Special Article

Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper

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Abstract

Methadone has several unique characteristics that make it an attractive option for pain relief in serious illness, but the safety of methadone has been called into question after reports of a disproportionate increase in opioid-induced deaths in recent years. The American Pain Society, College on Problems of Drug Dependence, and the Heart Rhythm Society collaborated to issue guidelines on best practices to maximize methadone safety and efficacy, but guidelines for the end-of-life scenario have not yet been developed. A panel of 15 interprofessional hospice and palliative care experts from the U.S. and Canada convened in February 2015 to evaluate the American Pain Society methadone recommendations for applicability in the hospice and palliative care setting. The goal was to develop guidelines for safe and effective management of methadone therapy in hospice and palliative care. This article represents the consensus opinion of the hospice and palliative care experts for methadone use at end of life, including guidance on appropriate candidates for methadone, detail in dosing, titration, and monitoring of patients' response to methadone therapy. J Pain Symptom Manage 2019;57:635–645. © *2018 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Methadone, hospice, palliative care, medication safety, arrhythmias

Introduction

Methadone hydrochloride is a synthetic mu-opioid agonist, and N-methyl-D-aspartate receptor antagonist used for the treatment of pain and substance use disorder.[1] Methadone has several unique characteristics that make it an attractive option for pain relief in serious illness, including long duration of action, availability of multiple dosage formulations (tablet, oral solution, highly concentrated oral solution,

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intravenous), high oral bioavailability, low cost, lack of pharmacologically active metabolites, and perceived enhanced effectiveness in difficult pain syndromes. Although methadone is considered a valuable analgesic, the safety of methadone has been called into question after reports of a disproportionate increase in the opioid-related death rate in recent years.[2]

In 2014, the American Pain Society (APS), College on Problems of Drug Dependence, and the Heart Rhythm Society collaborated to issue guidelines on best practices to maximize methadone safety and efficacy.[3] This guidance is valuable in many practice settings that focus on populations with anticipated long-term survival where safety is a significant concern. The level of monitoring suggested by those authors may not fully reflect the risk vs. benefit in an end-of-life scenario where goals of care have shifted, as with patients with anticipated shorter survival who need rapid pain relief, in whom the utility of aggressive monitoring is questionable.

In preparation of this document, a systematic search of the methadone literature was performed (Pubmed/Medline), and relevant articles were culled and forwarded to a panel of 15 interprofessional hospice and palliative care (HPC) experts from Canada and the U.S. for review. Subsequently, an all-day consensus-building meeting was held with all 15 panelists in February 2015 to consider the APS methadone recommendations and their application to hospice and palliative care. The purpose was to develop guidance for hospice and palliative care practitioners to help maximize benefit and minimize risks of methadone therapy in patients with serious illness. Hospice or palliative care for methadone maintenance treatment program patients was considered beyond the scope of this article. The group consisted of eight physicians, six pharmacists, and one nurse. Consensus was achieved among the group after several draft iterations.

Appropriate and Inappropriate Candidates for Methadone

The HPC consensus group considered criteria for palliative patients who are appropriate or inappropriate candidates for methadone therapy. As noted in the APS guidelines, clinicians should "perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone" to determine the appropriateness of methadone for an individual patient.[3] However, the risk-benefit consideration in patients with a serious illness is different from a chronic pain or substance use disorder population. Patients with serious illnesses experience multiple transitions in care, potentially to a less experienced clinician. They may experience rapid disease progression resulting in pain escalation and may not be in a highly monitored environment. Potentially appropriate and inappropriate candidates for opioid therapy, with special consideration for methadone, are described in the HPC recommendations (Table 1).

Risk Assessment Before Starting Methadone Therapy

A baseline risk assessment for therapy must be conducted after the patient is determined to be an acceptable candidate for methadone. This assessment is individualized to account for the patient's situation, prognosis, pain severity, previous use of opioids, and other variables. Precautions and contraindications to opioid therapy in general, and methadone specifically, are shown in Table 2.

A targeted history and physical examination should include the patient's age, diagnosis, pain assessment, average daily opioid use, past medical history, prognosis, medication history, risk of drug diversion, and personal or family history of alcoholism or substance use disorder. The patient's cognitive status, ability to adhere to the treatment plan, and ability to swallow dosage formulations should be assessed. Community-dwelling patients who do not have a competent caregiver and do not have sufficient mental acuity to take methadone as directed should not be started on methadone. Comprehensive medication reconciliation is essential because numerous pharmacokinetic and pharmacodynamic drug interactions are associated with methadone (see Interacting Medications section).

