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Methadone Safety Guidelines

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Abstract: Methadone is used for the treatment of opioid addiction and for treatment of chronic pain. The safety of methadone has been called into question by data indicating a large increase in the number of methadone-associated overdose deaths in recent years that has occurred in parallel with a dramatic rise in the use of methadone for chronic pain. The American Pain Society and the College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, commissioned an interdisciplinary expert panel to develop a clinical practice guideline on safer prescribing of methadone for treatment of opioid addiction and chronic pain. As part of the guideline development process, the American Pain Society commissioned a systematic review of various aspects related

Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. As part of a shared decision-making approach, it may be appropriate for the clinician to inform a patient that a particular recommendation may not be applicable, after considering all circumstances pertinent to that individual.

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A list of authors with disclosed conflicts of interest is shown in Appendix 1.
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to safety of methadone. After a review of the available evidence, the expert panel concluded that measures can be taken to promote safer use of methadone. Specific recommendations include the need to educate and counsel patients on methadone safety, use of electrocardiography to identify persons at greater risk for methadone-associated arrhythmia, use of alternative opioids in patients at high risk of complications related to corrected electrocardiographic QTc interval prolongation, careful dose initiation and titration of methadone, and diligent monitoring and follow-up. Although these guidelines are based on a systematic review, the panel identified numerous research gaps, most recommendations were based on low-quality evidence, and no recommendations were based on high-quality evidence.

***Perspective:** This guideline, based on a systematic review of the evidence on methadone safety, provides recommendations developed by a multidisciplinary expert panel. Safe use of methadone requires clinical skills and knowledge in use of methadone to mitigate potential risks, including serious risks related to risk of overdose and cardiac arrhythmias.*

Key words: *Clinical practice guideline, methadone, safety, chronic pain, opioid addiction.*

Dear Reader,

The development of guidelines is a complex and costly enterprise. Funding is increasingly reliant on providing impact and outcome data. The American Pain Society requests your assistance in evaluating the impact of the Methadone Safety Guideline. Please follow this link (http://www.surveygizmo.com/s3/1548754/APS-Methadone-Survey) to complete a brief questionnaire before reading the guideline. The survey consists of 11 multiple-choice questions and should take no more than a few minutes.

We also seek readers willing to take a follow-up survey (see instructions at the end of this survey). These data will assist the APS in developing data on guideline impact and thus assist us in securing and determining allocation of funding in the future. We are offering a token incentive for your participation.

Thank you for your cooperation.

Clinical Practice Guidelines Committee
American Pain Society

Methadone is a synthetic opioid used for the treatment of opioid addiction and for treatment of chronic pain.[15,61] The safety of methadone has been called into question by data indicating a large increase in the number of methadone-associated overdose deaths.[38] This increase appears largely related to the dramatic rise in the use of methadone for chronic pain, though a small proportion of deaths occur in patients treated for opioid addiction.[21,37,68,76,91,103] Methadone poisoning deaths in the United States increased steadily from about 800 in 1999 to a high of about 5,500 in 2007; there was a decrease to about 4,900 in 2008.[101] The rate of increase in mortality has been substantially larger than for any other opioid.[32] About 1 of every 3 opioid-related deaths is associated with methadone ingestion, a substantially higher proportion than any other opioid.[11] Although this guideline focuses on methadone, clinicians should also be aware of the overall rise in morbidity and mortality due to other prescription opioids.

The interpretation of data on methadone-associated deaths is complicated by a number of factors, including increased surveillance, differentiating prescribed versus nonprescribed use of methadone, effects of other potential contributing factors (such as use of other medications and substances), and uncertainty regarding the degree to which increases in deaths are proportionate to increased prescribing. Ascribing cause of methadone-associated death is a particular challenge. In the vast majority of cases, it is not possible to determine whether the death occurred as a result of respiratory depression related to overdose or to other factors, such as arrhythmia. Nonetheless, it is widely acknowledged that the pharmacology of methadone may be associated with unique safety concerns. This pharmacology includes a long and variable half-life, potential interactions with multiple medications, variability in equianalgesic dose ratios depending on dose, and association with prolongation of the corrected electrocardiographic QT (QTc) interval, which may predispose patients to the ventricular arrhythmia torsades de pointes.[5,45,58,66,67,69,85,89] Data from the Food and Drug Administration's (FDA's) Adverse Event Reporting System indicate that since 2000, methadone was the second most commonly suspected primary cause of drug-related arrhythmia, after dofetilide.[51] The proportion of methadone-associated deaths related to arrhythmia is likely to be small relative to the proportion related to accidental overdose, though reliable estimates are not available.

Three previous guidelines published between 2008 and 2011 addressed methadone safety, each focusing on prevention of cardiac arrhythmias due to the association between methadone and prolonged QTc interval seen on electrocardiogram (ECG).[60,70,92] Two of these guidelines were not fully endorsed by a professional society or government entity[60,92]; the third was endorsed by the Substance Abuse and Mental Health Services Administration.[72] Although systematic literature reviews were conducted for these guidelines, a limitation is that none graded the strength of the recommendations or the quality of the evidence supporting the recommendations. In addition, they did not address methadone safety issues other than cardiac arrhythmias.

