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Patterns of Care and Side Effects for Patients Prescribed Methadone for Treatment of Chronic Pain

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Abstract

Objectives—This manuscript evaluates physician monitoring practices and incidence of cardiac side effects following initiation of methadone for treatment of chronic pain as compared to patients who began treatment for chronic pain with morphine sustained release (SR).

Design—We retrospectively reviewed medical record data on all new initiations of methadone and compared results of physician monitoring practices to patients with new initiations of morphine SR. A standardized chart tool was used to capture clinical data. Data related to health service utilization and clinical diagnoses were obtained from the VA clinical information system.

Setting—A single VA medical center in the Pacific Northwest.

Patients—Chronic pain patients prescribed methadone (n=92) or morphine (n=90) in the calendar year 2008.

Results—There was no difference between patients prescribed methadone versus patients prescribed morphine SR in the likelihood of receiving an electrocardiogram (ECG) prior to initiating medication (53% versus 54%) or in the year after opioid initiation (37% versus 40%). The two groups also did not differ in rates of developing prolonged QTc intervals (>450 ms) (11% versus 17%). Seventy-two percent of all patients discontinued their long-acting opioid regimens before 90 days due to adverse effects or insufficient pain relief.

Conclusion—Despite recommendations for standardized assessment and cardiac risk monitoring, few patients prescribed methadone received an ECG, and this occurred at a rate that did not differ from patients prescribed morphine SR. Patients discontinued both medications at high rates. Further research is needed to evaluate the clinical significance of QTc prolongation in patients treated with methadone.

Keywords

Chronic pain; Opioids; Veteran; Pain/drug therapy; Methadone; QTc prolongation; ECG; medication side effects

Introduction

The use of opioid medications to treat chronic pain continues to steadily increase since the 1990s¹. The sales of opioid analgesics quadrupled between 1999 and 2010, and the epidemic of chronic pain with its related disabilities and opioid use and related fatalities remain an issue in modern medicine¹. Current recommendations for chronic opioid therapy (COT) are to consider long-acting opioids in patients with persistent pain. Although the evidence base to support use of long-acting over short-acting opioids is weak², potential advantages of long-acting opioids include more stable blood levels of opioids, decreased risk for addiction, fewer adverse effects, and improved analgesia³. Methadone is a long-acting synthetic opioid that is structurally dissimilar to morphine that originally received U.S. Food and Drug Administration (FDA) approval for opioid replacement therapy, and is now widely used to treat chronic pain⁴.

Methadone may be considered for chronic pain due to its analgesic properties, long half-life, and low cost^{5,6}. It has been reported to result in reduced tolerance to analgesic effects³ and is commonly prescribed. For example, in a recent study of veterans returning from the wars in Iraq and Afghanistan treated in the Veterans Affairs (VA) care system, of the long-acting opioids, methadone and morphine sustained release (SR) were the most frequently prescribed chronic opioid therapies⁷. Despite its increasing use, methadone has unique risks due to its variable half-life and its potential for numerous drug interactions⁴. Identifying these risks is necessary to provide sufficient patient safety to patients prescribed methadone.

Methadone use has been associated with rate-corrected (QTc) prolongation. A formal consensus definition for QTc prolongation is lacking; however, it is generally defined as a QT interval >450 ms for men and >470 ms for women⁸. QTc prolongation can lead to the potentially fatal arrhythmia 'torsade de pointes'⁵. Electrocardiograms (ECGs) have been recommended for all patients prescribed methadone prior to starting treatment, within 30 days after starting methadone, and annually as follow-up^{6,9-11}. Additional recommendations for patients prescribed methadone include patient education about the risk for arrhythmia and a thorough history to evaluate for cardiac abnormalities like structural heart disease⁶.

Methadone dosing is complex. It has potential interactions with commonly prescribed medications, such as antidepressants (**monoamine oxidase inhibitors and tricyclics**), anticonvulsants (**carbamazepine**), anxiolytics (**diazepam**), **cardiac medications (nifedipine)**, and anti-inflammatories (dexamethasone) which depending on the medication can act as inducers or inhibitors of methadone metabolism at the CYP P-450 enzyme^{4,12,13}. There are reports of life threatening side effects and death in patients prescribed methadone^{12,14}. Deaths related to licit and illicit methadone use have increased nearly 600% between 1999 and 2008¹⁴. However, although methadone-related deaths in the general population have increased, a recent study of patients receiving care within the

Department of Veterans Affairs found no difference in mortality rates between patients prescribed methadone or morphine SR¹⁵. As a result of these safety concerns, both the FDA and the Medicines and Healthcare Regulatory Agency have issued “black box” warnings when prescribing methadone.