History of Liver Disease

Methadone does not have a high hepatic extraction ratio because it has an oral bioavailability of 80% and therefore low first-pass hepatic clearance. Liver disease reduces hepatic extraction but does not influence methadone bioavailability to any appreciable degree. Methadone is highly bound to alpha-1 acid glycoprotein, which is reduced in liver disease.[4] This influences methadone distribution and unbound serum concentration, potentially contributing to interpatient variability with methadone dosing.[4–7]

Methadone metabolism is highly dependent on multiple Phase 1 enzymes (mixed function oxidases), which are impaired or diminished as the liver fails, as in cirrhosis. Methadone clearance will not be further impaired with hepatorenal syndrome because methadone metabolites are pharmacologically inactive. Methadone should be used with caution in advanced liver disease (Child–Pugh Class C) owing to impaired metabolism and increased free drug availability.[8,9] Practitioners should consider lower doses and allow extra time between methadone dosage increases (e.g., wait 10–14 days instead of five to seven days) in patients with severe (Child-Pugh Class C) liver disease because

Table 1
Patient Selection for Methadone Therapy

Potentially Appropriate Candidates for Methadone in HPC	Potentially Inappropriate Candidates for Methadone in HPC
• Moderate to severe pain (especially as a second-line opioid choice) • Pain refractory to other opioids • True phenanthrene (e.g., morphine) allergy • Significant renal impairment • Need for a long-acting opioid (particularly as an oral concentrate solution) • High opioid tolerance • Poorly controlled opioid-induced adverse effects with other opioids • History of dysphagia, inability to swallow, or feeding tube placement	• Patient lives alone, or poor cognitive functioning, without a responsible caregiver • Lack of knowledgeable practitioner on transfer • History of opioid/medication nonadherence • History of substance misuse or SUD (patient or family) • Multiple risk factors for methadone toxicity (e.g., clinical instability, multiple transitions in care, history of transplant) • History of QTc prolongation or at high risk for such • Prognosis less than projected time to methadone steady state (i.e., five to seven days) • Obstructive or central sleep apnea • Determined to be medically inappropriate after risk assessment (see next section)

HPC = hospice and palliative care.

it will take longer to achieve a steady-state serum concentration.

In general, methadone should be avoided in the setting of severe, acute hepatic impairment, although there are no specific recommendations for methadone dosing in these patients. Decreased cytochrome enzyme activity should be expected, which prolongs the metabolism of methadone.

History of Substance Use Disorder

Individuals in hospice and palliative care settings with a history of substance use disorder are likely at higher risk for overdose and other adverse events when prescribed methadone (or any opioid).[10] Risk mitigation strategies should be implemented. Ideally the patient should be co-managed by an addiction specialist. Active use of an illicit substance is a contraindication to methadone therapy. Although controversial in advanced illness, most practitioners would agree that the professional obligation to treat pain is contingent on the patient's adherence to the plan of care and abstinence from use of illicit substances that may increase risk of methadone overdose or adverse event.

History of Disordered Breathing

Several studies have shown that methadone has been associated with central and obstructive sleep apnea,[11–17] which often goes undetected by practitioners. There is little correlation between the methadone dose and development of sleep apnea, but a study of individuals on chronic methadone reported a 30% rate of central sleep apnea by polysomnography.[18] In that study, antidepressants played a role in potentiating methadone-related sleep apnea and methadone was associated with reduced responsiveness to PCO_2 and a wide awake alveolar-arterial oxygen gradient. A second study found sleep-disordered breathing in 75% of individuals who received stable doses of opioids for at least six months.[16] There was a direct relationship between methadone and the apnea-hypopnea index, which was not found with other scheduled opioids. Benzodiazepines had an additive effect on the breathing disorders associated with methadone.

There are no guidelines for the management of sleep disorders associated with methadone. Traditional treatments with continuous positive airway pressure and bi-level positive airway pressure are often not effective.[19] Avoidance of methadone is the safest

Table 2
Precautions and Contraindications to Methadone Therapy

Risk Factor	Precaution	Contraindication	Applies to all Opioid Including Methadone	Applies Specifically to Methadone
Impaired liver function or liver failure	x		x	
Acute or unstable liver injury/damage	x (avoid use)		x (precaution)	x (contraindicated)
Active illicit drug use or misuse (cocaine, amphetamines, ephedrine, heroin, opioids)		x	x (overall risk)	x (additional risk of QTc prolongation)
Congenital QTc syndrome (patient or family)		x	(buprenorphine and methadone only)	x
Structural heart disease (congenital heart defects, history of endocarditis, or heart failure)[a]	x			x
Electrolyte abnormalities, or at risk for same (e.g., hypokalemia, hypomagnesemia)	x			x
Disordered breathing syndromes	x		x	
Paralytic ileus		x	x	

[a]See ECG monitoring section.

option for individuals with central or obstructive sleep apnea. Concurrent use of methadone and benzodiazepines should be avoided unless the benefit clearly outweighs the risk.[7,20–22]

History of Cardiovascular Disease

Risk of cardiac death on methadone is reversible by stopping the drug because methadone does not have a direct adverse effect on the myocardium.[23] A history of heart failure has been associated with an increased risk of a prolonged QTc interval with methadone use. Patients with heart failure in a palliative care program had an odds ratio of 11.9 (95% CI, 3.7–38.2) of having a prolonged QTC interval on methadone.[24] The authors of that retrospective study did not define congestive heart failure, and therefore, it is not clear whether this finding was based on echocardiographic criteria and reduction of ejection fraction or impaired diastolic dysfunction or on clinical presentation or history. However, congestive heart failure was an independent risk factor when correcting for methadone dose.

