Chapter 1
Prescribing Methadone Safely

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Introduction

Methadone, a very useful analgesic and the most utilized drug for replacement therapy in patients with opioid-related addiction, is now also widely used for the management of chronic pain. Methadone was synthesized in Germany before the WWII and imported to the USA by Lilly after the war and was utilized for several years as an opioid analgesic but lost popularity in the 1950s. In the early 1960s, Dole and Nyswander proposed that patients abused opioids to compensate for an endogenous opioid deficiency, and it was introduced as a maintenance medication to control craving in patients treated for drug addiction [1]. Due to the widespread use in Methadone Maintenance Treatment Programs (MMTPs), it became a social stigma associated with drug addiction; consequently, chronic pain patients often refuse methadone as a possible analgesic option, and practitioners often avoid

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prescribing it for chronic pain management. Nonetheless due to its long half-life (although variable), low cost, and good analgesic properties, it resurged as a good alternative in patients requiring long-term opioid therapy [2].

Importance of Methadone Pharmacokinetic in Safe Prescribing

Methadone has several unique pharmacokinetic characteristics that set it apart from other opioids, and some of these characteristics have raised concerns about its safety. First, the half-life of methadone is variable and ranges from 15 to 150 h depending on the individual. The prolonged half-life is an advantage for the management of chronic nonmalignant pain in patients that require opioid analgesia with a long-acting agent, but the variability can result in unpredictable dosing and drug accumulation [3]. Second, the main mechanism for methadone metabolism is hepatic through the cytochrome P450, specifically isoenzymes 2B6, 3A4, and 2D6 [4]. Methadone can be displaced by other substrates for the same enzymatic complex, resulting in an elevation of free drug concentration, thereby increasing the risk for side effects and toxicity. In addition the isoenzymes can be inhibited or induced by a variety of substances contributing to the changes in plasma levels [5]. The degree to which other opioids are metabolized by this set of isoenzymes varies, and while hydromorphone, oxymorphone, and morphine are not significant substrates, hydrocodone, codeine, oxycodone, and methadone are widely metabolized [2]. This is important because patients with chronic pain are often treated with multiple medications (a phenomenon known as "polypharmacy") that are also metabolized through this pathway.

There is a wide variety of medications for the treatment of chronic pain, including adjuvant analgesics used to treat chronic neuropathic pain such as antidepressants and anticonvulsants, among others. In addition depression is a common comorbidity among chronic pain patients. Indeed several surveys have shown that up to 50 % of patients have dual diagnoses [6]. Some of the antidepressants are also substrate of the cytochrome P450 and may compete with methadone resulting in an increase in free drug concentration of methadone, predisposing the patient to side effects and toxicity.

Methadone Safety and the QTc Interval Duration

Another characteristic of methadone is its ability to block the delayed rectifying potassium current. This current is responsible for the repolarization of the action potential bringing the electrical activity of the fibers back to their resting membrane potential. The blockade of the potassium channels results in a prolongation of the depolarized state predisposing to ventricular arrhythmias including Torsades de Pointes (TdP). Interestingly, in vitro studies have shown that other opioids have also the ability to block this delayed rectifying current, including LAAM, fentanyl, methadone, buprenorphine, and codeine (in descending order of potency) [7]. From

Table 1.1 Risk factors for QTc prolongation and Torsades de Pointes (TdP)

- Elderly women
- Advanced heart disease
- Congenial and acquired long-QT syndromes
- Concomitant use of drugs with potential to prolong QTc
- Family history of sudden death
- Hypokalemia
- Hypomagnesaemia
- CYP 3A4 inhibitors
  - Potent inhibitors
    - Protease inhibitors: ritonavir, nelfinavir, indinavir
    - Macrolide antibiotics: erythromycin, clarithromycin, troleandromycin
    - Antifungal agents: ketokonazole, itraconazole
  - Less potent inhibitors
    - Saquinavir, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, clotrimazole
- Potential of commonly used medications in HIV/AIDS and chronic pain patients to produce QT prolongation
  - Very probable: quinidine
  - Probable: pimozide, ziprasidone
  - Possible: clarithromycin, erythromycin, pentamidine, chlorpromazine, haloperidol, olanzepine, risperidone, amitriptilyne, desipramine, imipramine, sertraline, venlafaxine
  - Improbable: fluconazole, levofloxacin, trimetropin-sulfamethoxazole, fluoxetine, paroxetine, sumatriptan, zolmitriptan, methadone
  - Very improbable: azythromycin, ciprofloxacin, clindamycin
- Drugs associated with TdP
  - Amiodarone, arsenic trioxide, bepridil, chlorpromazine, cisapride, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, mesoridazine, methadone, entamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine

