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2.1 Case Presentation

A 69-year-old male presents to the pain clinic with a history of seronegative rheumatoid arthritis, multiple lumbar spine surgeries for radiculopathy, chronic myalgias, cervicgia, and recently diagnosed antecedent acute myelogenous leukemia (AML). He suffers from severe neck and low back pain that at one time responded to oxycodone and fentanyl patch and triggers point injections with steroid, local anesthetic, and botulinum toxin, and physical therapy. Unfortunately, his symptoms have progressively worsened, deteriorating his ability to function. He was referred to the pain clinic after an emergency department visit for refractory pain symptoms. He had tried, without relief, NSAIDs, acetaminophen, gabapentin, amitriptyline, tizanidine, cyclobenzaprine, baclofen, and hydrocodone. Pain not only impaired his function significantly but also was affecting his sleep, relationships, and mood. His range of motion was unremarkable, but he was diffusely tender across his upper back and upper pelvis. Numbness and weakness were absent.

The patient was prescribed oral methadone 5 mg every 8 h with immediate-release hydromorphone for breakthrough pain. Oxycodone was discontinued; baclofen and a short course of diclofenac were initiated. His pain and function improved in the following days and weeks. Methadone was gradually titrated to 7.5 mg orally every 8 h and denied side effects from the therapy. During this time, he was enrolled on a clinical trial for the treatment of his AML using a combination of azacitidine, high-dose cytarabine, and mitoxantrone. His therapy was complicated by persistent neutropenic fevers

and radiographic evidence identifying a probable invasive fungal pneumonia, at which time voriconazole therapy was initiated. The oncology clinic decreased the tamsulosin dose while the patient was taking voriconazole. The potential for an interaction with methadone was not noted or discussed with the patient or prescribing pain physician. During the following 2 weeks, the patient's control of pain continued to improve, but he and his wife reported increased and progressive sedation, fatigue, and cognitive dysfunction. The decision was made to halve the methadone dose during voriconazole treatment. Within a week the patient experienced a resolution of the aforementioned side effects. His pain remained well controlled, and AML remission permitted a 2-month vacation to Florida. Unfortunately, the patient's AML relapsed 3 months later and shortly thereafter succumbed to an episode of severe sepsis.

2.2 Discussion

Methadone is a synthetic opioid discovered in Germany in 1937 and approved by the US Food and Drug Administration (FDA) in 1947 for a number of pain-related syndromes. It is available as a racemic mixture of the L-stereoisomer, levomethadone, responsible for the mu, kappa, and delta opioid binding and a D-stereoisomer, dextromethadone, responsible for blocking the NMDA receptor [1]. This unique pharmacology partially explains methadone's apparent increased potency when administered to patient's already taking another opioid. Furthermore, methadone seems to offer a broader coverage of multidimensional pain syndromes—including ones only partially responding to opioids. In recent year, methadone has garnered interest based on its unique pharmacology, potential efficacy in difficult to treat pain syndromes, and low cost. Yet unique challenges are posed by dosing a medication with an uncertain potency, a long and variable half-life, and numerous pharmacokinetic and pharmacodynamic drug-drug interactions.

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Methadone is readily absorbed after oral administration with approximately 85% of the dose reaching the bloodstream, three times that of morphine [2]. Unlike other opioids, methadone has a rapid and extensive drug elimination phase (α -elimination) from the bloodstream into the adipose tissue (analgesic period) followed by a slow and variable elimination phase (β -elimination) that does not contribute to additional analgesia but attenuates withdrawal [3]. Delayed β -elimination may result in drug accumulation and toxicity [4]. Methadone is highly bound to α -1 acid glycoprotein (AAG), a plasma protein and acute phase reactant. As a result nonprotein bound (active) drug fluctuates during times of stress, opioid dependence, malignancy, and coadministration of other highly protein-bound medications [5, 6]. Methadone's metabolism is highly reliant on the hepatic cytochrome enzyme system primarily CYP3A4 and, to a lesser extent, CYP2B6, CYP2D6, and CYP1A2, resulting in two biologically inactive metabolites via *N*-demethylation [7]. High reliance upon the CYP system, particularly CYP3A4, predisposes methadone to a myriad of drug-drug interactions.