Although recommendations have been provided for best strategies to manage pain in patients prescribed methadone¹⁶, little is known about the monitoring practices that patients receive or the subsequent adverse effects associated with methadone initiation. In this study, we sought to examine provider opioid monitoring practices of cardiac adverse effects among a sample of patients with pain who had new prescriptions of methadone. In order to provide a comparison of opioid monitoring practices and adverse effects, we collected similar data on patients who had new starts of morphine SR. Morphine SR was chosen for comparison because it is a commonly prescribed long-acting opioid medication¹⁷. Common side effects associated with morphine SR (and all opioids) include nausea, vomiting, constipation, fatigue, nausea, purposeful abuse, and diversion; as opioid dose or duration is increased, adverse events may include endocrinologic dysfunction, fractures, emergency room visits, poorer pain treatment outcomes, overdose and death¹⁸⁻²⁴.

Methods

This study was approved by the local VA Medical Center Institutional Review Board.

Study Sample

We identified all pain patients from a single VA medical center whose providers initiated opioid therapy, for patients with moderate to severe chronic pain, with methadone or morphine SR in 2008. To classify patients as having chronic pain, we used results from routinely administered pain intensity screenings. Currently the VA healthcare system uses pain numeric rating scores (NRS) to screen for pain in clinical settings as part of its “Pain as the fifth vital sign” initiative²⁵. The NRS rates pain intensity on a scale of 0–10, with 0 representing no pain and 10 representing the worst possible pain. To identify patients with moderate to severe chronic pain, we examined patients who had NRS pain scores >4 recorded in at least three different months during 2008. This is consistent with common definitions of chronic pain that require at least three to six month duration of moderate to severe pain²⁶. Within this sample of patients with chronic pain, we identified patients who were newly prescribed either methadone or morphine SR in 2008. An index date was calculated for each subject, defined as the date of initiation of methadone or morphine SR. Patients were excluded if they had any visits to a VA opioid substitution program (i.e., methadone maintenance) in the prior year or were currently receiving palliative or hospice care.

Patient data were extracted from the electronic medical record from the Veterans Integrated Service Network-20 (VISN-20) Data Warehouse²⁷. The VISN-20 Data Warehouse extracts data from the clinical records of regional VA facilities and two national VA databases.

Demographic, Diagnostic, and Pharmacy Data

Demographic data including age, sex, marital status, ethnicity, and VA service connection were extracted from the VISN-20 Data Warehouse. Inpatient and outpatient diagnoses were derived from International Classification of Diseases, Clinical Modification–9th Revision (ICD-9-CM) codes. If a diagnostic code for a disorder was documented by a provider within 12 months prior to the index date, the patient was coded as having the disorder. We collected information regarding pain, psychiatric, and substance use diagnoses. Pharmacy data were reviewed to characterize opioid prescriptions for twelve months beginning at the 2008 index date. Opioid prescription dosages were converted into morphine equivalent dosages²⁸. Equianalgesic dose ratios for conversion of methadone to morphine are variable depending on the dose of methadone or morphine²⁹, and therefore in this study we also reported methadone equivalents. Receipt of COT was defined as receiving prescriptions for opioids for 90 consecutive days.

Manual Chart Review

Medical record notes were systematically reviewed for 12 months after the initiation of methadone or morphine SR. ECG results were collected one year prior to opioid initiation and one year post opioid initiation. Clinically significant ECGs (>450 ms and >500ms) were noted; a single cutoff was used for both men and women³⁰. Both QTc intervals (>450 ms and >500ms) have been previously defined as a categorical thresholds for non-gender specific absolute QTc intervals and used as criteria in other studies^{31,32}. Prescribed methadone or morphine SR that was discontinued was recorded. **Information on medication-related side effects and reasons for stopping either long-acting opioid were also documented.**

For patients who had prolonged QTc intervals, we documented test results for liver function and electrolytes, as these may prolong QTc intervals. Liver function tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. Electrolyte tests included magnesium, calcium, and potassium. If any of the three electrolyte or three liver function tests were abnormal, as defined in the Veterans Affairs Computerized Patient Record System (CPRS), the patient's liver function and electrolyte tests were recorded as abnormal.