the clinical prospective, however, since fentanyl is about two log units more potent than methadone, the plasma concentration required to produce analgesia in vivo is lower than the concentration required to interfere with the delayed rectifier potassium current. Lastly, recent data suggest that prolongation of the depolarization state could be clinically relevant with oxycodone but more studies are necessary to clarify this point [8].

The blockade of the rectifier current by methadone can be even more significant when administered concomitantly with other drugs that also have the ability to block the same current. For instance, the HIV/AIDS patient population often requires polypharmacy, and may receive multiple medications with potential to block the rectifying potassium currents. Indeed, patients with HIV/AIDS may be taking a variety of agents including antibiotics (e.g., trimetroprim-sulfamethoxazole), antipsychotics (e.g., haloperidol), antifungals (e.g., ketoconazole), and antidepressants (e.g., venlafaxine), all of them with the potential to predispose to arrhythmias such as TdP through the blockade of the potassium rectifier current (Table 1.1) (full list available at www.torsades.org).

Understanding Racemic Methadone and Methadone Enantiomers

In the USA, methadone is commercialized as a racemic mixture where 50 % of the molecules deviate polarized light to the left (levorigirous) and 50 % of the molecules deviate polarized light to the right (dextrogirus). The two enantiomers (*R* and *S*) have some differences in terms of efficacy, receptor affinity, and effect on the delayed potassium rectifying current. The *R*-enantiomer has higher affinity for the mu opioid receptors while the *S*-enantiomer has lower affinity for the mu opioid receptors but blocks the delayed rectifier potassium current more efficiently, thus predisposing to cardiac toxicity [9]. Indeed, Ansermot et al., replaced (*R*,*S*)-methadone by (*R*)-methadone (half-dose) in 39 opioid-dependent patients receiving maintenance treatment for 14 days. (*R*)-methadone was then replaced by the initial dose of (*R*,*S*)-methadone for 14 days ($n=29$). The QTc interval decreased when (*R*,*S*)-methadone was replaced by a half dose of (*R*)-methadone by a mean of −3.9 ms per week ($P=0.04$) and increased when (*R*)-methadone was replaced by the initial dose of (*R*,*S*)-methadone for 14 days. These observation needs to be replicated, but suggests that (*R*)-methadone is safe to treat patients in need of substitution therapy [10].

Reports of Increased Deaths and ED Visits Attributed to Methadone

In 2006, the FDA placed a warning box on methadone to alert the public about the observed increase in death rates attributed to this drug. The increase in popularity of methadone as an analgesic resulted in higher number of prescriptions written for the management of chronic pain. The CDC reported that the number of deaths that were attributed to methadone climbed from 800 in 1999 to close to 5,000 in 2006 [11]. These surveys, however, have significant flaws, and in many cases the results are difficult to interpret. The most common weaknesses in these reports include variable sources for data gathering, reliance on retrospective data collection, difficulties defining the denominator, and coexistence of other drugs in the system at the time of death (e.g., cocaine, benzodiazepines). Despite the limitations in these reports, the absolute increase in number of deaths where methadone was present at the time of death raises concerns about safety.

In 2002, Krantz and coworkers published a case series of sudden deaths occurring in the ICU setting, in which many of these patients were on methadone at the time of death [20]. Although most of the 17 patients in the case series had other findings that could have been responsible for the poor outcome (e.g., electrolyte abnormalities), this study has the merit of raising awareness in the pain and drug

addiction community about the possibility of cardiac toxicity related to methadone. This study was followed by a wide range of publications that included cross-sectional, retrospective, prospective, and controlled studies and a number of case series and case reports, but the issue is not yet fully understood.

