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Inpatient Initiated Methadone for Chronic Non-Cancer Pain at the University of New Mexico

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ABSTRACT

Introduction

Inpatient initiation of methadone is ideal due to associated risks of cardiac arrhythmias and a high incidence of overdose. Evidence based guidelines have been developed for initiation of methadone for chronic noncancer pain (CNCP). The purpose of this study is to describe the frequency of pretreatment testing and high-risk prescribing in patients initiated on methadone at the University of New Mexico Hospital (UNMH).

Methods

A retrospective observational study was conducted using electronic health record data from UNMH, a southwest tertiary care center. We collected data on frequency of (1) pretreatment testing and (2) discharges with concomitant high-risk prescriptions. We then compared the frequency of these outcomes among those who received a consultation with the acute/chronic pain or palliative medicine services to those who did not.

Results

Seventy-two individuals had electrocardiogram testing performed in the 7 days prior to methadone initiation. Seventy-nine individuals had potassium testing performed 24 hours prior to methadone initiation. We noted a minority of individuals had magnesium tested within the prior 24 hours (n = 58), AST tested within the prior 24 hours (n = 35), ALT tested within the prior 24 hours (n =35), and total bilirubin tested within the prior 24 hours (n = 35). Patients were discharged on methadone with high-risk prescriptions including benzodiazepines (n = 15) and other drugs that are known to prolong the QTc interval (n = 18) in a minority of circumstances. Patients who received consultation were more likely to be older and have a longer length of stay. However, no differences in pretreatment testing or concomitant high-risk prescribing were detected between groups with consultation and those who did not, even when controlling for age and length of stay.

Conclusion

Our study describes the paucity of pretreatment electrolyte and electrocardiogram testing in our population. We also identified a number of instances of concomitant prescriptions with high risk medications. There were no differences for patients who received pain or palliative medicine consultation. Our study underscores the continued need for guidelines to assist clinicians on safe methadone prescribing for patients with CNCP.

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CHAPTER 1

INTRODUCTION AND BACKGROUND

Chronic non-cancer pain affects 100 million Americans per year (4–7). As the epidemic of opiate-related morbidity and mortality ravages America, patients with CNCP struggle with limited management options. Over the past 2 decades, methadone, a long-acting opioid therapy conventionally used to treat substance use disorder, has been adopted for treating CNCP (8). Increasingly, CNCP patients with a history of opioid use have been transitioned to methadone for management of CNCP, as methadone is a viable alternative to frequent doses of short-acting opiates (8). In addition, it is ideal to initiate methadone for CNCP under inpatient observation due to the associated risks of cardiac arrhythmias and overdose (1–3). Current guidelines indicate that before initiating methadone, measurements of electrolyte levels, liver function and cardiac electrical function should be performed to assess patients risk (4,9–11). Patients are then discharged home with a pain-control plan that consists of methadone and other short-acting opioids. Screening for pre-disposing conditions has the potential to reduce morbidity and mortality associated with inpatient methadone initiation. *The American Pain Society* and *The Heart and Rhythm Society* have collaborated to develop guidelines recommending cardiac risk assessment including laboratory and electrocardiogram testing prior to initiating methadone. (9) Additionally, the compounded risk of concomitant prescription of methadone with benzodiazepines and other QTc-prolonging drugs has significant potential to be fatal or disabling.

Chronic Pain

Pain is a common and significant condition that puts tremendous burden not only on individual patients, but also on the healthcare system (12). Pain is the most common complaint for which patients seek medical attention (13,14), and when it lasts longer than three months, it is defined as chronic (15). We distinguished noncancer related pain from cancer pain in our study because each diagnosis has different treatment goals. The patient with noncancer pain must be able to leave the hospital and maintain a long-term outpatient therapy plan. The prevalence of CNCP is expected to rise as the US population ages. Pain is also the most expensive condition seen in the primary care setting totaling over 200 million dollars in total costs in the year 2016 (12). CNCP can lead to a cascade of stressors that include unemployment, social isolation, withdrawal from family roles and inability to fully participate in activities of daily living and hobbies (14).