The American Pain Society (APS) and the College on Problems of Drug Dependence (CPDD), in collaboration with the Heart Rhythm Society (HRS), commissioned an interdisciplinary panel to develop a clinical practice guideline on safer prescribing of methadone for treatment of opioid addiction and chronic pain. As part of the guideline development process, APS commissioned a systematic review on various aspects related to safety of methadone.[17]

Methods

Panel Composition

The APS and CPDD convened a panel of 16 members with expertise in pain, addiction medicine, cardiology, primary care, nursing, palliative care, pharmacology, adolescent medicine, obstetrics and gynecology, epidemiology, and social work to review the evidence and formulate recommendations on methadone safety (see Appendix 1 for list of panel members). Two cochairs (R.A.C. and D.A.F.) were selected by the APS and CPDD to lead the panel, which also included the APS Director of Clinical Guidelines Development (R.C.). The HRS was invited to join the guideline development process after cochair and initial panel selection had taken place, and it appointed 2 members with expertise in arrhythmia (M.C.H. and D.M.) to the panel.

Target Audience and Scope

The intent of the Guideline is to provide, where possible, evidence-based recommendations for use of methadone in persons of all ages (including pregnant women) for treatment of chronic pain in primary care or specialty settings or for treatment of opioid addiction in licensed opioid treatment programs. The target audience is all clinicians who prescribe methadone. Methadone is not approved by the FDA for use in acute or postoperative pain, and its off-label use for these indications is outside the scope of this guideline, as is illicit use.

Funding and Conflicts of Interest

Funding for the Guideline was provided by the APS. The Guideline was approved by APS and CPDD, but the content of the Guideline is the responsibility of the authors and panel members. All panelists were required to disclose conflicts of interest within the preceding 5 years at all face-to-face meetings and prior to submission of the Guideline for publication, and to recuse themselves from votes if a conflict was present. Conflicts of interest of the authors and panel members are listed in Appendix 1.

Evidence Review

This Guideline is informed by a systematic evidence review that addressed a variety of topics related to methadone safety conducted at the Oregon Evidence-based Practice Center and commissioned by APS and CPDD.[17] With the Oregon Evidence-based Practice Center, the panel developed the key questions, scope, and inclusion criteria used to guide the evidence review. Literature searches were conducted in multiple electronic databases from their start date through July 2012. An update search was performed in January 2014 for new studies on methadone-related overdose and arrhythmia. Details about the methods used to conduct the review, including complete search strategies, are available in the full report.[17] Investigators reviewed 3,746 abstracts from electronic databases, reference lists, and suggestions from expert reviewers. Two systematic reviews and 168 primary studies (not included in previously published systematic reviews) were included in the evidence report.[17]

Grading of the Evidence and Recommendations

The panel used methods adapted from the Grading of Recommendations Assessment, Development, and Evaluation Working Group to rate the recommendations included in this Guideline.[40] Each recommendation received a separate grade for the strength of the recommendation (strong or weak) and for the quality of evidence (high, moderate, or low) (Appendix 2). In general, a strong recommendation is based on the panel's assessment that the potential benefits of following the recommendation clearly outweigh potential harms and burdens, or that the potential harms clearly outweigh potential benefits. Given the available evidence, most clinicians and patients would choose to follow a strong recommendation. A weak recommendation is based on the panel's assessment that benefits of following the recommendation outweigh potential harms and burdens (or vice versa), but the balance of benefits to harms or burdens is smaller or evidence is weaker. Decisions to follow a weak recommendation could vary depending on specific clinical circumstances or patient preferences and values. For grading the quality of a body of evidence that supports a recommendation, we considered the type, number, size, and quality of studies; strength of associations or effects; and consistency of results among studies.[41] The quality of evidence indicates the level of certainty in the recommendation and the likelihood that future research could change recommendations. A recommendation based on low-quality evidence has a high probability of being affected by new evidence, and a recommendation based on high-quality evidence has a low probability. Strong recommendations based on low-quality evidence indicate that until better evidence becomes available, the panel determined that the benefits of following the recommended course of action clearly outweigh harms. In some cases, recommendations based on low-quality evidence are followed by "practice advice" with more specific suggestions for implementing the recommendation in clinical practice, based on panel consensus.

Guideline Development Process

The Guideline panel met in person in May 2010 and July 2011. At the first meeting, the panel developed the scope and key questions used to guide the systematic evidence review. At the second meeting, the panel reviewed the results of the evidence review and drafted initial potential

recommendation statements. Following the second meeting, additional draft recommendation statements were proposed. The panelists then participated in a multistage Delphi process, in which each draft recommendation was ranked on clinical importance and usefulness, and revised. At each stage of the Delphi process, the lowest-ranked recommendations were eliminated. A two-thirds majority was required for a recommendation to be approved. However, unanimous or near-unanimous consensus was achieved for all recommendations. After finalization of the recommendations, the Guideline was written by various panel members and drafts distributed to the panel for feedback and revisions. More than 20 external peer reviewers from multiple clinical and scientific disciplines and professional societies were solicited for additional comments. After another round of revisions and panel approval, the Guideline was approved by the APS Board of Directors on May 7, 2013, and by the CPDD Board of Directors on November 5, 2013.

The APS intends to update its clinical practice guidelines regularly. This Guideline and the evidence report used to develop it will be reviewed and updated by 2018, or earlier if critical new evidence becomes available.

The panel formulated the recommendations to be generally applicable across age groups, though the great bulk of evidence was in adult populations. Recommendations were also developed to be applicable to methadone prescribing for treatment of both opioid addiction and chronic pain, unless otherwise noted.