Methadone Induced QTc Prolongation and TdP

Several mechanisms have been proposed to explain methadone toxicity: (1) QTc prolongation leading to fatal arrhythmias including TdP; (2) PR interval prolongation; (3) non-obstructive sleep apnea (more prominent with the coadministration of benzodiazepines); (4) syncope. TdP is caused by prolonged depolarization that leads to a ventricular arrhythmia with a characteristic pattern for which the condition is named [12]. The upper limit of the normal range for the QT interval has been established at 450 ms for men and 470 ms for women, and QTc prolongation over 500 ms is considered to be high risk for TdP regardless of the sex [13].

There is significant controversy on the role of ECG to help prevent cardiac toxicity induced by methadone. While some clinicians take the position that an ECG should be performed on every patient on methadone, addiction specialists argue that requiring ECGs on patients attending MMTP could result in abandonment of treatment and an increase in morbidity and mortality. Indeed, after an increase in death attributed to methadone was detected in Wales, the dispensation of maintenance methadone was discontinued. Shortly afterwards, deaths related to methadone decreased, but a concomitant increase in deaths related to heroin abuse was reported. The death rate related to heroin abuse was higher than that observed with methadone before it was discontinued. Once the methadone programs were reinitiated, death rates decreased again and eventually reached baseline levels [14].

The literature on the role of routine ECG monitoring in prevention of cardiac toxicity attributed to methadone is controversial, and the recommendations range from “never necessary” to “do ECG on every patient on methadone,” [15] while other groups recommend performing ECGs on patients receiving doses over 100 mg/day [16]. However, in the guidelines soon to be published by the American Pain Society (APS) and the College on Problems of Drug Dependence (CPDD), no dose limit is included (Table 1.2).

The observation that methadone can increase the duration of the QTc interval was first noted by Stimmel and coworkers in a study published in 1973. In this study, an increase in the duration of the QTc interval was observed in 34 % of patients, but no TdP was reported [17]. Some investigators questioned the relevance of this observation in view of the 27-year gap during which no other study on this phenomenon was published, until the more recent observations were reported by

Table 1.2 ECG recommendations to decrease risk of cardiac toxicity

"Vigilant for doses >600 mg/day"	Walker [35]
"Patients on high doses"	Almehmi [36]
"Never necessary"	Krook [37]
"Consider ECG in patients on high doses"	Martell [38]
"Consider ECG before starting QT-prolonging medications"	Maremmani [39]
"Repeat ECG after every change in drug regime"	Sticherling [40]
"ECG screening in patients at risk, especially after starting CYP2A4 inhibitors or increase in dose"	Ehret [41]
"ECG for patients on >120 mg/day" "ideally every patient at entering treatment"	Peles [42]
"For HIV-infected patients receiving drugs with QTc prolongation potential"	Chinello [43]
"ECG for high risk patients"	Krantz [44]
"ECG in methadone users … with inhibitors of methadone metabolism"	Rothier [45]
"An ECG is a convenient way with little cost to screen for an increased risk of TdP"	Ehret [46]

Krantz and coworkers on a possible association between methadone use and TdP [20]. It is important to highlight that at the time the Stimmel study was done, a typical dose of methadone in MMTPs was 40–60 mg a day, and it was not a popular opioid analgesic. Furthermore, during the 1970s, opioids including methadone were under-prescribed even for the management of malignant pain. More recently, however, it was shown in MMTP that higher doses of methadone resulted in lower morbidity and mortality rates [18].

In recent years, pain specialist started prescribing methadone more readily, and at higher doses than prescribed in MMTPs in the 1960s, often up to 120–140 mg/day. Indeed, there are reports of doses of up to 1,200 mg/day [19] and even higher, prescribed for the management of malignant and nonmalignant pain. As a result, the doses of methadone prescribed in the last 10 years are overall significantly higher than the doses prescribed when the first observations about the effect of methadone on cardiotoxicity were reported. Since the study by Krantz et al. in 2002 [20], many reports addressing the same topic resurfaced. However, most of the studies did not provide convincing data to favor one position over the other.