Issues with Opioids

To address the problem of CNCP, opioid therapy gained popularity over the last two decades, but came with significant morbidity and mortality as deaths attributed to opioids have escalated at alarming rates (16). According to the Centers for Disease Control and Prevention March 17, 2017 MMWR Weekly Report, Methadone deaths peaked in 2007, then declined 39% by 2014 (17). This decline was largely attributed to the Food and Drug Administration's Public Health Advisory issued in December 2006. This advisory warned prescribers about possible adverse side effects including; respiratory depression, cardiac arrhythmias, unintentional overdoses, and drug-drug interactions. Despite this decline, methadone was involved in 23% of prescription opioid related deaths in 2014 (6). Overdose deaths from methadone have increased in parallel with increased rates of methadone prescribing for CNCP (18). Methadone is tightly regulated when used for treatment of substance use disorder, which includes an extra set of special standards and regulations. Because of this, it is widely viewed that the majority of recent deaths from methadone likely arise from its use to treat CNCP (17). A recent observational study showed risks of methadone vary widely by practice settings and with differing monitoring protocols (19). Further research is required to determine how CNCP patients can benefit from methadone's therapeutic effects without the increased risk of side effects, overdose and death.

Pharmacology

Methadone has been a well-studied and successful pharmacotherapy for the treatment of opiate-addicted patients (20,21). Because of its properties the drug has been successfully integrated as a strategy to manage CNCP (8,9). The drug has many potential benefits including low cost, ability to treat patients with end stage renal disease and patients unresponsive to other opioids. It also is ideal for patients with morphine allergy or other opioid intolerance.

Methadone is a potent synthetic drug that acts as an agonist at the mu-opioid receptor and the N-methyl-D-aspartate (NMDA) receptor. Methadone is unique among the opioids in its abilities to act on two different receptors. Methadone exists in two isomer forms, the L and D isomers. The L isomer acts primarily at the mu opioid receptor while the D isomer acts at the NMDA receptor, a mediator of modifying neuropathic pain. Methadone acts as a weak noncompetitive NMDA receptor antagonist (22). Because of its mechanism at NMDA and mu opioid receptors, methadone provides benefits for those with neuropathic and nociceptive pain (23). This mechanism allows methadone to treat individuals with pain that is not responsive to other opioid therapies (24).

Methadone is slowly metabolized and is highly soluble in fat tissue, making the drug's effects long lasting (6). Methadone is metabolized in the liver primarily by the cytochrome P isoenzymes CYP3A4 and CYP2B6 (25,26). The time of onset of analgesia for methadone is approximated at 12 hours, however the plasma half-life can be up to 72 hours (27). The

pharmacokinetic properties of methadone, including its bioavailability and half-life elimination, make the drug highly variable on an inter-individual basis. Approximately five to six half-lives are necessary for the drug to reach stable concentrations in the blood. The duration of time in which methadone reaches a stable concentration in the blood can vary from days to weeks (28). During the time methadone is increasing in blood levels the patient is considered to be high risk from unintentional overdose and side effects. Close monitoring in the inpatient environment is highly desirable as a means to minimize unintentional overdose and side effects of the drug(29).

Regulation

Under federal law, methadone is tightly regulated for those with a diagnosis of substance use disorder. The drug can be prescribed for this indication in ambulatory patients only by physicians who have specialized licenses and are affiliated with an opioid treatment program. However, when prescribing the drug for CNCP, different regulations apply. Any physician with a standard Drug Enforcement Administration (DEA) license can prescribe methadone for hospitalized patients for conditions unrelated to substance use disorder, such as CNCP (30).

Concerns

Because of its long and individualized half-life, methadone toxicity is a major cause of concern. Toxicity is attributed to several factors, including insufficient pretreatment laboratory testing and inadequate monitoring (31). Methadone is high risk for accumulation in the body during the initial titration and when dosages are adjusted (28). Methadone's action at the NMDA receptor produces non-opioid analgesia which can aid with opioid tolerant patients. This property, however, causes methadone to be more potent than other opioids at the same converted dosages (32). If the initiation dose is high or rapidly increased, patients can experience sedation and respiratory depression. This concern over unexpected potency requires close follow up with cautious monitoring during the initiation of methadone therapy. In 2006 the Food and Drug Administration revised its packaging for methadone. This included warning of addiction, abuse, misuse, respiratory depression, accidental ingestion, QT prolongation, neonatal opioid withdrawal syndrome, CYP450 interactions, and risks of concomitant use with benzodiazepines (33).

For CNCP patients who are hospitalized, methadone can be initiated if a patient requires high frequency and dosage of short-acting opioids. A longer acting analgesic is superior to multiple short acting doses because of its ability to maintain levels of drug within the body and prevent recurrence of pain (34). It is recommended that methadone be prescribed only by those who are trained in its pharmacology and who can employ safe prescribing practices (32). Those who have questions about the drug or who lack experience may wish to seek assistance

from a consultant with such skills before prescribing for CNCP. Acute/chronic pain medicine and palliative medicine services have expert clinicians who are trained to recognize the concerns related to the safe use of methadone. These specialized consulting services can alert general inpatient teams of current practices and guidelines. This will include informing on proper pretreatment testing and dangers of concomitant prescriptions with benzodiazepines and drugs that are known to prolong the QTc on electrocardiogram. At the University of New Mexico, inpatient clinicians in the acute/chronic pain medicine services as well as the palliative medicine service have been trained in the proper use of methadone prescribing.