Recommendations

Patient Assessment and Selection

- When considering initiation of methadone, the panel recommends that clinicians perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile (strong recommendation, low-quality evidence).

  Proper patient selection is critical when considering the use of any opioid, whether for chronic pain or treatment of addiction.[16] This requires a comprehensive benefit-to-harm evaluation based on a thorough history, review of records, and physical examination. Opioid therapy generally is considered the mainstay in the treatment of chronic moderate or severe pain associated with active cancer or at end of life. In contrast, for other types of chronic noncancer pain, opioids are usually considered after other reasonable pain management strategies have proved ineffective. In all populations, opioids should be considered only in the context of information that weighs the potential beneficial effects of prescribed opioids against risks, including those related to their potential for abuse, addiction, diversion, overdose, relapse (for patients treated for addiction), and other adverse events. The assessment should include evaluation of biomedical, psychosocial, and cultural issues that may affect use of and adherence to methadone treatment. An American Pain Society–American Academy of Pain Medicine (APS-AAPM) Guideline provides additional details on patient assessment and selection when opioid therapy is under consideration for chronic pain.[16] This Guideline recommends that clinical findings or the results of specific assessment tools be used to stratify patients according to the assessed risk of substance abuse outcomes, and that this assessment be used in deciding whether to proceed with a trial of an opioid.

  Once a decision is made to undertake a trial of long-term opioid therapy for pain, or to continue treatment that has provided benefit, a second analysis is needed to determine whether methadone may be an appropriate analgesic. This assessment is informed by many factors, as described below. When methadone is considered for the treatment of opioid addiction, other factors are considered, such as the level of physical dependence, presence of a structured environment, involvement in ongoing treatment and recovery activities, patient stability, prior experience with addiction treatments, concurrently prescribed medications, other drug abuse, current comorbidities, and patient preferences for opioid therapy. When treating patients with chronic pain, given the availability of alternatives, clinicians should always consider whether another opioid may be a more appropriate therapy, when an opioid is indicated.

  The necessity for additional evaluation concerning the specific use of methadone for pain and addiction is based on unique pharmacologic properties that can affect determinations of benefits relative to risks, which include a long and variable half-life, numerous drug-drug interactions (including alcohol), and effects on the electrocardiographic QTc interval and respiratory depression. For example, a patient otherwise assessed as an appropriate potential candidate for opioid treatment who is taking a medication with potential methadone interactions or has risk factors for QTc interval prolongation or known QTc interval prolongation may be more appropriately treated with an alternative opioid (see below).[45,58,67,69]

Patient Education and Counseling

- The panel recommends that clinicians educate and counsel patients prior to the first prescription of methadone about the indications for treatment and goals of therapy, availability of alternative therapies, and specific plans for monitoring therapy, adjusting doses, potential adverse effects associated with methadone, and methods for reducing the risk of potential adverse effects and managing them (strong recommendation, low-quality evidence).

  As with any other opioid, clinicians should counsel patients about potential risks and benefits before initiating a trial of methadone. During treatment, clinicians should periodically review risks and benefits of therapy. An APS-AAPM guideline on opioid therapy for chronic pain provides additional details regarding suggested elements of patient education in the setting of pain management, as well as a sample informed consent form.[16]

In addition to common opioid-related adverse events, clinicians should discuss specific risks associated with methadone and factors that may be associated with overdose.[32,38] These include methadone's long and variable half-life, the potential association between use of methadone and QTc interval prolongation and cardiac arrhythmia, and the potential for drug-drug interactions.[45,58,67,69] Patients should be specifically informed about methods for mitigating risks, including the importance of taking methadone as prescribed and adherence with recommended follow-up and monitoring. Patients seen in clinical settings other than the one in which methadone is prescribed should be informed that their receipt of methadone will not be apparent if it is not linked to the electronic medical records of that setting or to state prescription-monitoring programs, and they should be educated about the importance of disclosing its use. Patients, as well as caregivers and family members who are actively engaged in the patient's care, should be notified about the risks of respiratory depression and instructed to withhold additional doses of methadone and contact the prescribing or dispensing entity if signs of respiratory depression or somnolence are present. Patients should be instructed to never share methadone and to store methadone in a safe place, such as a locked cabinet or box if necessary, to safeguard against theft.

An opioid management plan describes how methadone will be prescribed and monitored in an individual patient. It is distinct from the informed consent process, which refers to a discussion of the potential benefit and harms of a therapy. As for all opioids, the management plan when prescribing methadone for treatment of chronic pain may include elements intended to help monitor and verify use. These may include the stipulation that methadone is obtained from one prescriber or facility, prescriptions are filled at one designated pharmacy, drug screening is performed periodically, office visits are required at a specified minimum interval, pill counts are conducted at office visits, and prescription size is limited (eg, weekly or biweekly instead of monthly amounts in higher-risk patients).[16] To ensure that key messages are conveyed to patients consistently, prescribers should consider the use of a written methadone management plan.[16] This plan may also include enumeration of behaviors that may result in discontinuation of methadone.

Baseline Electrocardiograms

- The panel recommends that clinicians *obtain* an ECG prior to initiation of methadone in patients with risk factors for QTc interval prolongation, any prior ECG demonstrating a QTc >450 ms, or a history suggestive of prior ventricular arrhythmia. An ECG within the past 3 months with a QTc <450 ms in patients without new risk factors for QTc interval prolongation can be used for the baseline study (strong recommendation, low-quality evidence).
- The panel recommends that clinicians *consider* obtaining an ECG prior to initiation of methadone in patients not known to be at higher risk for QTc interval prolongation; an ECG within the past year with a QTc <450 ms in patients without new risk factors for QTc interval prolongation can be used for the baseline study (weak recommendation, low-quality evidence).