Congestive heart failure was one of the three independent risk factors for prolonged QTc interval in a separate study of patients on methadone maintenance.[25] A large epidemiological pharmacovigilance study conducted by addiction specialists found that individuals with cardiac disease were at significant risk for QTc prolongation on methadone.[26] The percentage of patients with arrhythmia and coronary artery disease could not be determined. Similarly, a population base nested case-control study of persons receiving methadone found that heart disease, defined as coronary artery disease or arrhythmia, was associated with 5.3-fold (95% CI 2.0–14.0) greater odds of opioid-related death.[10] In that study, individuals were relatively young (median age 42 years) and on methadone MAT.[10]

In patients with cancer pain, the median age is likely to be higher, with a greater prevalence of coronary artery disease and arrhythmia, potentially increasing the absolute risk of opioid-related death due to methadone. The SAMSHA guidelines recommend ECG monitoring for patients with a history of heart disease, preexisting arrhythmia, or unexplained syncope.[27] These recommendations for ECG interval monitoring are largely based on expert opinion and need prospective validation. There are no randomized trials of ECG interval monitoring for cardiac risk in patients on methadone, which validate its benefits in reducing mortality.[28]

Individuals with heart failure have a greater incidence of sleep disordered breathing[29] Methadone will worsen this and may cause nocturnal arrhythmias and hypoxia leading to sudden deaths unrelated to the QTc interval. The use of adaptive servoventilation in this group of patients actually increases mortality.[30]

Prolonged QTc Syndrome

Preexisting (before initiating methadone) QTc prolongation is relatively common and is usually asymptomatic.[27,31,32]

Many QTc-prolonging drugs commonly used in palliative medicine (such as haloperidol, olanzapine, ondansetron, tricyclic antidepressants, and citalopram) may potentiate the repolarization caused by methadone. The APS guidelines[3] recommend reconsideration of methadone use with a QTc interval between 450 and 500 ms and avoidance of methadone with a QTc above 500 ms. There is no consensus about the safe or clinically important upper limit or amount of change of the QTc interval in response to drug exposure, particularly in patients with serious illness. Considerations relevant to this population include the availability of ECG monitoring, prognosis, type of pain, and anticipated methadone total daily dose. Guidance from the HPC consensus group on ECG monitoring and action steps is shown in Table 3. Individuals who elect comfort measures may decline ECG monitoring.

Interacting Medications

Drug interactions with methadone can manifest as opioid receptor–mediated adverse effects, such as sedation or respiratory failure, or non–opioid receptor–mediated adverse effects, including QTc prolongation, TdP, and sudden cardiac death. Drug interactions can result in additive pharmacodynamic effects, such as increased risk of sedation and sleep-disordered breathing when using lorazepam (and other benzodiazepines) and methadone together.[16] The Food and Drug Administration Adverse Event Reporting System reported that 3.4% of methadone-induced harm was due to QTc prolongation and TdP combined, with a mean of 3.5 cases reported monthly.[30] Adding methadone to regimens containing other QTc interval-prolonging drugs increases the risk of QTc prolongation and TdP, especially with patients with multiple risk factors.[33] The most commonly reported concomitant medications were HIV antiretroviral medications, lorazepam, morphine, trimethoprim, and ceftriaxone accounting for ~42% of the drug interactions.[34] Most risk assessment has been extrapolated using case studies and pharmacokinetic modeling, which is the best guidance currently available to determine risk.[35] A complete list of medications that can prolong the QTc interval is available at https://crediblemeds.org/. Supplementary Table 1 highlights common pharmacodynamic drug interactions with methadone.

Numerous cytochrome P450 enzymes are involved in methadone metabolism; major enzymes include CYP2B6, CYP2C19, CYP3A4, and CYP2D6.[36–38] Of

Table 3
ECG Monitoring and Action Steps

Level of Vigilance	Goals of Care	Methadone Role	Baseline ECG	Follow-Up ECG
High	Curative, life-prolonging	First line	Obtain baseline ECG: • Positive risk factors[a] • Prior QTc >450 ms • History suggestive of prior ventricular arrhythmia Consider baseline ECG: • No risk factors • QTc <450 ms in the previous year Recommendation: • QTc >500 ms—do not use methadone • QTc 450–499 ms—consider alternate opioid (or correct reversible causes of QTc prolongation and reassess)	Obtain ECG within two to four weeks: • Positive risk factors • Prior ECG with QTc > 450 ms • History of syncope Obtain additional ECG: • TDD methadone reaches 30–40 mg • TDD methadone reaches 100 mg • New risk factors or signs/symptoms suggesting arrhythmia Recommendation: • QTc > 500 ms—switch to alternative opioid or reduce methadone dose • QTc 450–499 ms—consider switching to alternative opioid or reduce methadone dose
Moderate	Curative, life-prolonging	Second line	• Discuss risks and benefits with patient/family in light of goals of care	• Reinitiate discussion of risks/benefits if goals of care change
	Comfort measures only	First line	• Routine baseline ECG monitoring not recommended; may consider ECG depending on patient's risk status, wishes, and goals of care (e.g., curative) • Document informed consent if no ECG • If ECG obtained, follow recommendations above	• Routine follow-up ECG monitoring not recommended; may consider ECG depending on patient's risk status, wishes, and goals of care • Document informed consent if no ECG • If ECG obtained, follow recommendations above
Low	Comfort measures only	Second line	• No ECG unless compelling indication • If ECG obtained, follow recommendations above	• No ECG unless compelling indication • If ECG obtained, follow recommendations above