Electrocardiogram and Laboratory

Methadone is known to prolong the QTc interval on the electrocardiogram. QTc interval prolongation is a highly undesirable side effect that can lead to life threatening cardiac abnormalities including arrhythmias. The clinical practice of obtaining an electrocardiogram prior to methadone initiation varies markedly by practice location. *The American Pain Society* and *The Heart and Rhythm Society* have collaborated to develop guidelines to aid clinicians in safe methadone prescribing (9). An electrocardiogram is the only way to detect asymptomatic QTc interval prolongation. Patients with asymptomatic QTc interval prolongation are at higher risk for cardiac arrhythmias (torsades de pointes) than those without asymptomatic QTc interval prolongation. These guidelines also suggest that clinicians assess patient risk for cardiac arrhythmia including checking for electrolyte abnormalities prior to initiation of methadone.

In vitro studies have demonstrated that methadone blocks the potassium channels in the myocardium. In addition, hypokalemia and hypomagnesemia are risk factors that contribute to QTc prolongation and potentiate life threatening cardiac arrhythmia in those initiated on methadone. Measurement of serum electrolytes including potassium and magnesium levels is recommended prior to the initiation of methadone (9,35). It is recommended to evaluate the liver function before the initiation of methadone (9,26,27). Since methadone is metabolized by cytochrome P isoenzymes, drugs that function as inhibitors of the CYP enzymes may increase methadone levels requiring patient doses of methadone to be lowered to compensate for the slower metabolism. There are several inhibitors of the CYP3A such as erythromycin, ciprofloxacin and fluconazole that elevated levels of methadone in the blood. Interactions with medications that interact with cytochrome P isoenzymes should be carefully analyzed when methadone therapy is initiated or adjusted.

Concomitant Prescriptions and Overdose

Several drug classes have higher risk when prescribed with methadone. Benzodiazepines are one such class that act at the central nervous system and have antianxiety, sedative, and muscle relaxing effects (36). Taking opioids with benzodiazepines can be dangerous because of the potential synergistic effects on central nervous system depression. Benzodiazepines also act to enhance other opioid medication actions at the central nervous system. When combined with other opioids such as methadone, benzodiazepines can increase the risk of respiratory depression and sedation increases significantly (37). Benzodiazepines are commonly prescribed

for the treatment of anxiety and insomnia. They are often associated with physical dependence and addiction. Patients on methadone maintenance therapy for opioid use disorder have been shown to have high rates of benzodiazepines abuse (36–38). Approximately 18% of patients receiving methadone therapy for opioid treatment abuse are also dependent on benzodiazepines. In a study of managed care patients who had an opioid related overdose or death, benzodiazepines were present in 31% of identified cases (39). Patients with a history of combining benzodiazepines and opioids have also demonstrated higher rates of hospitalization compared to benzodiazepines alone (40). The American Society of Interventional Pain Physicians recommends evaluating relative and absolute contraindications of prescribing benzodiazepines with any opioid and avoiding this practice in most circumstances (5). These include allergy to opioids, actively selling or trafficking prescriptions, and concomitant high-risk prescription capable of generating life limiting drug interactions (38).

New Mexico

Pretreatment testing and concomitant high-risk prescriptions for patients initiated on methadone have not been well studied in the state of New Mexico. Although, methadone death rates in New Mexico have declined the proportion that have high risk prescriptions as well as the proportion that are linked to pain diagnoses have increased (41). We wish to evaluate pretreatment testing and concomitant high-risk prescriptions at the University of New Mexico because it provides secondary and tertiary care for the state and serves a high-risk population including many with chronic non-cancer pain.

Purpose

The purpose of this study is to describe the frequency of pretreatment testing and concomitant high-risk prescriptions for patients initiated on methadone for CNCP at the University of New Mexico. We believe that describing pretreatment testing and high-risk concomitant prescriptions could compel system changes at the University of New Mexico for patients initiated on high risk medications such as methadone. We also compared these outcomes among those who received consultation with the acute/chronic pain or palliative medicine services. This is of interest to the authors because we believe experts with advanced training in prescription of methadone can make methadone initiation safer. We have three research questions:

1. *What percentage of CNCP patients discharged with new methadone prescriptions received electrocardiogram, electrolyte, and liver function screening during their stay in the hospital?*
2. *What percentage of CNCP patients discharged with new methadone prescription received a concomitant prescription for a benzodiazepine or a drug that is known to prolong the QTc interval on electrocardiogram?*
3. *Does pain medicine consultation during the hospital stay have an association with rates of electrocardiogram, laboratory or concomitant prescription of benzodiazepines or drugs that are known to prolong the QTc?*

Hypothesis:

1. The majority of CNCP patients discharged with methadone will have had laboratory and electrocardiogram screening.
2. A minority of patients leave the hospital with a concomitant prescription of a QTc prolonging medication or benzodiazepine.
3. Patients who receive an acute/chronic pain or palliative medicine consultation during the hospitalization will show higher rates of appropriate pretreatment screening and lower rates of concomitant QTc-prolonging prescriptions and benzodiazepines upon discharge than those who do not receive a pain medicine consultation.