"Windows" for Risk of Toxicity

Overall methadone is a safe drug when utilized according to current guidelines; however, it is important to become familiar with instances when patients can be prone to more marked side effects and toxicity. A common denominator to these possible scenarios is the discontinuation and re-initiation of methadone therapy at the same dose that the patient was taking before discontinuing therapy. Although the

level of evidence is low, the current recommendation is to consider patients to be "opioid naïve" if methadone is to be reinitiated, when methadone has been discontinued for more than a week [22]. The rationale is that during that period of time, patients may lose tolerance to the drug secondary to lack of exposure, and they might become relatively "naïve" or at least recover some of the original sensitivity to the drug both for analgesia and side effects. The time course to become "naïve" to methadone after discontinuation is not clear but siding on caution is recommended. The reasons that may account for methadone discontinuation are multiple, some of them are patient-related but others are imposed on them. Patient-related causes are: losing the medication, taking more than prescribed and running out of the medication early and not having refills, taking methadone "only when the pain gets worse," dropping out of a methadone clinic and reinitiating therapy in other facility, and drifting from a methadone clinic to a pain clinic. Taking methadone "only when the pain is worse" is equivalent to taking it for breakthrough pain. But prescribing methadone in this fashion has been less popular due to the possibility of toxicity. Situations that are imposed on the patient may include opioid rotations, imprisonment (where the medication may be discontinued), or discharge from an MMTP or pain clinic.

Opioid Rotation

This is one of the scenarios that a practitioner may encounter where methadone might be initiated at a higher dose than what is now considered safe. In general when opioids are rotated (except for methadone), the recommendation is to add all the doses of the opioid that the patient is taking, including extended release and breakthrough medication, convert the amount into the new opioid utilizing the available conversion tables, then cut down 25 % of the estimated dose for incomplete cross-tolerance, prescribe 80 % of the total dose as a long acting formulation of the new opioid, and 20 % in divided doses for breakthrough pain [21]. The evidence that supports this practice is not strong but it has been adopted by many practitioners in the pain management community. One of the criticisms of this approach is the limitations of the conversion tables [22, 23] as they have been developed based on single comparative doses rather than on full dose–response curves [24].

When an opioid rotation to methadone is done, the usual recommendation is to calculate the equianalgesic dose to the opioid that the patient has been taking, and then cut down by 75–90 %. However in patients that are taking high doses of an opioid (e.g., 500 mg a day), even the most conservative conversion to methadone (cutting down by 90 %), would result in 50 mg a day, and that is over what some experts consider to be a safe starting dose in opioid tolerant patients (i.e., 10 mg 3 times a day) [22]. A more sound strategy would be to do a stepwise conversion where every incremental step would be kept below 30 mg a day of methadone. In patients without a baseline ECG, one should be performed after four half-lives of methadone (4–7 days). Although the level of evidence for these recommendations is low, there is enough clinical experience that justifies this algorithm.

Resuming Methadone Prescribing After Imprisonment

One of the circumstances in which patients are vulnerable to increased risk of side effects due to inappropriate methadone dosage is imprisonment. Inmates do not always receive appropriate opioid substitution therapy or opioids for the management of chronic pain during the period of incarceration. After release from prison, patients may inadvertently be restarted at the previous dose that they were taking before it was discontinued, even though they should now be considered "opioid naïve." Indeed, one study showed a high risk for mortality associated with decreased tolerance to heroin during the transition period from inmate back into the community [25]. There is no data on chronic pain management, but the assumption of inadequate treatment during incarceration is reasonable (as extrapolated from the data on maintenance therapy), and these patients should be considered "opioid naïve" at the time of reinitiating of opioids.

Importantly, it has been noted that continuing patients that are on opioid substitution therapy on the same dose of medication during incarceration seems to correlate with better outcomes than when it is discontinued [25]. It has also been observed that patients who reached a moderate-to-high methadone dose for opioid substitution therapy during incarceration had higher rates of reporting to community MMTPs vs. those on lower doses [26], and the likelihood of re-incarceration was reduced by 20 % in those inmates that received opioid substitution therapy during incarceration [27]. In addition, treatment of inmates with opioid substitution therapy during incarceration has been correlated with decreased rates of blood-born infectious diseases, including HIV [28, 29]. A call for restructuring the system and allocating more funding to support opioid substitution therapy during incarceration has been made [30].

