pain.

Methods. This was a retrospective, descriptive, cohort study in patients 18 years or older receiving methadone for pain management during 2010. Patients were followed for 12 months and were categorized as "chronic" or "non-chronic" methadone users. The primary outcomes were a cardiac event, at risk for an event, or neither. Patients were grouped on their outcome and were compared on risk factors and methadone monitoring.

Results. A total of 1246 patients were included. Thirty (2.4%), 628 (50.4%), and 588 (47.2%) patients had a cardiac event, were at risk for an event, or had neither an event nor a risk factor, respectively. Overall, the rate of QTc prolongation was 49.4% and the rate of adherence to recommended cardiac monitoring was 39.0%. Similar percentages of chronic and non-chronic users had a cardiac event ($P > 0.05$). Among the patients who had a cardiac event and were at risk for an event, factors independently associated with having had an event included age (odds ratio = 1.06; 95% CI = 1.03–1.09) and a dose 100 mg/day or higher (odds ratio = 6.18; 95% CI = 1.08–35.45).

Conclusion. Few cardiac adverse events resulting from methadone use for pain were detected. However, a large proportion of patients were at risk for an adverse event, especially patients who were older and had received ≥100 mg/day of methadone. J Pain Symptom Manage 2014;48:333–342.

Key Words

Methadone, pain management, long QT syndrome, electrocardiography, analgesic-opioid/adverse effects, primary health care

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Introduction

Historically, methadone has been used for the treatment of heroin addiction and drug rehabilitation. However, methadone is increasingly being used for the treatment of chronic pain because of its mechanism of action, high oral bioavailability, absence of active metabolites, prolonged analgesic effects, and relatively low cost.[1–3] Reports of methadone-related cardiac adverse effects, including ventricular arrhythmias and deaths, have increased in recent years, which may be attributed partially to methadone's expanded use and its risk for QTc prolongation.[4,5]

Despite its similarities to other opioids, methadone can prolong the QTc interval and has the potential to induce torsades de pointes (TdP), a potentially fatal polymorphic ventricular arrhythmia. A QTc interval, detected with an electrocardiogram (ECG), ≥500 milliseconds (ms) is concerning because of the increased risk for TdP.[6] Additional known risk factors for QTc prolongation include cardiac structural abnormalities, age, gender, hypokalemia, and hypomagnesemia.[7,8] Methadone's product labeling includes a black box warning for the risk of QTc interval prolongation and TdP.[9]

Consensus guidelines regarding the cardiac adverse effects with methadone were published in 2009 by an independent expert panel.[10] The guidelines encourage providers to: 1) inform patients of methadone's arrhythmia risk; 2) review patient history for structural heart disease, arrhythmias, and syncope; 3) obtain an ECG before and 30 days after starting therapy, then annually; 4) discuss the risks and benefits of therapy if the patient's QTc is >450 ms but <500 ms; and 5) be aware of the concomitant use of potentially interacting or other QTc prolonging medications. In addition, the guidelines recommend providers consider decreasing the dose or discontinuing therapy if the QTc is >500 ms and obtain an ECG when methadone doses are >100 mg/day or when clinically indicated.

Most studies examining methadone's adverse effects were conducted among patients with drug addiction. Such studies have reported QTc prolongation rates ranging from 9% to 83% with methadone doses ranging from 4 to 1200 mg.[11–14] Relatively few studies have been conducted in patient populations prescribed methadone for pain management. One prospective study of 100 palliative care patients receiving methadone for pain at a median dose of 23 mg per day reported 31% of patients had QTc prolongation at two weeks of therapy and 11% of patients had QTc prolongation at eight weeks of therapy.[2] A larger, retrospective study of over 500 patients found no patients with a QTc interval >500 ms with a median methadone dose of 30 mg per day (range 2–480 mg per day); however, only 11% of the patients had ECG monitoring within three months before and after starting methadone.[15] Additionally, most studies primarily measure surrogate endpoints (i.e., QTc interval effects) and not clinical outcomes. The purpose of this study in primary care patients prescribed methadone for pain was to describe the rates of cardiac adverse events, hospitalizations or emergency department (ED) visits for QTc prolongation/TdP, and cardiac deaths, and identify the risks for cardiac adverse events.

Methods

Study Design

This was a retrospective, descriptive, cohort study that examined cardiac adverse effects in patients prescribed methadone for pain management. This study was conducted at Kaiser Permanente Colorado (KPCO), a not-for-profit, integrated health care delivery system with approximately 500,000 members in the Denver-Boulder metropolitan area. Primary care physicians at KPCO have been prescribing methadone for treatment of pain for more than 10 years.

Kaiser Permanente uses an electronic medical record (EMR) system in all medical offices. Administrative data from EMR and other sources, including membership (including dates and causes of death), prescribing and laboratory data, are captured in electronic databases. In addition, claims data from non-KPCO providers, including hospital stays and ED visits, are captured in separate electronic databases. Furthermore, KPCO accounts for deaths of members who did and did not terminate membership before death via queries of the National Death Index, U.S. Social Security Administration, state death registries, and death-records.com. This study used data from queries of these databases and manual reviews of EMR. The KPCO Institutional Review Board