CHAPTER 2

METHODS

Data Collection

Data were obtained by querying the clinical database that supports the Cerner electronic health record at the University of New Mexico (UNM) using the *PowerInsite* tool. We identified all patients admitted to UNMH who were initiated on methadone and discharged with a methadone prescription between January 1, 2007 and December 31, 2017. Patients were then included in the study if they met the following criteria; aged 18 years of age or older, admitted to UNMH during the last 10 years, and initiated on methadone during an inpatient encounter and subsequently discharged with an outpatient prescription of methadone. Patients were excluded if they had ICD-9 diagnosis listed during their encounter of cancer or a diagnosis listed during their encounter of opioid use disorder. Patients were also excluded if they were discharged to the criminal justice system (e.g. jail or prison). We also identified patients who received consultation with either the acute/chronic pain medicine service or the palliative medicine service. Acute or chronic pain medicine service consultation and palliative medicine consultation was determined by the presence of a consultation note within the chart.

The following demographic information was extracted; age, sex, length of stay, and payer status. Pretreatment laboratory testing was obtained in the 24 hours prior to the initiation of methadone. This included potassium, magnesium, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin serum concentrations. Twenty-four hours was used as a cutoff value because previous studies have stated this time frame to be the

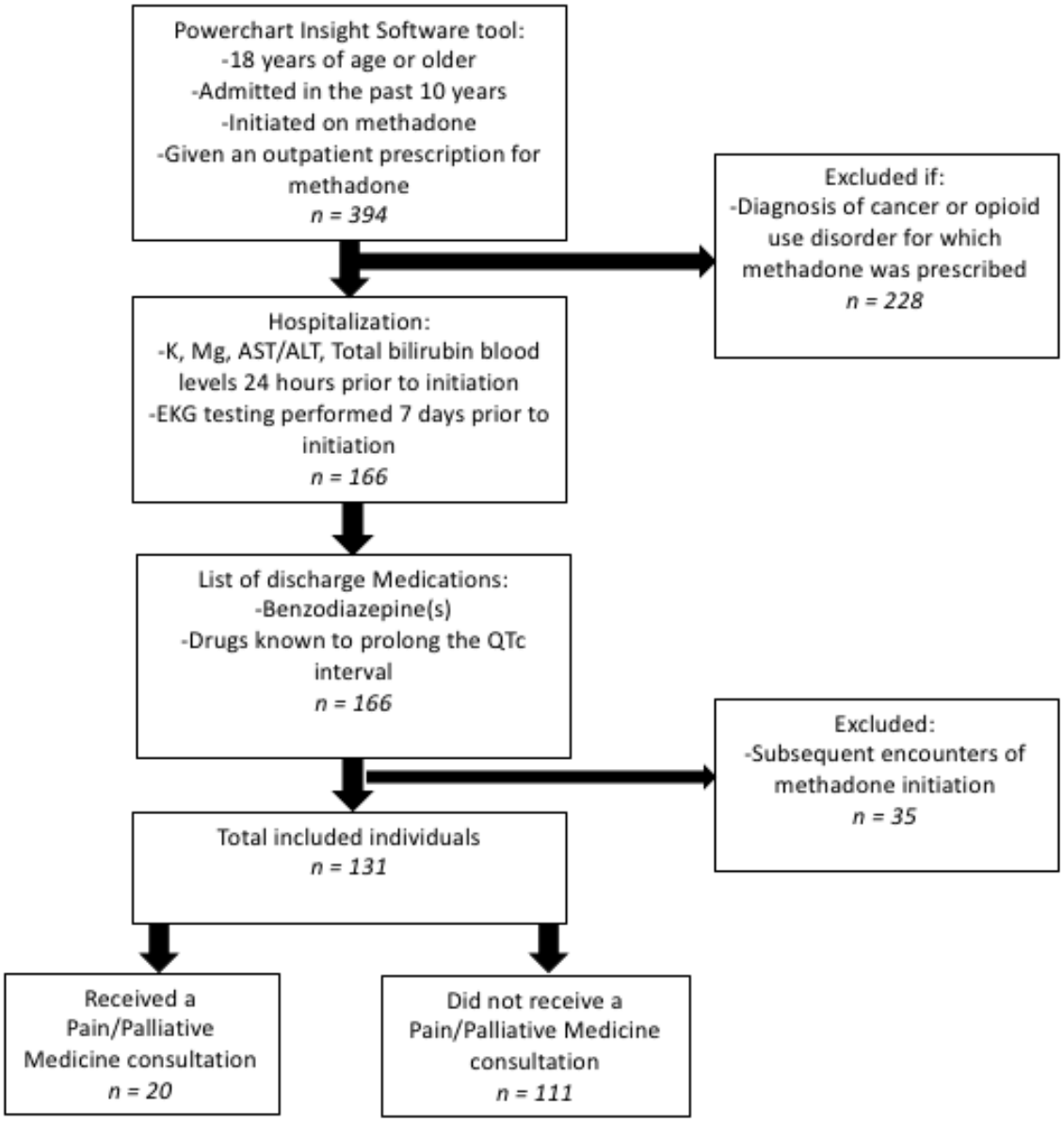
conservative for correction of laboratory abnormalities such as hypokalemia or hypomagnesemia (31). Electrocardiogram orders were obtained in the preceding 7 days of the initiation of methadone. We tabulated the number of prescriptions at hospital discharge of benzodiazepines and drugs that are known to prolong the QT interval on electrocardiogram. Because the number of medications that may prolong the QTc interval is vast, we used the list of drugs that are known to prolong the QTc interval on electrocardiogram from the CredibleMeds organization. This federally funded university-based organization is maintained by the Arizona Center for Education and Research on Therapeutics (AZCERT) under contract from the Food and Drug Administration's Safe Use Initiative. CredibleMeds uses a rigorous and scientific process for the development of its classification systems *(42).* Our methodology is summarized in Figure 1. This study was approved by the University of New Mexico Institutional Review Board and Clinical Data Use Committee.