Missing Doses at the Methadone Clinic

Another scenario is that of patients missing doses of methadone at the methadone programs. It has been recognized at MMTP clinics that missing doses have to be taken into consideration in determining the dose of medication that will be prescribed at the time of return to the clinic. The recommendations are the following: (1) if the patient missed 1–2 doses, give the usual dose; (2) if missed 3–5 doses, give half of the usual dose, assess tolerance, then increase 15 mg/day back to the usual dose; (3) if missed >5 doses, start at 30 mg or less, assess tolerance, and increase 15 mg/day back to usual dose. Except in the case of extenuating circumstances, consider the client to have withdrawn from the program after three consecutive missed doses. However, extenuating factors should be taken into consideration when discontinuation of methadone is entertained [31]. Other variations of this algorithm are used at other MMTPs with the same underlying concept of restarting at a reduced methadone dosage after a period of missed doses.

Exit Strategy as an Intervention for Safe Prescribing

This is a concept that has been introduced recently to assist practitioners in addressing circumstances in which opioids need to be discontinued for various reasons: it is no longer safe to prescribe to a particular patient [32], benefits of the drug do not outweigh the risks, or the opioid is not effective despite titration of the dose. The exit strategy is embedded in the overall algorithm of frequent reassessment during the course of opioid treatment. When the patient is initially evaluated and a plan of care developed, different possibilities for the management of the pain should be considered. Possible treatments are outlined in Table 1.3.

The strategy should be tailored to individual patient preferences. The armamentarium includes pharmacology, interventional approaches, alternative, complementary, and behavioral strategies. Non-opioid analgesics should be considered first. Opioids are part of the pharmacological strategy, and are usually introduced after non-opioid medications have shown to be insufficient to manage the pain. The selection of a specific opioid depends on analgesic efficacy and the side effect profile. Some clinicians and researchers choose to include opioids at the beginning of the

Table 1.3 Strategies for the management of chronic pain

- Interventional approaches
  - Injections
  - Neurostimulation
  - Neuroaxial infusion
  - Neuroablative
- Pharmacotherapy
  - Non-opioid analgesics
  - Adjuvant analgesics
  - Opioid analgesics
- Others
  - Rehabilitative
  - Psychological
  - Complementary and alternative strategies
  - Lifestyle changes
  - TENS
- Neurostimulation
  - Invasive
    - Motor cortex stimulation
    - Deep brain stimulation
  - Noninvasive
    - rTMS
    - tDCS

TENS transcutaneous electrical nerve stimulation; *rTMS* repetitive transcranial magnetic stimulation; *tDCS* transcranial direct current stimulation

Table 1.4 Domains to be assessed during the patient visits to decrease risk of opioid diversion and proper opioid prescribing

• Assess and document level of **Analgesia** and modify therapy if necessary
• Assess and document drug-related **Adverse effects** and, if present, modify therapy
• Assess and document **Activity** (level of function) and consider modification of therapy if not improved
• Assess and document drug-related **Aberrant behavior** and modify therapy if present

treatment when other alternatives have failed previously [33]. Appropriate patient selection is crucial if opioids are used, and patient characteristics such as history of drug abuse should be considered (see next section for further discussion).

Once a decision is made to use an opioid, a trial is initiated. During the trial, the patient should be assessed for level of analgesia, the presence of side effects, level of function, and the presence of drug-related aberrant behavior. These domains, based on earlier observations, have been coined by Passik as the four "As" and they assist the clinician in making a decision on the safety and efficacy of opioid therapy [34] (Table 1.4).

At the time of every reassessment (follow-up visit), the patient should be evaluated for alternative strategies to treat the pain, and when indicated, they should be added to the plan of care. If the patient experiences intolerable side effects or reports no improvement in the level of function, or if the clinician notes aberrant drug-related behaviors, then the trial should be discontinued and emphasis should be placed on alternative strategies to treat the pain. The dilemma is that when we "exit" the use of opioids, the patient may not have effective alternatives to address the pain. Further research is clearly needed to explore alternative approaches (Fig. 1.1).