All medical records in CPRS were reviewed by two trained researchers, to document laboratory test results and reasons for opioid treatment discontinuation. Initially, the two raters independently coded medical records from the same 20 patients. The two raters reviewed and discussed any discrepancies. Once the agreement for reviewing medical records was higher than 80% on all variables, the raters each coded charts separately. In order to prevent drift and ensure high inter-rater reliability, coders switched between reviewing charts independently and in collaboration. Of the 182 records, 42 (23%) were jointly reviewed, and inter-rater agreement exceeded 80% on all clinical variables.

Statistical Analyses

Demographic and diagnostic data were analyzed using chi-square or Fisher's exact tests for categorical variables and t-tests for continuous variables. Patients prescribed methadone or morphine SR were compared for the described clinical variables.

Results

In 2008, there were 92 new initiations of methadone to treat moderate to severe chronic pain and 90 new initiations of morphine SR for moderate to severe chronic pain, within this VA medical center. Table 1 compares differences in demographic characteristics between chronic pain patients initially prescribed methadone and those prescribed morphine SR at the time of the index date. There were no significant demographic differences between the two groups (all p -values > 0.05). The majority of the sample was male (90%), white (67%), and the average age was 55 (SD=12) years. Approximately half of the patients were married (51%) and the majority had a VA service-connected disability (65%). Table 2 reports clinical variables among patients prescribed methadone compared to patients prescribed morphine SR. There were no differences between the proportions of patients prescribed methadone with documented pain diagnoses compared to patients prescribed morphine SR. However, there were differences between groups in the rates of major depressive disorder (63% versus 44%, $p=0.012$) and panic disorder (1% versus 9%, $p=0.015$) in patients prescribed methadone and morphine SR, respectively.

Of the 92 patients with new initiations of methadone, the average duration of methadone prescription was 5.6 (SD=7.1) months compared to 7.2 (SD=8.1) months for patients prescribed morphine SR ($t(180)=5.716$, $p=0.176$). There was no difference in the proportions of patients who were prescribed chronic opioid therapy (defined as receiving medication for 90 or more consecutive days) (46% versus 51%; $p=0.461$). Patients who were initially prescribed methadone did not significantly differ on the average daily opioid dose in morphine equivalent (61.5 mg, SD=103) compared to patients prescribed morphine SR (47.2 mg, SD=40) ($p=0.220$). Patients who were initially prescribed methadone averaged 29.3 mg per day (SD=51.3).

Of patients who were prescribed methadone, 53% received a baseline ECG in the year prior to the initiation of methadone compared to 54% of patients prescribed morphine SR ($p=0.873$) (Table 3). Of the patients who received baseline ECG testing, the mean QTc interval of the baseline ECG did not differ between patients prescribed methadone (435 ms) compared to patients prescribed morphine SR (441 ms) ($p=0.263$). Following opioid administration, 37% of patients prescribed methadone (mean QTc=423 ms) received an ECG compared to 40% of patients prescribed morphine SR (mean QTc=437 ms) ($p=0.673$ and $p=0.579$, respectively). Of the patients who had an ECG, there was no difference between the two groups in rates of QTc prolongation. Ten patients prescribed methadone had a prolonged QTc interval >450 ms but <500 ms and 4 patients had QTc intervals >500 ms. As a comparison, 15 patients prescribed morphine SR had an ECG with a QTc interval >450 ms but <500 ms and 3 patients had an interval >500 ms.