[a]Clinical risk assessment is always indicated and may alter recommendation for ECG monitoring. Risk factors include hypokalemia, hypomagnesemia, impaired liver function, structural heart disease (congenital heart defects, history of endocarditis, or heart failure), and genetic predisposition including patient or family history of congenital QTc syndrome, use of QTc-prolonging medications.[3]

these enzymes, CYP2B6 is primarily responsible for methadone levels and clearance.[37–41] Methadone is also a weak substrate for CYP2C8 and CYP2C9.[37,38] Medications that inhibit CYP2C19 and CYP2C8 contribute to an increased risk of respiratory depression and mu-opioid receptor–mediated side effects, whereas medications that inhibit CYP3A4, CYP2B6, or CYP2D6 contribute to increased risk of TdP and respiratory depression.[37,38] An example of nonmedication interaction is cigarette smoking, which can induce CYP2B6.[42] Smoking cessation returns CYP2B6 to normal levels, causing a higher concentration of methadone.[43] Pharmacogenetics complicate methadone pharmacokinetics because genetic polymorphisms result in a range of variable phenotypes from poor to ultrarapid metabolizers. CYP2B6 has been associated with numerous allelic variants, including 16 variants that result in no or reduced CYP2B6 expression and/or activity, higher methadone levels, and prolonged elimination.[44] CYP2B6 polymorphisms occur in a variable ethnic distribution.[36,40,45,46]

The panel made these recommendations a comprehensive patient-specific risk evaluation and routine review of medication regimens to assess the following:

- Initiation or discontinuation of medications that may impact methadone levels (Table 4).
- Initiation or discontinuation of medications that may have additive clinical effects to methadone, such as sedation, disordered breathing, and QTc interval prolongation.

Methadone Dosing Considerations

Dosing in Opioid Naïve (Nonopioid Tolerant) Patients. Patients generally begin methadone therapy by converting from a different opioid; however, in the hands of experienced practitioners, it may be considered in opioid-naïve patients with moderately severe pain. The European Association for Palliative Care recommends that methadone may be used as a Step III opioid under these circumstances.[47]

According to the APS guideline, the initial dose of methadone in opioid-naïve patients should not exceed 7.5 mg oral methadone daily in the management of pain (e.g., 2.5 mg by mouth three times daily).[3] Those guidelines also include patients receiving up to 40–60 mg per day of oral morphine equivalents. Salpeter demonstrated that the use of low-dose methadone (median dose titrated to 5 mg per day) in both home-based hospice patients and hospitalized patients provided excellent pain control.[48,49]

Table 4
Drug Therapy Modification for Patients on Stable Methadone Dose

Desired Modification	Recommendation
Initiating an inducer	Monitor carefully for increased pain or withdrawal symptoms. Provide breakthrough opioid for pain.
Discontinuing an inducer	Empirically reduce methadone dose by 25%–33%, monitor carefully, and use generous breakthrough (consensus recommendation).
Initiating an inhibitor	Empirically reduce methadone dose by 25% and monitor carefully.
Discontinuing an inhibitor	Monitor carefully for increased pain or withdrawal symptoms. Provide breakthrough opioid for pain.

The HPC consensus group largely agreed with the APS recommendation, explicitly recommending a dosage range of 2 to 7.5 mg oral methadone per day. This specifically allows for very low dose methadone such as 1 mg by mouth twice daily as a starting dose. The APS and HPC guidelines agree that the dose should not be increased before five to seven days and should not be increased by more than 5 mg/day. Methadone has a long and unpredictable half-life of elimination (ranges from 5–130 hours, with a mean of 20–35 hours[50]). Allowing five to seven days before adjusting the dose allows for most patients to achieve steady state, but this may take longer in some patient populations.

Dosing in Opioid-Tolerant Patients

When switching from other opioids to methadone, the HPC guidelines suggest the following conversions, which take into account the potential for incomplete cross-tolerance and are based on expert consensus, given variability in published methadone dose conversion ratios:

- <60 mg oral morphine per day or equivalent (OME)—refer to opioid-naïve dosing;
- 60–199 mg OME and patient < 65 years of age—10:1 conversion (10 mg OME:1 mg oral methadone);
- ≥ 200 mg OME and/or patient > 65 years of age—20:1 conversion (20 mg OME:1 mg oral methadone).

In addition, the APS and HPC guidelines recommend converting to a methadone dose no greater than 30–40 mg per day regardless of the previous opioid dose[3]. The dose should not be increased before five to seven days and should not be increased by more than 5 mg/day up to 30–40 mg/day, then can be increased by 10 mg/day (after five to seven days). For clinicians experienced in using methadone, a more aggressive titration method has been used and may be feasible in a closely monitored environment.