Torsades de pointes is a polymorphic ventricular arrhythmia usually preceded by QTc interval prolongation[22,96] that can lead to ventricular fibrillation and result in sudden death or cardiac arrest.[22,84] The risk of torsades de pointes increases with greater prolongation of the QTc interval. Torsades de pointes primarily occurs in patients with QTc intervals >500 ms, though risk is increased starting around QTc intervals of 450 ms.[22,74,80,88] Although normal QTc intervals are longer in women than in men, with an average difference of 10 to 20 ms, it is unclear whether there are sex differences in risk of torsades de pointes at increased QTc intervals. Therefore, for pragmatic purposes, the panel recommends that clinicians utilize the same QTc interval parameters for men and women. Risk factors for QTc interval prolongation include[22,26,31,47,93,96]

- electrolyte abnormalities such as hypokalemia or hypomagnesemia;
- impaired liver function;
- structural heart disease (such as congenital heart defects or a history of endocarditis or heart failure);
- genetic predisposition such as congenital prolonged QT syndrome or familial history of prolonged QT syndrome; and
- use of drugs with QTc-prolonging properties (Table 1).

Methadone use appears to be associated with risk of prolongation of the QTc interval,[26,55,59,66,69,89] presumably because of its potent inhibitory effects on the human ether à go-go-related gene (hERG) cardiac channel,[52,95] and case reports describe torsades de pointes in patients prescribed methadone.[47,57,77] Other medications associated with QTc interval prolongation and torsades de pointes include various antiarrhythmics, antipsychotics, citalopram, tricyclic antidepressants, fluoroquinolones, and cisapride.[106] The estimated risk of torsades de pointes varies widely, ranging from approximately .001% for cisapride to approximately 8% for quinidine.[22] In the case of cisapride, the manufacturer discontinued marketing of the drug in the United States in 2000, based on 341 cases of cardiac arrhythmias (including 80 deaths) between 1993 and 1999.[98] Although estimates for the degree of risk associated with drug-induced QTc interval prolongation vary, in patients with long QT syndrome, a QTc interval >500 ms was associated with an odds ratio for syncope or sudden death (presumably due to torsades de pointes) of 4.2 (95% confidence interval [CI] 1.1–16).[8] Because of potential cardiac arrhythmia risk, a baseline ECG is recommended prior to initiating a number of these medications, with periodic ECG monitoring of patients taking the medications, though evidence showing the effectiveness of ECG monitoring is lacking.[1-3,18,22,23]

Similarly, in patients being considered for methadone, a baseline ECG may help clinicians assess for

Table 1. Selected Methadone Drug-Drug Interactions

Drug	Effects on Methadone Levels*	Effects on QTc Interval	Additive Sedative or Respiratory Depressant Effects
Antibiotics			
Ciprofloxacin	↑		
Clarithromycin	↑	↑	
Erythromycin	↑	↑	
Itraconazole	↑		
Ketoconazole	↑		
Fluconazole	↑		
Rifampin	↓		
Telithromycin	↑		
Anticonvulsants			
Carbamazepine	↓		
Phenytoin	↓		
Antihistamines			
Diphenhydramine			↑
Promethazine			↑
Antipsychotics			
Quetiapine	↑	↑	
Barbiturates			
Phenobarbital	↓		↑
Benzodiazepines			
Alprazolam	↑		↑
Clorazepate	↑		↑
Diazepam	↑		↑
Estazolam	↑		↑
Flurazepam	↑		↑
Lorazepam	↑		↑
Midazolam	↑		↑
Triazolam	↑		↑
Zopiclone	↑		↑
HIV medications			
Abacavir	↓		
Nevirapine	↓		
Delavirdine	↑		
Efavirenz	↓		
Ritonavir-boosted lopinavir	↓		
Nelfinavir	↓		
Amprenavir	↓		
Atazanavir	↓		
Opioids			↑
Heroin	↓*		↑
Selective serotonin reuptake inhibitors			
Fluoxetine	↑		
Fluvoxamine	↑		
Nefazodone	↑		
Paroxetine	↑		
Sertraline	↑		
Tricyclic antidepressants			
Amitriptyline		↑	
Desipramine		↑	
Imipramine		↑	
Nortriptyline		↑	
Protriptyline		↑	
Urinary alkalinizers			
Bicitra	↑		
Polycitra	↑		
Verapamil	↑		
Other			
Aprepitant	↑		
Cimetidine	↑		
Cocaine	↓	↑	
Disulfiram	↑		
Ethanol	↓*		↑
Grapefruit juice or whole fruit	↑		
Omeprazole	↑		
St. John's wort	↓*		

NOTE. Most effects are predicted or expected drug interactions; in most cases direct evidence on changes in methadone levels on and off the second medication are not available. Cytochrome P450 inducers decrease methadone blood levels; inhibitors increase methadone blood levels. More comprehensive and periodically updated lists of cytochrome P450 interactions and drugs associated with QTc prolongation are available at http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.aspx and http://QTdrugs.org.

*Data not as strong for interaction.