Additional analyses were conducted just with the subset of patients who were prescribed COT (defined as receiving prescriptions for opioids daily for 90 or more consecutive days). Of the subset of patients who received COT, 50% of patients prescribed methadone received a baseline ECG compared to 52% of patients that were prescribed morphine ($p = 0.839$), and mean ECG intervals were 436 ms and 446 ms, respectively ($p = 0.251$) (See Table 3). Following opioid initiation, 36% of COT patients prescribed methadone (mean QTc=455 ms) and 35% of COT patients prescribed morphine SR (mean QTc=446 ms) had an ECG performed within 12 months ($p = 0.927$ and $p = 0.636$, respectively). Of the COT patients who had an ECG, there was no statistically significant difference between the two groups in rates of QTc prolongation. Six of 15 COT patients prescribed methadone had a prolonged QTc interval >450 ms but <500 ms and 2 patients had QTc intervals >500 ms. As a comparison, 7 of the 16 COT patients prescribed morphine SR had an ECG with a QTc interval >450 ms <500 ms and 1 patient had an interval >500 ms.

Of patients who were prescribed COT and who had QTc prolongation (>450 ms), 25% (2 of 8) of patients prescribed methadone had a concurrent elevated liver function test. Conversely, 50% of the eight patients prescribed morphine SR who had QTc prolongation had a concurrent elevated liver function test ($p = 0.302$). Elevated bilirubin levels were not detected in either group. Patients with QTc prolongation had decreased electrolyte levels when prescribed methadone (37.5%) or morphine SR (50%) ($p = 0.614$). Patients prescribed methadone had hypokalemia ($n = 1$), hypocalcemia ($n = 1$), and one patient had both hypomagnesemia and hypokalemia in addition to increased QTc prolongation. Hypocalcemia ($n = 1$) and hypokalemia ($n = 3$) were detected in patients prescribed morphine SR with QTc prolongation.

The majority of patients prescribed methadone (76%) or morphine SR (68%) stopped taking the opioid for several reasons, including treatment-related side effects, limited pain relief, patient request, non-compliance, or unknown (Figure 1). Over half of patients who discontinued methadone (54.5%) or morphine SR (57%) were started on another opioid. Patients who were prescribed methadone (26%) and morphine SR (34%) reported adverse side effects. As documented in the medical record, adverse side effects included changes in cognition (memory loss, decreased activity, dizziness, drowsiness, fatigue, headaches, and insomnia), mental health (aggressiveness, decreased sexual function, depression, drug seeking behavior, fear, irritability, panic attacks, and social stigma), gastrointestinal (constipation, diarrhea, nausea, vomiting, and stomach discomfort, weight gain/loss), and cardiopulmonary effects (difficulty breathing, high blood pressure, shortness of breath, prolonged QTc interval, flushing, and itching) following initiation of either opioid. More patients who were prescribed methadone reported inadequate pain relief as a reason for stopping the medication, as compared with patients prescribed morphine SR (25% versus 10%; $\chi^2 = 13.216$, $p = 0.040$). Non-adherence with medication regimen was reported for 9% of patients prescribed methadone, compared to 4% of patients prescribed morphine SR.

Discussion

A common treatment recommendation is to conduct ECG testing for patients prescribed methadone to evaluate for QTc prolongation ⁶. In this study, which included all patients with

moderate to severe chronic pain from a single hospital in 2008 who were newly prescribed methadone, we found that less than half of patients received an ECG prior to beginning treatment with methadone. We also examined new initiations of morphine SR in order to provide context on the frequency of opioid management techniques and treatment-related side effects. The frequency of ECG testing did not differ between patients prescribed methadone or morphine SR. Among the subset of patients who received COT, the rate of developing of QTc prolongation did not differ between patients prescribed methadone or morphine SR; 19% of patients prescribed methadone and 17% of patients prescribed morphine SR developed QTc prolongation. The majority of patients prescribed methadone or morphine SR discontinued their opioid treatment regimens for reasons including limited pain relief and adverse side effects.

There is limited empirical information available about the care patients with chronic pain receive while prescribed methadone. Though treatment guidelines remain inconsistent, increased awareness of potential cardiac events as well as additional factors such as potential medication interactions, should be incorporated into methadone prescribing practices. In a recent report, the dose of methadone and the use of stimulants were associated with QTc prolongation in patients on methadone maintenance for opiate dependence, though there were no known cases of torsade de pointes³⁰. In our study of the patients who received follow-up ECG testing, 4% of patients who were prescribed methadone and 3% patient prescribed morphine SR had very high risk QTc prolongation (>500 ms). These results indicate that there was a limited proportion of clinically significant QTc prolongation observed in our patient population. However, the number of ECGs administered to patients was limited, and the rates of identified QTc prolongation may have been higher or lower, had all patients received follow-up ECG testing.