Analysis

Data were summarized using counts and proportions. We then performed the following analyses to test our hypothesis. First a bivariate analysis was performed testing the differences in frequency of pretreatment testing and concomitant high-risk prescriptions by consultation status using Fisher Exact Tests. We utilized Wilcoxon rank sum tests to assess patient age and length of stay differences by consultation status. These variables were skewed and not normally distributed. We also performed logistic regression to estimate the association between pretreatment testing and concomitant high-risk prescriptions with and without adjustment for

age and length of stay. We reported our results as odds ratios and 95% Confidence intervals (alpha = 0.05). Analyses were conducted using SAS version 9.4 software.

Figure 1: Criteria for which study subjects were selected, excluded and grouped.



CHAPTER 3

RESULTS

The initial query of the *PowerInsite* software tool identified 394 patient encounters where the individual was 18 years of age or older, received methadone during an inpatient admission and was discharged with a prescription for methadone from the time period January 2007 to December 2017. After excluding encounters with ICD-9 diagnoses related to cancer or opioid use disorder (n = 228), 166 individual encounters remained. Thirty-five individuals who met initial inclusion criteria had multiple encounters. Because we wished to evaluate cases of first methadone initiation we excluded subsequent encounters where patient had another methadone prescription. The remaining 131 individuals were included in the analysis. Demographic data are summarized in Table 1. Our cohort was middle aged on average (45.6 years, $\pm$ 16.9 years SD), roughly equal among sexes (n =70, 53.4%), and had an average length of stay of approximately 10 days ($\pm$ 18.1 days SD). Medicare (n = 26) and Medicaid (n = 49) represented the majority (57.2%) of the total payer status. No patients who were reported as Self pay received a pain or palliative medicine consultation.

Frequency of Pretreatment Testing

Consultation with the acute/chronic pain or palliative medicine services was obtained in 20 cases (15.3%). Potassium serum concentration was obtained 24 hours prior to methadone initiation in 79 cases (60.3%), while magnesium serum concentration was obtained 24 hours

prior to initiation in 58 cases (44.3%). Liver function studies, including AST, ALT and total bilirubin were obtained in the prior 24 hours in 35 cases (26.7%). Electrocardiogram testing was performed seven days prior to initiation in 72 cases (55.0%). These results are visualized in Table 2.

Frequency of Discharges with Concomitant High-risk Prescriptions

Benzodiazepines were prescribed at hospital discharge in 15 cases (11.5%). Drugs that were known to prolong the QT interval were prescribed at discharge occurred in 18 cases (13.7%). These results are visualized in Table 2.