Switching From Opioid Addiction Methadone Maintenance Therapy to Methadone Analgesia

Methadone is dosed once daily when used as an opioid agonist therapy to treat those recovering from SUD because it blocks opioid craving for 24–36 hours.[51,52] Methadone is generally dosed two or three times daily for pain because the duration of analgesia ranges from six to 12 hours.[53] Methadone maintenance patients require more frequent dosing to manage pain and may need a higher dose because of a high level of opioid tolerance.[54] If the patient is unable to continue receiving care from the methadone maintenance clinic (e.g., a patient admitted to hospice), a common clinical strategy is to administer the total daily dose in three divided doses and titrate the dose up as needed. It is important to advise the methadone clinic that the patient is no longer able to return and to clearly document in the medical record that the methadone is being used for pain management and to maintain abstinence.

Methadone as an Adjuvant Analgesic

Patients with a serious illness may experience opioid dosage escalation due to a variety of potential reasons, including disease progression, tolerance to the analgesic effects of opioid therapy, or development of opioid-induced hyperalgesia.[55] In cases of poorly responsive neuropathic pain, or with the development of tolerance or opioid-induced hyperalgesia, use of an N-methyl-D-aspartate receptor antagonist such as methadone may be beneficial,[56] although evidence is sparse and not of high quality. This may be a particularly useful strategy in cases where the patient's life expectancy is shorter than the time to steady state. Courtemanche and colleagues[57] evaluated the impact on pain control in 146 cancer pain patients receiving chronic opioid therapy. The median oral morphine dose was 120 mg per day, and a median dose of 3 mg oral methadone was added to the medication regimen. Results showed that 72 of the 146 patients (49.3%) had at least a 30% reduction in pain intensity, with a median time of seven days to first significant response.

Wallace and colleagues[58] evaluated the addition of oral methadone to the opioid regimen of 20 cancer patients in an outpatient palliative care clinic. The mean daily routine oral morphine equivalent was 338 ± 217.8 mg/day at initiation of the study, and 332 ± 191 mg/day at evaluation (one-month evaluation or closest available Edmonton Symptom Assessment Scale). The mean dose of

methadone at initiation was 4.4 ± 1.4 mg/day, and 15.5 ± 5.9 mg/day at evaluation. Eight patients (40%) achieved a decrease in pain score of two or more points at one month, and an additional seven patients (35%) had a decrease in pain score of two or more points at the closest available point in time. Additional research is needed in this area to determine optimal strategies for using methadone as an adjuvant.

Methadone and Alternate Routes of Administration

Methadone is commonly administered orally, but palliative care patients often require alternate routes of administration. Methadone can be administered through several different routes, allowing clinicians to conveniently maintain long-acting analgesia for patients unable to swallow. Methadone is highly lipophilic and has an oral bioavailability of 80%, making sublingual administration oral concentrated solution (10 mg/mL) a commonly well tolerated first-line alternative with absorption rates of 35% to 75% depending on pH.[59–61] Dosing may be modified to limit the volume of liquid administered. For example, volumes in excess of 1.5 mL may be divided into both buccal cavities, or smaller doses may be administered more frequently. The lipophilicity of methadone is also conducive to effective rectal administration, but this is not commonly done in practice.[62] Intravenous methadone requires decreasing the dose by 50% (oral: parenteral ratio, 2:1), which is conservative considering the 80% bioavailability. Conversion from parenteral to oral methadone should be 1:1.3 (parenteral:oral), based on clinical practice and oral bioavailability.[63] The risk of QTc prolongation is greater with parental methadone due to the inclusion of the solvent chlorobutanol. Therefore, additional electrocardiographic monitoring should be considered in this setting. Solvent-free parenteral preparations are extremely expensive and are generally reserved for neuraxial use.[64] Subcutaneous administration of methadone has been reported in a few small studies.[65–67] Although subcutaneous administration is generally well tolerated in volumes less than 3 mL/hour, there are risks of local toxicity (such as erythema and induration).[65–67] The risks can be mitigated using concurrent infusions of dexamethasone or hyaluronidase, frequent injection site changes, flushing the site with normal saline, and limiting dose[65–67] Spinal methadone rapidly distributes to systemic circulation and has little to offer in advantages over oral or parenteral methadone.[68,69]

Patient Monitoring

A systematic approach is necessary to monitor patients on methadone for adverse effects and response to therapy. Patients on methadone should be monitored for therapeutic response, adverse reactions, home environment oversight accountability, and outcomes of risk mitigation strategies as appropriate.

Recommendations exist to advise clinicians on ECG monitoring in chronic pain patients and in managing opioid addiction. However, the risk-benefit profile differs in patients with serious illness. The HPC consensus group recommended additional considerations to account for the proarrhythmic risks associated with monitoring methadone use in patients with serious illness (Table 3). Three categories of monitoring vigilance were identified based on the patient's goals of care (curative vs. comfort) and the role of methadone (first line or second line).

- High level of vigilance (patients using methadone as a first-line therapy, with curative goals of care): ECG monitoring per APS guidelines is indicated.[3]
- Moderate level of vigilance (patients using methadone as a first-line therapy with comfort-based goals of care and patients using methadone as a second-line therapy with curative goals of care).
- Low level of vigilance (patients using methadone as a second-line therapy with comfort-based goals of care).