Our study results also suggest that low-dose methadone is not associated with significant QTc prolongation. The average daily dose of methadone was 29 mg (SD=51.3) for COT patients prescribed methadone in this study. Other recent studies reported no significant association between QTc prolongation and opioid dose among patients receiving daily doses of methadone below 100 mg per day^{33,29}. In contrast, there may be a significant association between prolonged QTc intervals and high methadone doses^{32,34,35}. However, careful monitoring of cardiac events in patients prescribed methadone, regardless of dose, is necessary to prevent mortality.

In this study, the most common reasons for discontinuation of methadone were inadequate analgesia (25%) and treatment-related side effects (26%). The rate of medication discontinuation and reasons for stopping treatment did not significantly differ from patients who were prescribed morphine SR. Of the patients who discontinued methadone, 54.5% were started on another opioid compared to 57% of patients who discontinued morphine SR. In a systematic review on the safety and efficacy of long term opioid therapy for pain, the highest rate of discontinuation of opioid regimen due to inadequate pain relief was observed in long-term studies of oral opioids compared to intrathecal and transdermal administration, respectively³⁶.

Several limitations should be considered when interpreting the results of our study. This was a retrospective study using data that were obtained from the electronic medical record. Participants were predominantly male, white veterans receiving healthcare at one VA Medical Center located in the Pacific Northwest portion of the U.S.; generalizability to other groups is therefore limited. Because prescription medication information was obtained from administrative data, patient adherence to prescribed medications cannot be confirmed. Non-opioid adjunct pain medications were not included in the analyses and could impact side effects attributed to opioids in this study. Further, patients may have received care elsewhere, which we were unable to document. There were differences in rates of some psychiatric diagnoses between the two groups, which could impact opioid-related outcomes, such as discontinuation and pain relief. Further, clinical diagnostic data were extracted from the medical record and we could not determine if substance use disorders (where diagnosed) were active, which could affect study results. The side effects we found are dependent on the thoroughness and accuracy of clinical notes documented in the medical record. We also specifically examined opioid prescribing practices for the treatment of pain, and the results may not be generalizable to other patient populations, including patients enrolled in methadone maintenance programs.

Guidelines recommend the careful monitoring of cardiac events for patients prescribed methadone. In this study, 53% of patients with moderate to severe chronic pain prescribed methadone received an ECG prior to initiating methadone. Additionally, of the patients that received methadone long-term, 36% received follow-up ECG testing. The cardiac monitoring rates for patients prescribed methadone did not differ from patients prescribed morphine SR, a medication that has no known cardiac adverse effects. More explicit clinical guidelines regarding treatment with methadone are needed to raise provider awareness of the potential harms of methadone, as well as additional system support to aid providers in delivery of care.

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Reported Reasons for Opioid Discontinuation

Figure 1.

Patients prescribed methadone (24%) or morphine SR (32%) continued chronic opioid therapy, but a majority of patients in both groups did not. Patients stopped taking either long-acting opioids for several reasons, including prevalence of side effects, limited pain relief, non-compliance, as requested by the patient, not self-administered, or for reasons not reported. ($\chi^2=13.216$, $p=0.040$).

Table 1

Demographic Characteristics of Patients Prescribed Methadone or Morphine SR.

Initial Opioid	Methadone (n=92)	Morphine SR (n=90)	Test (df)	p-value
Age	54.8 (11.5)	55.1 (12.5)	$t(179) = -0.154$	0.878
Male Gender	85 (92.4%)	79 (87.8%)	$\chi^2(1) = 1.087$	0.297
Marital Status			$\chi^2(3) = 0.214$	0.975
Single/Never Married	12 (13.0%)	12 (13.3%)		
Married	48 (52.2%)	44 (48.9%)		
Separated/Divorced/Widowed	31 (33.7%)	33 (36.7%)		
Unknown	1 (1.1%)	1 (1.1%)		
Race			$\chi^2(3) = 0.263$	0.967
Caucasian	61 (66.3%)	62 (68.9%)		
Black	3 (3.3%)	2 (2.2%)		
Other	1 (1.1%)	1 (1.1%)		
Unknown or Declined to answer	27 (29.3%)	25 (27.8%)		
VA Service-Connected Disability	64 (69.6%)	54 (60.0%)	$\chi^2(1) = 1.826$	0.177

Table 2

Clinical characteristics of patients prescribed methadone and morphine SR.