Leavitt[63]; McCance-Katz et al,[72] Lintzeris et al,[65] and Gourevitch et al.[40]

risk of torsades de pointes, based on the presence and degree of QTc interval prolongation prior to medication initiation. Accurate estimates on the risk of torsades de pointes or sudden cardiac death are not available. Recent data suggest that methadone is the most common drug-related cause of ventricular arrhythmias reported to the FDA.[4,51] However, some studies suggest that in patients on methadone for opioid addiction, attributable mortality appears low.[4] Although no study has evaluated the effect of ECG screening and monitoring on clinical outcomes, and the clinical opinion on the need to obtain ECGs in patients being considered for methadone varies markedly, in part because of concerns about delayed or reduced access to methadone, an ECG is the only way to detect asymptomatic QTc interval prolongation. Patients with QTc interval prolongation might benefit from efforts to address causes of QTc interval prolongation, consideration of alternative opioids or other interventions, or additional monitoring if prescribed methadone. Although no study has compared outcomes associated with different ECG strategies in this setting, the panel recommends that clinicians routinely obtain an ECG prior to initiation of methadone in patients with known risk factors for QTc interval prolongation, a prior ECG with QTc interval >450 ms, or a history suggestive of prior ventricular arrhythmia (such as prior cardiac arrest and unexplained syncope or seizure). Approximately 85% of cases of cisapride-associated cardiac arrhythmias occurred in patients with known risk factors for QTc interval prolongation.[98] Although data are limited, studies of methadone-associated torsades de pointes similarly indicate that a high proportion of patients had identifiable risk factors.[47,58,77,99]

For persons not known to be at a higher risk of QTc interval prolongation, the panel found insufficient evidence to routinely recommend ECG screening.

However, given that QTc interval prolongation without arrhythmia is asymptomatic and may not be associated with recognized risk factors, the panel suggests that clinicians consider obtaining an ECG prior to initiation of methadone in all patients.

Although there is no evidence to guide recommendations on how recent an ECG should be to guide risk assessments accurately prior to initiation of methadone, the panel suggests that in patients with risk factors for QTc interval prolongation that are unchanged, an ECG within the last 3 months showing no QTc interval prolongation can be used as the baseline study and a repeat ECG is unnecessary prior to initiating methadone. In patients with no risk factors for QTc interval prolongation, an ECG within the last year showing no QTc interval prolongation can be used as the baseline study.

The panel found extremely limited evidence to guide use of screening ECGs prior to initiation of methadone in children. Although research on long QT syndrome in families indicates a two- to fourfold increased risk of cardiac events in children with QTc intervals between 460 and 500 ms,[109] the panel found no reported cases of torsades de pointes in children prescribed methadone, despite relatively common pediatric use in some hospital settings. Nonetheless, given the potential for increased cardiovascular risk, the panel suggests that clinicians consider a screening ECG prior to initiating methadone in children with risk factors for prolonged QTc interval, as described above.

- The panel recommends against use of methadone in patients with a baseline QTc interval >500 ms (strong recommendation, low-quality evidence).
- The panel recommends that clinicians consider alternate opioids in patients with a baseline QTc interval ≥450 ms but <500 ms. If methadone is considered in a patient with a baseline QTc interval ≥450 ms but <500 ms, the clinician should evaluate for and correct reversible causes of QTc interval prolongation before initiating methadone (weak recommendation, low-quality evidence).
- The panel recommends that clinicians consider buprenorphine as a treatment option for patients treated for opioid addiction who have risk factors for or known QTc interval prolongation when an agonist/partial agonist is indicated (weak recommendation, moderate-quality evidence).

A QTc interval of ≥500 ms is associated with a substantially increased risk of torsades de pointes.[22,74,80,88] In adults, each 10-ms increase in QTc interval is associated with an approximate 5 to 7% exponential increase in risk of torsades, so that a patient with a QTc of 540 ms has a 63 to 97% greater risk than a patient with a QTc of 440 ms.[22] Patients with this degree of QTc interval prolongation prior to starting methadone may experience further QTc interval prolongation on methadone, placing them at greater risk.[2-14,28,30,31] Therefore, the panel recommends against use of methadone in adults with a QTc interval ≥500 ms at baseline. In such patients, the panel recommends that clinicians consider alternative treatments for chronic pain or opioid addiction. For patients being managed for chronic pain, a number of alternative opioids are available. Although QTc interval prolongation has been reported with oxycodone, its clinical significance is uncertain.[30] Other opioids have not been associated with QTc interval prolongation in clinical studies. For the treatment of opioid addiction, buprenorphine has similar efficacy to moderate doses of methadone but is associated with less QTc interval prolongation, and is one potential alternative.[4,6,28,29,42,56,102] A QTc interval of 450 to 500 ms in adults is also associated with increased risk of torsades de pointes.[47,57,77] Data from general populations of U.S. adults indicate that less than 5% of men and women have QTc intervals of >450 ms.[83,111] Although the risk associated with a QTc interval of 450 to 500 ms is lower than in patients with QTc intervals of >500 ms, the panel recommends that clinicians consider alternatives to methadone because there may be some additional risk. Factors to consider when deciding whether to initiate methadone include the degree of QTc interval prolongation (intervals close to 450 ms are associated with less risk than intervals closer to 500 ms) and whether there may be reversible risk factors. In patients who are prescribed other medications that prolong QTc interval or who have hypokalemia, the panel recommends that clinicians stop the other medications if clinically appropriate and correct hypokalemia. In such cases, the decision to initiate methadone would depend in part on whether the QTc interval improved after such measures. In patients with nonreversible risk factors such as structural heart disease or cirrhosis, the use of alternatives to methadone may be more strongly considered. However, the efficacy of alternative treatments, as well as the risks of inadequate or no treatment, must be considered, especially in treatment of addiction.