Relationship between Consultation with Acute/Chronic Pain or Palliative Medicine Services and Outcomes

Consultation with the acute/chronic pain or palliative medicine services was obtained in 20 cases (15.2%). Individuals with a pain or palliative medicine consult had a mean length of stay of 16.4 days (± 21 days SD). Those who did not receive a consult had a mean length of stay of 9.2 days (± 17.4 days). Individuals with a pain or palliative medicine consult had a mean age of 55.9 years (± 16.9 years SD). Those who did not receive a consult had a mean age of 43.7 years (± 16.6 years SD). These results are visualized in Table 3. The distribution of age and length of stay are visualized in Figures 2 and 3. After performing Wilcoxon rank sum tests we

found that individuals who received an acute/chronic pain or palliative medicine consult were significantly more likely to have a longer length of stay and were more likely to be older.

Table 1. Descriptive data showing demographic data by acute/chronic pain or palliative medicine consultation.

	Received Consult	**Did Not Receive Consult**	**All**
Demographic	N (%)	N (%)	N (%)
Sex			
Female	7 (35.0)	63 (56.8)	70 (53.4)
Male	13 (65.0)	48 (43.2)	61 (46.6)
Payer Status			
Medicare	5 (25.0)	21 (18.9)	26 (19.8)
Medicaid	4 (20.0)	45 (40.5)	49 (37.4)
Self Pay	0 (0.0)	6 (5.4)	6 (4.6)
PPO/HMO	4 (20.0)	10 (9)	14 (10.7)
Other	7 (35.0)	29 (26.1)	36 (27.4)
Total Patients	**20 (15.3)**	**111 (84.7)**	**131 (100)**

Table 2. Descriptive data showing pretreatment laboratory testing, electrocardiogram and concomitant high-risk prescription rates by consultation status.

	Received Consult	**Did Not Receive Consult**	**All**
Outcome Variable	N (%)	N (%)	N (%)
Laboratory testing			
Potassium	12 (60.0)	67 (60.4)	79 (60.3)
Magnesium	9 (45.0)	49 (44.1)	58 (44.3)
AST	4 (20.0)	31 (27.9)	35 (26.0)
ALT	4 (20.0)	31 (27.9)	35 (26.0)
Total bilirubin	4 (20.0)	31 (27.9)	35 (26.0)
Electrocardiogram			
7 Days Prior	12 (60.0)	60 (54.1)	75 (55.0)
Prescriptions			
Benzodiazepine	3 (15.0)	12 (10.8)	15 (11.5)
QTc Prolonging Drug	5 (25.0)	13 (11.7)	18 (13.7

Table 3. Descriptive data showing age and length of stay by acute/chronic pain or palliative medicine consultation. Results of Wilcoxon sum ranked tests shown as p-values.

	Received Consult	Did Not Receive Consult	
Demographic	**Mean (SD)**	**Mean (SD)**	**P-value**
Age in years	55.9 (15.3)	43.7 (16.6)	0.003
Length of Stay in days	16.4 (21.0)	9.2 (17.4)	0.002

Figure 2: Box plot of the distribution of patient age (years) by consultation status. Patients with consultation were significantly more likely to be older.

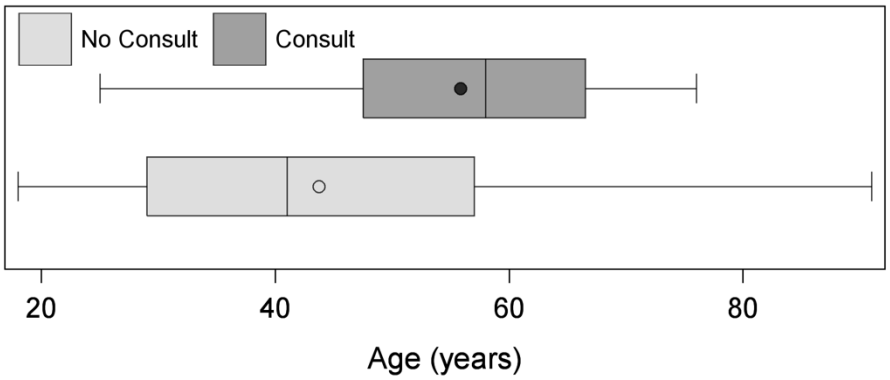
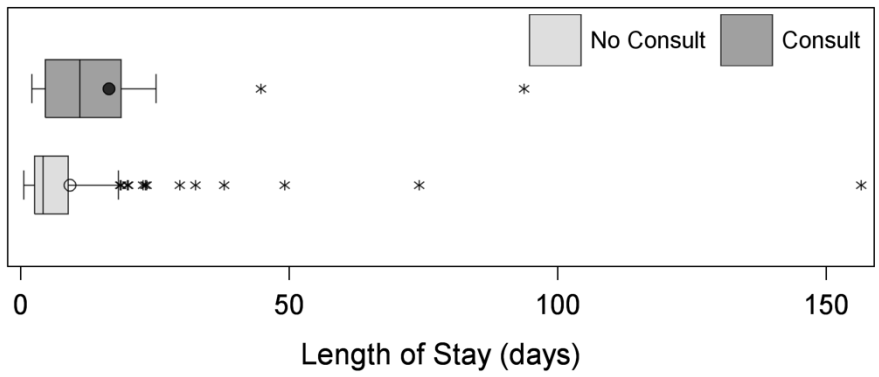