The World Health Organization reports that drug interactions are a leading cause of morbidity and mortality [8]. Although methadone represents less than 5% of all opioid prescriptions dispensed in the United States each year, it is identified in more than a third of opioid-related deaths with drug interactions frequently being implicated [9, 10]. A drug-drug interaction is the pharmacologic or clinical response to the coadministration of two or more drugs or substances beyond that expected from the known effects of the drugs given individually resulting in a synergistic, antagonistic, or idiosyncratic outcome [11]. Drug interactions are pharmacokinetic, if a drug alters the absorption, distribution, or elimination of a second drug, or pharmacodynamic, if multiple drugs act on the same receptor, site of action, or physiologic system [11].

Pharmacokinetic interactions are influenced by the degree to which a drug reduces (inhibits) or increases (induces) the activity of the target enzyme. CYP3A4 inhibitors are classified as either strong, moderate, or weak, based on the increase in exposure they cause in sensitive CYP3A4 substrates (Table 2.1). In our patient, methadone, a CYP3A4 substrate, was coadministered with voriconazole, a strong CYP3A4 inhibitor. Systemic exposure of methadone increased when metabolism of methadone was impaired, resulting in the increased and progressive sedation, fatigue, and cognitive

dysfunction. Pharmacodynamic interactions such as the potential to cause QTc prolongation and additive respiratory depression or sedation should be considered when initiating or maintaining a patient on methadone.

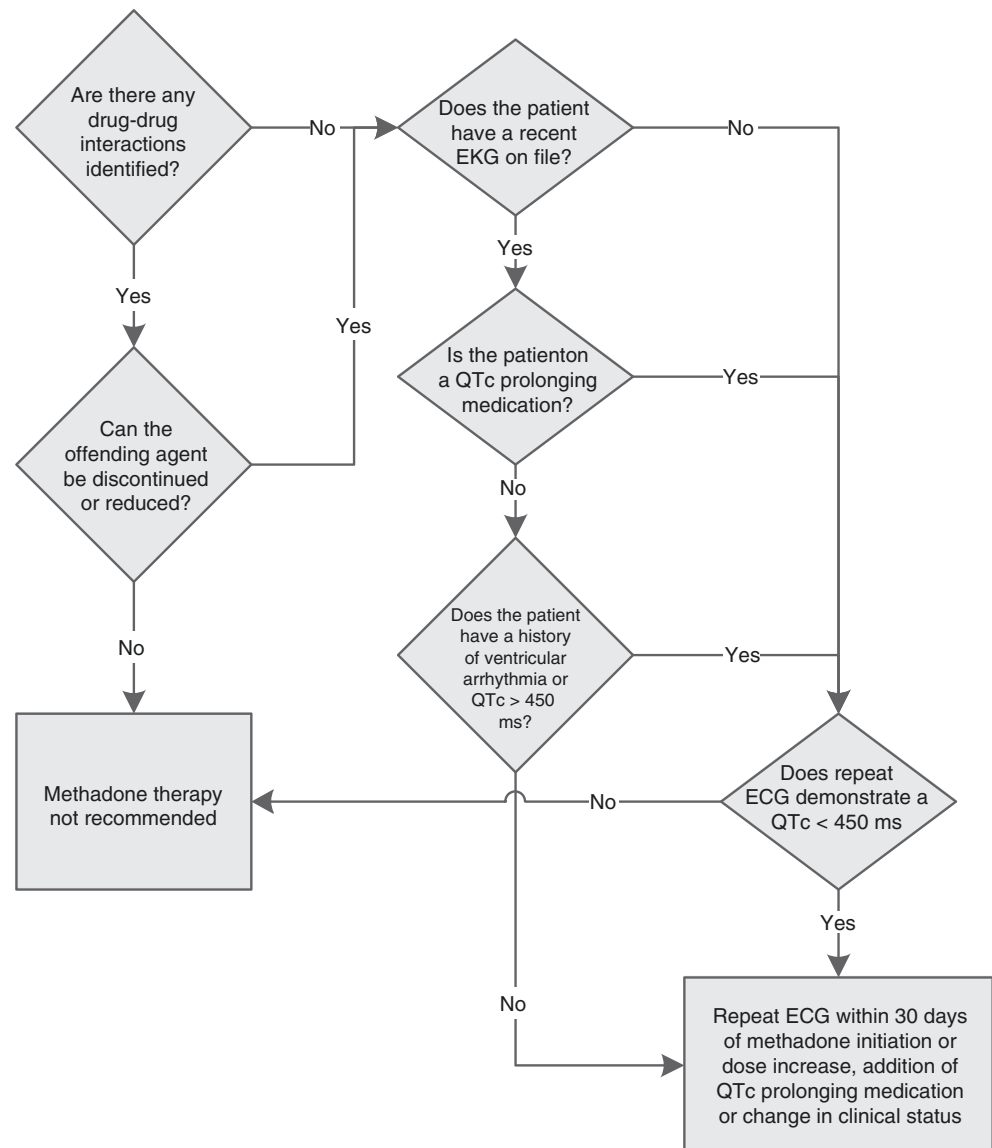