Patients with a QTc interval <450 ms at baseline are not considered to be at increased risk for torsades de pointes following initiation of methadone, and may be started on methadone with routine follow-up and monitoring (see below).

The panel found insufficient evidence to determine whether QTc thresholds for use of methadone should differ in children compared with adults. As in adults, data generally indicate that <5% of children have a QTc interval >450 ms.[44,79,97] In addition, as noted above, studies of siblings of children with long QT syndrome found increased risk of cardiovascular events at QTc intervals of 460 to 500 ms, though reported cases of torsades de pointes in children prescribed methadone are rare. Given the *potential* for increased risk and the availability of alternative opioids, the panel suggests that clinicians apply similar QTc parameters for use of methadone in children as in adults, until more evidence is available.

Initiation of Methadone

- The panel recommends that clinicians initiate methadone at low doses individualized based on the

indication for treatment and prior opioid exposure status, titrate doses slowly, and monitor patients for sedation (strong recommendation, moderate-quality evidence).

Practice Advice: *Based on limited research evidence and clinical experience, the panel suggests the following parameters:*

1) When used to treat opioid addiction, the panel suggests that clinicians start methadone at no more than 30 to 40 mg once daily. The dose should be titrated based on objective signs of withdrawal and self-reported craving and methadone dose increased by no more than 10 mg/d and no more frequently than every 3 to 4 days. Methadone should be withheld if there is evidence of sedation.
2) When used to treat chronic pain in adults on relatively low doses of other opioids (eg, <40–60 mg/d of morphine or equivalent), the panel suggests that clinicians start methadone at 2.5 mg tid, with initial dose increases of no more than 5 mg/d every 5 to 7 days. In children, the recommended starting dose is 100 μg/kg (maximum 5 mg/dose) every 6 to 8 hours. Methadone should be withheld if there is evidence of sedation.
3) When used to treat chronic pain and switching to methadone from higher doses of another opioid, the panel suggests that clinicians start methadone therapy at a dose 75 to 90% less than the calculated equianalgesic dose and at no higher than 30 to 40 mg/d, with initial dose increases of no more than 10 mg/d every 5 to 7 days. Methadone should be withheld if there is evidence of sedation.

- The panel recommends that clinicians consider those patients previously prescribed methadone, but who have not currently taken opioids for 1 to 2 weeks, opioid-naïve for the purpose of methadone reinitiation (strong recommendation, low-quality evidence).

The panel recommends that clinicians start methadone at low doses and titrate slowly. Evidence to guide optimal methadone initiation and dose titration strategies is limited. Therefore, suggestions for practice are based on panel consensus and clinical experience, and depend on the degree to which a patient is opioid-experienced, with an overarching goal of more conservative (lower) initial dosing regimens in order to prioritize patient safety. The rationale for the panel's recommendation for careful initiation and dose titration of methadone is related to the drug's long and highly variable half-life.[67] Slow titration may reduce the risk of unintended accumulation that can occur as the serum concentration slowly rises toward steady state once a dose is selected. It is possible that rapid titration of the dose to a level that is efficacious for pain could be followed by toxicity over the course of the next days or even weeks as the concentration rises. In the most serious outcome, this late toxicity could take the form of respiratory depression and death. Consistent with this principle is evidence showing that the period shortly following methadone initiation appears to be associated with increased risk of overdose and other adverse events.[27,37,108] Although the half-life of methadone is usually assumed to be approximately 1 day, and is rarely outside a range of 15 to 60 hours, in some reports the half-life is as high as 120 hours.[67] By comparison, the plasma half-life of morphine, hydromorphone, oxycodone, fentanyl, and codeine range from 2 to 3.5 hours.[45] In a patient for whom the methadone half-life is 60 hours, it would take almost 12 days on a stable dose of methadone to approach a steady state (5 half-lives). In addition, patients with a long half-life will have more prolonged exposure to a given methadone dose, potentially increasing their risk for adverse events. Without knowing the half-life in an individual patient, risk can be minimized only by cautious titration. Clinicians should be aware that the variable half-life of methadone means that some patients may not reach steady state (5 half-lives) for over 3 weeks. Therefore, it is critical that clinicians not increase the dose solely based on preset parameters, but also evaluate patients clinically and withhold the dose if there is evidence of sedation. Once the sedation has resolved, methadone may be reinitiated at a lower dose (eg, at least 20% lower than the dose that caused sedation) and the period between dose titrations extended.