General Recommendations for Successful Methadone Prescribing

The practitioner should evaluate risk related to methadone-prescribing for every patient before embarking on a medication trial. During this assessment special attention should be paid to the patient's social history as it can provide information on predictors of aberrant drug-related behavior, including current or past drug or alcohol abuse and history of sexual abuse (a more relevant predictor in women). Clinicians should also be aware of patient behaviors that may suggest opioid abuse. These "red flags" include running out of medications early, having multiple prescribers for opioid medications, and utilizing multiple pharmacies for opioid prescriptions. Stratification of risk level will assist in structuring the visits, including length of follow-up intervals, the institution of an opioid treatment agreement, limiting the amount of medication prescribed, or pill counting.

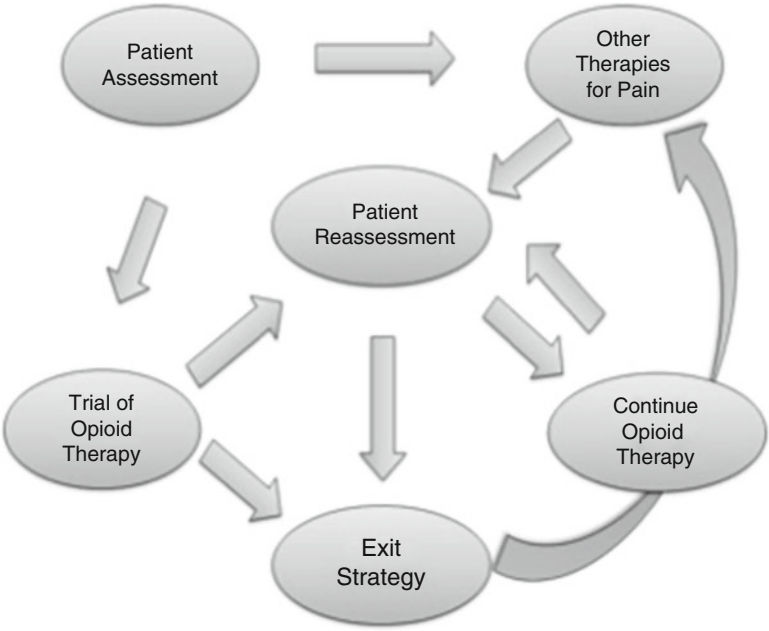

Fig. 1.1 Algorithm to assist reassessment of opioid prescribing over time

Table 1.5 Strategies that can help increase successful opioid prescribing

Implementing the strategy
• Stratify risk in every case
• Structure therapy commensurate with risk
• "Dose for success"
• Repeatedly assess an array of outcomes
• Make changes in dosing or risk management based on outcomes
• Document and communicate

The result of this assessment will help the practitioner determine whether or not this patient will benefit from continued opioid therapy. Should the treatment with opioid medications continue, then at every visit the dose should be adjusted for analgesia and side effects, and an evaluation for the addition of adjuvant therapy should also be done. Documentation of the rationale behind each decision is very important as there is no consensus on how chronic opioid therapy should be conducted. If aberrant drug-related behavior is detected, then a referral to addiction psychiatry is strongly recommended (Table 1.5).

Conclusions

Methadone is a very useful analgesic and the most widely utilized medication for opioid substitution therapy. However, recent data suggest an increase in methadone-related deaths, likely due to methadone-induced QTc prolongation, thereby leading to fatal arrhythmias. Therefore, understanding certain principles of safe opioid prescribing is paramount. This entails an understanding of the "windows" of risk for toxicity, including patient-related factors such as missing doses or appointments, and external circumstances such as imprisonment. The strategy for safe prescribing involves taking a detailed patient history, noting behaviors that are "red flags" for opioid abuse, and instituting appropriate management strategies such as short follow-up intervals, an opioid treatment agreement, or pill counting. If used appropriately, methadone can be very effective as opioid substitution therapy and for the treatment of chronic pain. Further research is needed to explore alternative therapies for patients for whom the risk of methadone outweighs the benefits.

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