Prolonged QTc interval and ECG abnormalities have been reported in methadone-treated patients leading to the development of torsades de pointes and sudden death [12]. Torsades de pointes (TdP) is often caused by drugs that block potassium current channels in cardiac myocytes or in patients with a prolonged QT interval (>500 ms elevates risk). Methadone blocks the cardiac human ether-a-go-go related gene (HERG) potassium channel producing negative chronotropic properties [13]. Many factors contribute to QT interval prolongation and subsequent progression to TdP, such as age, female gender, hypokalemia, severe hypomagnesemia, bradycardia, recent conversion from atrial fibrillation, congestive heart failure, subclinical long QT syndrome, baseline QT interval prolongation, ion-channel polymorphisms, and concomitant medications [14]. The relative impact of each of these risk factors is unknown, but all must be considered before methadone or another therapy is started that increases the risk for QT prolongation. The effect on the QT interval is dose related and robust in patients taking greater than 100 mg orally every-day or with lower doses in cocaine users [15]. Preexisting QT prolongation appears to be a serious risk factor for drug-induced arrhythmia and remains the most consistent predictor in the development of TdP [16]. The international regulatory guidance for drug development suggests a gender-independent categorical threshold for QT prolongation of 450 ms [14]. In patients with long QT syndrome, a QTc interval >500 ms was associated with an odds ratio for syncope or sudden death of 4.2 [17]. Therefore, methadone should not be prescribed for patients with a QTc of >500 ms at any time. Alternative opioids should be considered in patients with a baseline QTc >450 ms, assuming all modifiable risk factors have been corrected.