Immediately after initiation or titration of methadone, intensive monitoring for opioid-related side effects such as sedation should be carried out for a minimum of five to seven days.[70–73] This interval may need to be increased to 10–14 days in older adults or in patients where it will likely take longer to achieve steady state (e.g., in liver disease) due to the long and unpredictable elimination half-life of methadone. One commonly overlooked monitoring indicator is the initiation or cessation of medications that interact with methadone, such as antidepressants, anti-infective agents, or amiodarone. The entire caregiving team should be educated and involved in the monitoring process, supported by protocols and guidelines to facilitate comprehensive monitoring including standard assessment scales. A sample protocol is shown in Supplementary Table 2. If the patient is in a home setting, the panel recommends daily in-person assessments by the clinical team for toxicity and therapeutic response. If there is a dependable caregiver in the home and in-person visits are not possible or practical, it can be acceptable to communicate daily during the intensive monitoring phase. With symptoms of overdose, methadone doses should be held until the patient is assessed by a clinician to ensure that symptoms of overdose are not misinterpreted as signs that the patient is actively dying (e.g., change in arousal, breathing pattern changes). Low-dose naloxone may be administered, but care should be taken to avoid full opioid reversal and reoccurrence of pain.

Employing risk mitigation strategies is an essential component of universal precautions when opioids are prescribed for chronic pain. Patients with serious illness may also suffer from concomitant substance use disorder or they may misuse or divert opioids. Treatment agreements and urine drug testing (UDT) are not always practical strategies for patients in the terminal phase of serious illness. Useful strategies include using a locked medication storage box, designating one caregiver to administer medications, and using an alternate route of administration as well as those listed previously. If UDT is warranted in a palliative care setting, one that is able to detect synthetic opioids (enzyme-mediated immunoassay is not useful in detecting methadone for that reason) should be ordered, such as gas chromatography/mass spectrometry, liquid chromatography tandem mass spectrometry, or high-performance liquid chromatography UDT.[74–76] These tests can distinguish drugs from the same class (such as methadone vs. oxycodone) as well as metabolites, including the primary metabolite of methadone 2-ethylidene-1,5-dimethyl 1-3,3-diphenylpyrrolidine.[77,78] The provider should be aware of substances that can cause false-positive results, such as quetiapine and diphenhydramine.[79–82] Although methadone is included in prescription drug monitoring programs when prescribed for pain, prescription drug monitoring programs do not typically include methadone when provided for an addiction treatment program. Federal facilities such as Veterans Affairs Administration are not currently required to submit data, but many participate voluntarily.

Patient, Family, and Caregiver Education

The panel emphasized the importance of an informed patient and caregiver as the most important factors for safe use of methadone.[83] Written and oral education should be provided including all key elements of methadone education, which can be found in Supplementary Table 3[84]:

Caregivers should have an action plan, which in some settings may include use of naloxone, for findings of concern such as pinpoint pupils and sedation, confusion, or change in arousal. This plan typically includes calling the hospice or palliative providers immediately and holding doses of methadone until symptoms resolve. Patients should be advised not to abruptly stop taking methadone because this may provoke withdrawal symptoms. Hospice and palliative providers should be engaged in closely monitoring patients for three to five days after methadone initiation or with dose increases because most methadone overdose deaths occur during this period.[70–73] As with all opioids, patients and families must be warned to avoid alcohol and sedatives, without talking to their health care provider. It is also important to provide information about safe storage and disposal.[85] The patient and the caregivers must be instructed to store opioids out of plain sight and preferably in a lock box. Particularly in patients with limited life expectancy or those with unused methadone, the HPC consensus group recommends addressing methods of safe disposal such as taking it to medication take-back programs, flushing down the toilet, mixing with unpalatable substances (such as coffee grounds, cat litter) and disposing in the trash, or other recommended methods from the U. S. Food and Drug Administration.[27] Counseling must be provided against sharing medication with others because of risk of overdose.

Conclusion

Methadone can be a valuable opioid in the hospice and palliative care provider's armamentarium to treat pain in serious illness. However, it is critically important that health care providers be informed about the unique pharmacokinetic and pharmacodynamic properties of methadone. Careful consideration of appropriate candidates for methadone and attention to detail in dosing and monitoring the patient's response to therapy are essential components of care. The consensus group was able to develop guidance for hospice and palliative care practitioners that aim to maximize benefit and minimize risks of methadone therapy in patients with serious illness, with an appropriate degree of patient monitoring.