Opioid Prescribed	Methadone (n=92)	Morphine SR (n=90)	Test (df)	p-value
Pain Diagnoses				
Fibromyalgia *	7 (7.6%)	11 (12.2%)	$\chi^2 (1) = 1.087$	0.297
Low Back Pain *	64 (69.6%)	54 (60.0%)	$\chi^2 (1) = 1.826$	0.177
Neck or Joint Pain *	70 (76.1%)	72 (80.0%)	$\chi^2 (1) = 0.406$	0.524
Migraine Headache *	10 (10.9%)	12 (13.3%)	$\chi^2 (1) = 0.260$	0.610
Rheumatism/ Arthritis *	44 (47.8%)	55 (61.1%)	$\chi^2 (1) = 3.237$	0.072
Psychiatric Diagnoses				
MDD	58 (63.0%)	40 (44.4%)	$\chi^2 (1) = 6.333$	0.012
Dysthymic Disorder	13 (14.1%)	12 (13.3%)	$\chi^2 (1) = 0.024$	0.876
Panic Disorder	1 (1.1%)	8 (8.9%)	$\chi^2 (1) = 5.891$	0.015
PTSD	38 (41.3%)	26 (28.9%)	$\chi^2 (1) = 3.076$	0.079
SUD	28 (30.4%)	24 (26.7%)	$\chi^2 (1) = 0.317$	0.574
Nicotine Use Disorder	38 (41.3%)	30 (33.3%)	$\chi^2 (1) = 1.235$	0.266

Note. MDD: major depressive disorder; PTSD: post traumatic stress disorder; SUD: substance use disorder.

* ICD-9-CM codes include fibromyalgia 729.1-729.19, Chronic low back pain 722-722.99; 724-724.99; Migraine headache 784.0; 346.9; Chronic neck or joint pain 716-719.99; 723-723.99; 729-729.99; Rheumatism or Arthritis 712-712.99; 714-716.99; 720-720.99; 729-729.99.

Table 3

ECG characteristics of patients prescribed methadone and morphine SR.

Initial Opioid	Methadone	Morphine SR		
All patients	(n=92)	(n=90)	Test (df)	p-value
Received baseline ECG	49 (53.3%)	49 (54.4%)	$\chi^2 (1) = 0.026$	0.873
Mean baseline ECG QTc interval	435 ms (28.6)	441 ms (28.4)	$t (96) = -1.127$	0.263
Received ECG following initiation	34 (37%)	36 (40%)	$\chi^2 (1) = 0.178$	0.673
Mean QTc interval following initiation	423 ms (118)	437 ms (82.4)	$t (68) = -0.572$	0.569
QTc prolongation >450<500 ms	10 (10.9%)	15 (16.7%)	$\chi^2 (1) = 1.290$	0.256
QTc prolongation >500 ms	4 (4.3%)	3 (3.3%)	$\chi^2 (1) = 0.127$	0.722
COT patients	(n=42)	(n=46)		
Received baseline ECG	21 (50%)	24 (52.2%)	$\chi^2 (1) = 0.042$	0.839
Mean baseline ECG QTc interval	436 ms (25.5)	446 ms (33.6)	$t (43) = -1.164$	0.251
Received ECG following initiation	15 (35.7%)	16 (34.8%)	$\chi^2 (1) = 0.008$	0.927
Mean ECG QTc interval following initiation	455 ms (58.6)	446 ms (38.0)	$t (29) = 0.479$	0.636
QTc prolongation >450<500 ms	6 (14.3%)	7 (15.2%)	$\chi^2 (1) = 0.015$	0.902
QTc prolongation >500 ms	2 (4.8%)	1 (2.2%)	$\chi^2 (1) = 0.447$	0.504

Note. Column values indicate number (%) for categorical variables or mean (standard deviation) for continuous variables. "COT patients" refers to the subset of patients who were prescribed opioids daily for 90 or more consecutive days.