The panel recommends particular caution when initiating methadone for pain treatment in patients with no prior exposure to opioids ("opioid-naïve"). In this situation, the panel suggests a starting dose of 2.5 mg every 8 hours (7.5 mg/d), with initial dose increases of no more than 5 mg/d every 5 to 7 days, in accordance with the APS-AAPM Guideline.[16] Once the dose has reached 30 to 40 mg/d and the patient has shown the ability to tolerate dose increases of 5 mg/d, clinicians may consider larger dose increases of up to 10 mg/d, though the duration between dose increases should not be shortened. Evidence indicates that the risk of overdose is increased at higher doses of opioids, suggesting that dose increases of methadone above 30 to 40 mg/d should only be done in patients who are clearly benefiting and can be monitored appropriately.[7,24,39]

In children, the panel suggests a starting dose of 100 μg/kg (maximum 5 mg/dose initially) every 6 to 8 hours. Although the World Health Organization suggests a higher potential starting dose (100–200 μg/kg) with several initial loading doses (2–3 doses given every 4 hours),[105] the panel felt that more cautious initiation of methadone is warranted in children with chronic pain, particularly in nonhospital settings. The panel suggests use of short-acting opioids for breakthrough pain or if more rapid initial pain control is needed, rather than loading doses of methadone. As in adults, the panel recommends dose increases in children no more frequently than once every 5 to 7 days, based on the amount of breakthrough pain medications needed to maintain pain control, by no more than 50% of the current methadone dose.

For patients treated for opioid addiction and engaged in ongoing opioid use, higher starting doses and more rapid dose titration may decrease the

likelihood of withdrawal and increase the likelihood of treatment success. In such patients, clinicians may consider starting at higher doses than used in opioid-naïve patients. The panel suggests initiating methadone at up to 30 to 40 mg once daily and titrating the dose based on objective signs of withdrawal and self-report of opioid craving, but by no more than 10 mg/d and with dose increases no more frequently than every 3 to 4 days.

In patients with chronic pain on higher doses of alternative opioids, conversion to methadone should be performed carefully. Proposed equianalgesic dose ratios for conversion of other opioids (in mg morphine equivalents) to methadone are variable and range from 3:1 to 10:1 at lower doses to 8:1 to 20:1 at higher doses.[78] In patients on lower doses of other opioids (eg, <40–60 mg morphine equivalents/d), the panel suggests starting methadone at doses similar to those recommended for opioid-naïve patients. For patients on higher doses of other opioids, the panel suggests that clinicians start methadone at a dose 75 to 90% less than the calculated equianalgesic dose, based on more conservative dosing ratios (eg, 15:1 to 20:1) and at no higher than 30 to 40 mg/d.[14] Initial dose increases should be no more than 10 mg/d every 5 to 7 days.

The panel recommends that clinicians reinitiate methadone cautiously in patients who have previously been prescribed methadone but are currently not taking an opioid. Such patients experience loss of tolerance and are at risk for accidental overdose if reinitiated at their previously tolerated methadone dose. Although there is insufficient evidence to determine with precision how quickly tolerance is lost, the panel suggests that clinicians treat patients not taking opioids for 1 to 2 weeks as opioid-naïve.

Because of its long half-life and variable pharmacokinetics, the panel recommends that methadone not be used to treat breakthrough pain or as an as-needed medication.[16]

Follow-Up Electrocardiograms

- The panel recommends that for patients prescribed methadone, clinicians perform follow-up ECGs based on baseline ECG findings, methadone dose changes, and other risk factors for QTc interval prolongation (strong recommendation, low-quality evidence).

Practice Advice: *Based on limited research evidence and based upon clinical experience, the panel suggests the following parameters:*

1) The panel suggests that for patients with risk factors for QTc interval prolongation, any prior ECG demonstrating a QTc >450 ms, or a history of syncope, clinicians perform follow-up ECG 2 to 4 weeks after initiation of methadone therapy and following significant dose increases.
2) The panel suggests that for all patients, clinicians perform follow-up ECG when the methadone dose reaches 30 to 40 mg/d in patients started at lower doses, and again at 100 mg/d.
3) The panel suggests that clinicians perform follow-up ECG for all patients prescribed methadone with new risk factors for QTc interval prolongation or signs or symptoms suggesting arrhythmia.

- The panel recommends that clinicians switch methadone-treated adults with a QTc interval ≥500 ms to an alternative opioid or immediately reduce the methadone dose; in all such cases, the panel recommends that clinicians evaluate and correct reversible causes of QTc interval prolongation, and repeat the ECG after the methadone dose has been decreased (strong recommendation, low-quality evidence).
- The panel recommends that clinicians consider switching methadone-treated adults with a QTc interval ≥450 ms but <500 ms to an alternative opioid or reducing the methadone dose. In patients in whom there are barriers to switching to alternative opioids, or who experience decreased treatment effectiveness with methadone dose reductions, the panel recommends that clinicians discuss with patients the potential risks of continued methadone. In all cases, the panel recommends that clinicians evaluate and correct reversible causes of QTc interval prolongation, and repeat the ECG after the methadone dose has been decreased (strong recommendation, low-quality evidence).

Follow-up ECGs in patients prescribed methadone may be useful for identifying QTc interval prolongation that increases the risk for torsades de pointes. Although there is no evidence to guide optimal strategies for performing follow-up ECGs, the panel suggests that clinicians obtain a follow-up ECG soon after initiating methadone in patients with QTc interval prolongation at baseline and in patients on methadone with new risk factors for QTc interval prolongation of signs or symptoms suggesting ventricular arrhythmia (such as palpitations, presyncope, or syncope). In addition, some evidence suggests that the degree of QTc interval prolongation is dose dependent.[13,26,29,53,57,69] Therefore, follow-up ECGs should also be obtained when methadone daily doses are increased to certain threshold levels. Although there are insufficient data to determine optimal methadone dose threshold levels for ECG monitoring, the panel suggests 30 to 40 mg/d in patients started at lower doses, and again at 100 mg/d.