Figure 3: Box plot of the distribution of patient length of stay (days) by consultation status. Patients with consultation were significantly more likely to have a longer length of stay.



After separating those who received acute/chronic pain or palliative medicine consultation and those who did not, odds ratios of pretreatment testing and high-risk prescribing were calculated. No significant differences were found among the two groups with respect to: (1) the number of patients who received potassium serum concentration, magnesium serum concentration, or AST/ALT/total bilirubin serum concentration within 24 hours of initiation of methadone; (2) the number of orders for electrocardiogram testing within a seven-day prior window period; and (3) the number of patients who had prescriptions of benzodiazepines or drugs that are known to prolong the QTc interval at hospital discharge. After logistic regression modeling was performed adjusting for length of stay and age, no significant differences were observed in laboratory pretreatment testing, electrocardiogram pretreatment testing or discharge prescribing between the consult group and those who did not receive a consult. These results are detailed in Table 4.

Table 4. Odds ratios of pretreatment testing and concomitant prescription among patients with acute/chronic pain or palliative medicine consultation compared to patients without consultation. Adjusted odds ratios show multivariable logistic regression analysis controlling for age and length of stay. No significant differences were detected.

Outcome Variable	Odds Ratio	95 % CI	Adjusted Odds Ratios	95 % CI
Laboratory testing				
Potassium	0.98	0.37-2.6	0.47	0.15-1.50
Magnesium	1.03	0.39-2.69	0.51	0.17-1.53
AST	0.64	0.2-2.08	0.43	0.125-1.49
ALT	0.64	0.2-2.08	0.43	0.125-1.49
Total bilirubin	0.64	0.2-2.08	0.43	0.125-1.49
Electrocardiogram				
7 days Prior	1.28	0.48-3.36	0.83	0.29-2.41
Prescriptions				
Benzodiazepine	1.46	0.37-5.7	1.12	0.27-4.60
QTc Prolonging Drug	2.51	0.78-8.06	1.71	0.48-6.17

CHAPTER 4

DISCUSSION

Our study evaluated the frequency of pretreatment testing and concomitant high-risk prescriptions among patients initiated on methadone during admission to the University of New Mexico Hospital. We compared these outcomes with patients who received acute/chronic pain or palliative medicine consultation to those who did not. We aimed to shed light on the prescribing patterns at the University of New Mexico in hopes of improving methadone prescribing safety.

Pretreatment laboratory testing in the 24 hours for magnesium serum concentrations and liver function studies were not performed in the majority of cases, yet potassium serum concentrations were performed 60% of the time. This mixed result likely represents a phenomenon whereby hospitalized patients routinely receive a standardized chemistry panel of electrolytes which includes a potassium serum concentration. This routine nature of this chemistry panel likely does not represent the active thinking by clinicians about the possible dangers of methadone. However, these potassium values are still reviewed by clinicians daily and therefore satisfy this part of the requirement. Electrocardiogram testing was ordered in the seven days prior in roughly half of cases and was consistent with our hypothesis.

We chose to evaluate baseline electrocardiogram rates in the preceding seven days because previous literature indicated this to be the appropriate time to obtain this study. Electrocardiogram testing is also routinely performed in hospitalized patients, and therefore it is difficult to determine the reasoning behind the ordering of the test. We chose the pretreatment testing of potassium and magnesium serum concentrations because they are factors in determining risk of cardiac arrhythmia leading to death. Liver function studies were also chosen because methadone is metabolized by the liver and should be avoided in patients with abnormalities in liver function.

Previous literature has focused on the high-risk of cardiac arrhythmia associated with methadone and ways to avoid this from occurring. In several studies pretreatment testing with electrolytes included potassium and magnesium serum concentrations was included as a component of total cardiac risk, and specifically abnormal values (43,44). Previous literature with electrocardiogram testing has focused on QTc interval lengthening and associated risk of death (45–47). Our study measured the frequency of obtaining an electrocardiogram and did not obtain the measurements of QTc intervals. The rate of pretreatment testing in our study is similar to a previous study evaluating baseline electrocardiogram testing and found 54% of methadone initiations had electrocardiogram testing in the seven days prior to initiation (31). However, the conclusion by the authors was that this was an insufficient level of electrocardiogram testing.