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Supplemental Table 1

Medications With Potential to Impact Methadone Levels[a]

Drug	Net Effect on Methadone Level	Effect on Major Metabolic Enzymes			Effect on Minor Metabolic Enzymes			Effect on QTc interval[b]/TdP[c] Reported With Concomitant Methadone Use
		CYP2B6	CYP2C19	CYP3A4	CYP2D6	CYP2C9	CYP2C8	
Anti-infectives								
Amprenavir	↑			↓↓↓				
Atazanavir	–[d]			↓↓↓				Possible[c]
Azithromycin								Risk[c]
Boceprevir	↑			↓↓↓				
Ciprofloxacin	↑			↓				Risk[c]
Clarithromycin	↑			↓↓↓				Risk[c]
Cobicistat	–[e]			↓↓↓	↓			
Delavirdine	↑			↓	↓↓↓			
Efavirenz	↓			↑↑				
Erythromycin	↑			↓↓				Risk[c]
Fluconazole	↑		↓↓↓	↓↓		↓↓		Risk
Nevirapine	↓	↑↑↑						
Efavirenz	↓	↑	↓↓	↑↑		↓↓	↓↓	
Isavuconazonium sulfate	↑		↓	↓↓	↓			
Isoniazid	↑		↓↓	↓	↓↓	↓		
Itraconazole	↑			↓↓↓				Conditional[c]
Ketoconazole	↑	↓	↓↓	↓↓↓	↓↓	↓↓	↓	Conditional
Levofloxacin								Risk[c]
Posaconazole	↑			↓↓↓				Conditional
Ritonavir	↓	↑↑↑	↓↑	↓↓↓	↓↓	↓↑	↓↓	Conditional[c]
Rifampin	↓	↑↑↑	↑↑↑	↑↑↑		↑↑↑	↑↑↑	
Saquinavir	↓[e]	↓		↓↓↓	↓	↓		Possible
Terbinafine	↑				↓↓↓			
Tipranavir	↓[e]				↓↓↓			
Voriconazole	↑	↓↓	↓↓	↓↓↓		↓↓		Conditional[b]
Central nervous system								
Alprazolam	↑			↓				
Amitriptyline								Conditional
Aripiprazole								Possible
Asenapine	↑				↓			Possible
Buprenorphine	↑		↓↓		↓↓			
Bupropion	↑				↓↓↓			
Carbamazepine	↓	↑↑↑	↑↑↑	↑↑↑		↑↑↑	↑↑↑	
Chlorpromazine	↑				↓↓			Risk
Citalopram	↑	↓	↓		↓			Risk
Clomipramine	↑				↓↓			Possible
Clozapine								Possible
Cocaine	↑				↓↓↓			Risk[c]
Desipramine	↑	↓↓			↓↓			Possible
Dexmedetomidine								Possible
Diazepam	↑		↓					
Doxepin								Possible[c]
Droperidol								Risk[c]
Duloxetine	↑				↓↓			
Escitalopram	↑				↓			Risk
Fluoxetine	↑	↓	↓↓		↓↓↓	↓		Conditional[c]
Fluvoxamine	↑	↓	↓↓↓	↓	↓	↓		Conditional[c]
Haloperidol	↑				↓↓			Risk
Imipramine								Possible
Midazolam	↑					↓	↓	
Mirtazapine								Possible
Modafinil	↓	↑	↓↓	↑↑		↓		
Nefazodone	↑	↓		↓↓↓	↓		↓	
Nortriptyline								Possible
Olanzapine								Possible
Paroxetine	↑	↓↓	↓		↓↓↓	↓		Conditional[c]
Phenytoin	↓	↑↑↑	↑↑↑	↑↑↑		↑↑↑	↑↑↑	
Phenobarbital	↓	↑↑↑		↑↑↑		↑↑↑	↑↑↑	
Primidone	↓	↑↑↑		↑↑↑		↑↑↑		
Quetiapine								Conditional[c]
Risperidone								Possible

(*Continued*)

Supplemental Table 1
Continued

Drug	Net Effect on Methadone Level	Effect on Major Metabolic Enzymes			Effect on Minor Metabolic Enzymes			Effect on QTc interval[b]/TdP[c] Reported With Concomitant Methadone Use
		CYP2B6	CYP2C19	CYP3A4	CYP2D6	CYP2C9	CYP2C8	
Sertraline	↑	↓↓	↓↓	↓	↓↓	↓	↓	Conditional[c]
Thioridazine								Risk
Tizanidine								Possible
Trazodone								Conditional
Venlafaxine								Possible
Ziprasidone								Conditional[c]
Cardiovascular								
Amiodarone	↑		↓	↓	↓↓	↓↓		Risk[c]
Clopidogrel	↑	↓↓				↓	↓↓↓	
Diltiazem	↑			↓↓	↓	↓		
Furosemide								Conditional[c]
Hydrochlorothiazide								Conditional
Indapamide								Conditional
Nicardipine	↑		↓↓	↓	↓↓	↓↓↓		Possible
Nifedipine	↑			↓	↓	↓		
Ticlopidine	↑	↓↓	↓↓↓		↓↓	↓		
Torsemide								Conditional
Verapamil	↑			↓↓	↓	↓		
Chemotherapeutics								
Abiraterone	↑		↓↓		↓↓	↓↓	↓	
Anastrozole	↑					↓	↓	
Doxorubicin	↑	↓↓			↓			
Imatinib	↑			↓↓	↓	↓		
Endocrine								
Estradiol	↓	↑					↑	
Gastrointestinal								
Cimetidine	↑		↓↓	↓	↓↓	↓		
Esomeprazole	↑		↓↓					
Lansoprazole	↑		↓		↓	↓		
Omeprazole	↑		↓↓		↓	↓↓		
Pantoprazole	↑		↓					Conditional
Ranitidine	↑				↓			
Famotidine								Conditional
Anti-emetics								
Aprepitant	↑		↓	↓↓		↑↑↑		
Dolasetron								Possible
Granisetron								Possible
Metoclopramide								Conditional
Ondansetron								Risk[c]
Other								
Celecoxib	↑				↓↓		↓↓	
Chlorpheniramine	↑				↓			
Cinacalcet	↑				↓↓↓			
Clemastine	↑				↓			
Cyclosporine	↑			↓		↓		
Darifenacin	↑				↓↓			
Dexamethasone	=/↓	↑		↑		↑	↑	
Diphenhydramine	↑				↓↓			Conditional
Grapefruit juice	↑			↓↓↓				
Hydroxyzine	↑				↓			Conditional
St. John's Wort (hypericum perforatum)	↓		↑↑	↑↑↑				