When considering a patient's candidacy for methadone treatment, initial assessment must include concomitant medications, the use of illicit substances, personal and family history of structural heart disease, and personal history of arrhythmia. Additionally, a review of a recent ECG evaluating the QTc interval is recommended for patients with baseline risk factors for prolongation of the QTc interval prior to initiating methadone therapy. Obtaining an ECG for such evaluation may be necessary. Figure 2.1 provides a stepwise approach for safely initiating methadone therapy. Concomitant medications should be evaluated for their ability to influence methadone's metabolism through CYP3A4 as well as potential to cause overlapping toxicity (i.e., somnolence or respiratory depression) or QTc prolongation. If a drug-drug interaction is identified, consider discontinuation or reduction of the dose of the offending medication. Once methadone is initiated, close

Table 2.1 Classification of CYP3A4 inhibitors

<i>Strong CYP3A4 inhibitors</i> (cause \geq fivefold increase in AUC of sensitive CYP3A4 substrate)	<i>Moderate CYP3A4 inhibitors</i> (cause ≥ 2 but $<$ fivefold increase in AUC of sensitive CYP3A4 substrate)	<i>Weak CYP3A4 inhibitors</i> (cause >1.25 but $<$ fold increase in AUC of sensitive CYP3A4 substrate)

Fig. 2.1 Methadone initiation and monitoring algorithm



monitoring is necessary. Overdose symptoms are typically not observed after a single dose but tend to accumulate over several days' dosing [18]. After monitoring for potential interactions, the methadone dose may be adjusted. When CYP inducers or inhibitors are coadministered, heightened monitoring is required [17]. Table 2.2 lists the medications with known interactions with methadone. Because novel therapeutics are continually emerging (44 drugs were granted FDA approval in 2014), the potential for drug-drug interactions increases necessitating vigilance and consultation with a medication expert. Additionally, the vast majority of patients receiving methadone are also on other drugs for associated comorbidities or pain. Thus polypharmacy should be considered the rule rather than the exception. A number of approaches to mitigate the risks for drug-drug interactions have been suggested [19]: (1) At each visit, review with the patient each

medication being taken and document the medication and dose. (2) Advise the patient to contact you if any physician has made any additions or changes to their medication regimen. (3) Educate the patient about potential side effects and potentially lethal side effects. (4) Educate the patient that street drugs, over-the-counter medications, and herbal supplements can accentuate drug-drug interactions and increase the risk of side effects. (5) Initiate the susceptible drug at a low dose and increase the dose gradually after assessing response. (6) Keep the dose of the inhibitor low or increase slowly. (7) Consider utilizing drugs that are metabolized by multiple P-450 enzymes rather than one CYP system. (8) Be aware of which drugs are strong inhibitors of the CYP system. (9) Therapeutic drug monitoring is indicated if relationship exists between drug-level and toxicity. (10) Utilize a computer software program to identify drug-drug interactions or consult with a pharmacist

or medication expert. And perhaps, most importantly, patients should be educated to fill all medications at the same pharmacy, so that the pharmacist can identify potential drug interactions.

Table 2.2 Clinically significant methadone drug-drug interactions

Drug	Effects on methadone levels	Effects on QTc interval	Sedative or respiratory depressant effects
<i>Antibiotics</i>			
Ciprofloxacin	Increased		
Clarithromycin	Increased	Increased	
Erythromycin	Increased	Increased	
Itraconazole	Increased		
Ketoconazole	Increased		
Fluconazole	Increased		
Voriconazole	Increased		
Posaconazole	Increased		
Rifampin	Decreased		
<i>Anticonvulsants</i>			
Carbamazepine	Decreased		
Phenytoin	Decreased		
Antihistamines			
Diphenhydramine			Increased
Promethazine			Increased
<i>Antipsychotics</i>			
Quetiapine	Increased	Increased	
Barbiturates			
Phenobarbital	Decreased		Increased
<i>Benzodiazepines</i>			
Alprazolam			Increased
Clorazepate			Increased
Diazepam			Increased
Estazolam			Increased
Flurazepam			Increased
Lorazepam			Increased
Midazolam			Increased
Triazolam			Increased
Zopiclone			Increased
Zolpidem			Increased
<i>HIV medications</i>			
Abacavir	Decreased		
Nevirapine	Decreased		
Delavirdine	Increased		
Efavirenz	Decreased		
Ritonavir-lopinavir	Decreased		
Nelfinavir	Decreased		
Amprenavir	Decreased		
Atazanavir	Decreased		
<i>Selective serotonin reuptake inhibitors</i>			
Fluvoxamine	Increased		
Nefazodone	Increased		
Paroxetine	Increased		

Table 2.2 (continued)

Drug	Effects on methadone levels	Effects on QTc interval	Sedative or respiratory depressant effects
<i>Tricyclic antidepressants</i>			
Amitriptyline		Increased	
Desipramine		Increased	
Imipramine		Increased	
Nortriptyline		Increased	
Protriptyline		Increased	
<i>Urinary alkalinizers</i>			
Bicitra	Increased		
Polycitra	Increased		
Verapamil	Increased		
<i>Other</i>			
Aprepitant	Increased		
Cimetidine	Increased		
Cocaine	Decreased	Increased	
Disulfiram	Increased		
Ethanol	Decreased		Increased
Grapefruit juice or whole fruit	Increased		
Omeprazole	Increased		
St. John's wort	Decreased		

Key Points

- Methadone while highly effective poses unique challenges due to a long and variable half-life and numerous drug-drug interactions.
- Close patient monitoring is imperative particularly in the days following methadone initiation, dose increase, or initiation of concomitant medications known to influence methadone's metabolism.
- Evaluation of the QTc interval is recommended for all patients prior to starting methadone therapy and within 30 days of methadone initiation or dose increase.

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