Patients were discharged with concomitant high-risk prescriptions of benzodiazepines in a minority of circumstances. This result is consistent with our hypothesis, yet we believe the rate is still too high because there are few clinical instances that justify a concomitant prescription with a benzodiazepine or QTc interval prolonging drug. Recommendations indicate that clinicians should switch methadone to a different long-acting opioid with less of an effect on the QT interval when using with drugs that prolong the QT interval (4). However, if methadone is used, a lower dose should be utilized with more frequent electrocardiogram monitoring. Also guidelines urge strongly against concomitant prescriptions with any benzodiazepines as the high death rates associated with combining the drugs is very high (18). Creation of an order set that would facilitate collection of recommended screening testing and identifying concomitant prescriptions may be helpful to meet appropriate guidelines and ultimately reduce risk to the patient.

Acute/chronic pain and palliative medicine consultation differences were not noted to be statistically significantly related to any of the outcomes presented. However, we found that patients with consultation were significantly older and have a longer length of stay. As expected, patients who were admitted to the hospital for longer lengths of stay would have more opportunities to receive care from the pain and palliative care teams. Also, older patients with multiple comorbidities would be expected to require more specialized treatment from the pain and palliative care teams.

Because of these differences in length of stay and age we performed logistic regression, where we controlled for these variables and still did not show statistically significant results in pretreatment testing, electrocardiogram, or concomitant high-risk prescriptions. Our sample of individuals receiving consultation was small as only 20 individuals were included. Our study criteria excluded more than half (over 250 individuals) of our initial query. Upon review of excluded individuals, many had ICD-9 codes for substance/opioid use disorder and acute/chronic pain or palliative medicine consultation. This shows that, although our study focuses only on chronic non-cancer pain patients, many patients may have a mixed clinical picture.

We chose to represent the association between variables and outcomes as odds ratios because our outcome was binary (consultation vs no consultation). Odds ratios were also chosen based on their facility in fidelity testing. Odds ratios also frequently appears in literature regarding pretreatment testing and concomitant prescription rates. We chose to perform Wilcoxon rank sum tests because of our small sample size. Also, age and length of stay were not normally distributed variables. We then performed logistic regression to control for length of stay and age to see if a difference in pretreatment and concomitant high-risk prescriptions could then be detected.

Strengths

To our knowledge, this is the first study to examine pretreatment testing and concomitant high-risk prescriptions using a large clinical database at the University of New Mexico. We also included individuals over a ten-year period that spans the course of increasing methadone prescription for chronic, non-cancer pain. The electronic health record system began recording data in 2001 and therefore our study included the vast majority of available records.

Limitations

Our study contains the typical limitations inherit in all retrospective, observational studies. During data collection, over half of our identified population was excluded because of cancer and opioid use disorder diagnosis codes. We also only included data from one academic medical center, making generalizability of the study to other practice settings difficult.

Guidelines created by the *American Pain Society* and *Heart and Rhythm Society* have been updated several times over the past 20 years. These updates included changes in recommendations for baseline electrocardiogram testing and risk stratification based upon the evidence at the time. We did not include risk stratification of patients and only looked at presence or absence of testing. Although the time frame for conducting pretreatment tests is

not specified in these guidelines, we chose 24 hours for laboratory testing and 7 days for electrocardiogram based upon other similar studies (11,31,48,49).

Descriptive statistics were performed that add to existing literature on CNCP patients prescribed methadone. Many of the comparisons were performed for educational purposes of the authors and were not meant to derive causative relationships. To better address questions regarding the effectiveness of acute/chronic pain or palliative medicine consultation, prospective trials are recommended.

There are possibly many confounding factors in our study. We discovered that the clinicians' thought process over reason to initiate methadone are important. A better study would attempt to collect this important data in some form. We also did not specifically address the rates of catastrophic outcomes that occurred in these individuals such as arrhythmia or overdoses. Longer term follow up would help us determine the actual rate of negative outcomes.

Conclusions and Recommendations

Our study describes practices at UNM that reflected evolving guidelines for the inpatient initiation of methadone for the treatment of chronic, non-cancer pain. This work highlights the importance of existing guidelines created to improve the safety of patients initiated on

methadone. We determined that pretreatment testing with laboratory and electrocardiograms were not performed as often as we would have hoped. Despite many limitations, we believe our study confirms the need for the existing guidelines and we hope our results inform the creation of systems that improve safety at the University of New Mexico and elsewhere.

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