[a]The table describes the major CYP450 enzyme interactions and identifies those with QTc risk. ↑, inducer; relative strength weak, ↑, moderate, ↑↑, or strong↑↑↑. ↓, inhibitor; relative strength weak, ↓, moderate, ↓↓, strong, ↓↓↓. A weak inhibitor causes a >1.25-fold but <2-fold increase in the plasma AUC values or 20% −50% decrease in clearance. A moderate inhibitor causes a > 2-fold increase in plasma AUC values or 50% to 80% decrease in clearance. A strong inhibitor causes a > 5-fold increase in plasma AUC values or more than 80% decrease in clearance. (FDA) Classification of inducers is not as clearly defined owing to a history of methodological variability in the pharmaceutical industry.[86–88] Therefore, literature was reviewed for each medication, and the consensus qualifier was used to define weak, moderate, or strong effect using relative induction score, if available.[89] QTc risk definitions: Risk, substantial evidence supports the conclusion that these drugs prolong the QTc interval and are clearly associated with a risk of TdP, even when taken as directed in official labeling; possible, substantial evidence supports the conclusion that these drugs can cause QTc interval prolongation but there is insufficient evidence that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP; conditional, substantial evidence supports the conclusion that these drugs are associated with a risk of TdP but only under certain conditions (e.g., excessive dose, hypokalemia, or congenital long QTc interval or by causing a drug-drug interaction that results in excessive QTc interval prolongation).[90]
[b]Definitions from CredibleMeds.org.[90]
[c]Evidence reports TdP with concomitant methadone use.
[d]No effect on methadone levels.[91]
[e]Boosted with ritonavir: net effect is lower levels.

Supplemental Table 2
Suggested Methadone Monitoring Protocol

Monitoring Parameter	Day 0[a]	Day 1	Day 2	Day 3	Day 4	Day 5[b]
Therapeutic effectiveness						
Pain rating (0–10)—best in past 24 hours						
Pain rating (0–10)—worst in past 24 hours						
Pain rating (0–10)—average in past 24 hours						
No. of doses of opioid for breakthrough pain						
Able to perform ADLs?						
Potential toxicity (new or worsening): RAPS						
R—RR; respirations slowed or irregular/apnea, snoring (assess respirations for 60 seconds)						
A—altered mental status or vision (e.g., hallucinations or nightmares)						
P—pupils, palpitations/lightheadedness						
S—sedation scale rating						
General opioid adverse effects (constipation, nausea, urinary retention, itching, dry mouth, myoclonus (drug-induced movement disorder)						
Additional monitoring (as appropriate):						
Changes in other prescription and nonprescription medications						
Prescription drug monitoring program update						
Patient's ability to swallow						
Informal caregiver reliability/living situation						
Substance misuse and chemical coping risk (patient and family)						
Risk mitigation strategies as appropriate (urine drug screens, opioid agreement, pill count, etc.)						

[a]Day 0, patient status before first dose of methadone. Day 1, patient status 24 hours after beginning methadone, and so on.
[b]Continue as needed.

Supplemental Table 3

Elements of Methadone Education

- The importance of taking methadone exactly as prescribed and reporting any changes in other medications immediately
- The need for communication about changes in patient's home and psychosocial situation
- Understanding of opioid-related side effects and risks, especially those that may be more specific to methadone (e.g., QTc prolongation)
  - Allergic reaction to methadone may manifest as troubled breathing, itching, and hives and requires immediate medical attention.
  - Constipation is a very common and easily preventable side effect. It is important to use the prescribed prophylactic bowel regimen to prevent opioid-induced constipation.
  - Nausea and vomiting may accompany opioid use, especially in the first few days or weeks of initiation of methadone. An antiemetic may be prescribed for use in case of nausea and vomiting.
  - Mild sedation may accompany initiation or uptitration of methadone. This effect usually resolves within a few days.
  - Symptoms suggestive of arrhythmia may include palpitations, lightheadedness, and syncope.
  - Opioid-induced neurotoxicity (excessive sedation, confusion, myoclonus, and hallucination), vivid dreams, and respiratory depression may occur. The patient should be instructed to stop methadone dosing and seek medical help immediately.