The panel suggests that clinicians obtain a follow-up ECG 2 to 4 weeks after initiation of methadone in patients with a QTc interval >450 ms at baseline, a history of syncope prior to initiation of methadone, or risk factors for QTc interval prolongation, as well as when patients develop new risk factors for QTc interval prolongation or report signs or symptoms suggesting potential arrhythmia. In patients started on low doses of methadone, the panel also recommends that clinicians perform follow-up ECG when the methadone dose reaches the thresholds noted previously. The panel found insufficient evidence to suggest parameters for follow-up ECGs in patients titrated to higher methadone doses who do not experience QTc interval prolongation at doses of 100 mg/d or lower. However, a high proportion of case reports of torsades de pointes in

patients prescribed methadone occurred at high doses (>200 mg/d), suggesting that additional monitoring at higher doses (eg, whenever the dose is titrated to 30–50% higher than the prior dose at which an ECG was obtained) may be warranted.[47,57] In patients with QTc interval prolongation on follow-up ECG, recommendations on use of methadone, consideration of alternatives, and correction of potentially reversible causes are similar to those described above for QTc interval prolongation on a baseline ECG. In addition, clinicians may consider lowering the methadone dose with follow-up to document improvement or normalization of the QTc interval.[28,42,59] For patients treated for opioid addiction who develop a prolonged QTc interval on methadone, buprenorphine is a potential alternative. Buprenorphine has similar efficacy to moderate doses of methadone for treatment of opioid addiction, and observational studies report normalization of prolonged QTc intervals after switching patients from methadone to buprenorphine.[28,42,59] For chronic pain, a number of opioids are available as alternatives to methadone. A potential limitation to use of buprenorphine is that it is a μ-opioid partial agonist and may exhibit analgesic ceiling dose effects at which further dose increases produce no additional effects.[100] Clinicians switching patients from methadone to buprenorphine should also follow recommended methods to avoid precipitated withdrawal due to initiation of a partial agonist.[10]

Monitoring for and Management of Adverse Events

- The panel recommends that patients receiving methadone be monitored for common opioid adverse effects and toxicities and that adverse effects management be considered part of routine therapy (strong recommendation, moderate-quality evidence).

In addition to QTc interval prolongation, methadone is associated with other adverse effects typically associated with opioids, including constipation, nausea, sedation, respiratory depression, pruritus, endocrinologic effects, and others. As outlined in the APS-AAPM guideline on use of opioids for chronic noncancer pain, the panel recommends that clinicians anticipate and routinely monitor patients prescribed methadone for opioid-related adverse effects.[16] Adverse effects management, including proactive interventions, should be considered part of routine therapy in all patients prescribed methadone. Clinicians should routinely consider initiation of a bowel regimen to prevent or manage opioid-induced constipation. Although evidence is anecdotal, regimens including increased fluid and fiber intake, stool softeners, and laxatives are often effective. For nausea and vomiting, a number of antiemetics, in both oral and rectal forms, are available, though some are associated with QTc interval prolongation (see below). Patients should be asked about signs or symptoms of hypogonadism and appropriately tested when present. Clinicians should recognize comorbidities that may increase the risk of opioid-related adverse effects such as sleep apnea or other underlying respiratory disease, dementia, or antecedent constipation. Close monitoring is recommended in such cases.

Clinicians should periodically monitor patients for the development of substance abuse and other mental health disorders. Such patients should be managed appropriately, including referral if necessary and potential discontinuation or restructuring of methadone therapy. Clinicians should also periodically review state prescription drug monitoring program data, which are now widely available, in order to help identify patients who are obtaining opioids or other controlled substances from other providers, as such behaviors are associated with increased risk of overdose.

Patients should be counseled on sedation after opioid initiation and with dose increases, including potential issues related to driving and work and home safety. However, most epidemiologic studies suggest that risk of motor vehicle accidents, traffic fatalities, and citations for impaired driving is not increased in patients on stable doses of opioids.[34,35] In the absence of signs of symptoms of impairment, the panel did not identify sufficient evidence to support restrictions in driving or most work-related activities in patients maintained on long-term opioid therapy.[16]

- The panel recommends face-to-face or phone assessment with patients to assess for adverse events within 3 to 5 days after initiating methadone, and within 3 to 5 days after each dose increase (strong recommendation, low-quality evidence).

The risk of methadone-associated mortality is higher shortly after initiating methadone.[9,61,73,107] Although evidence is sparse on the association between methadone dose increases and serious adverse events, a similar association appears plausible. Therefore, the panel recommends that clinicians reassess patients 3 to 5 days following methadone initiation or after methadone dose increases, with particular attention to signs of respiratory depression (such as decreased respiratory rate or sedation, which may accompany respiratory depression) and arrhythmia (such as palpitations). Although there is insufficient evidence to guide recommendations on optimal methods or timing for follow-up, the panel recognizes that follow-up assessments do not necessarily require an office visit with a provider, and may be performed over the phone by an appropriately trained medical assistant or nurse or via email for reliable patients.

Urine Drug Testing

- The panel recommends that clinicians obtain urine drug screens prior to initiating methadone and at regular intervals in patients prescribed methadone for opioid addiction (strong recommendation, low-quality evidence).
- The panel recommends that patients prescribed methadone for chronic pain who have risk factors for drug abuse undergo urine drug testing prior to initiating methadone and at regular intervals thereafter; it

recommends that clinicians consider urine drug testing in all patients regardless of assessed risk status (strong recommendation, low-quality evidence).

One method to monitor patients prescribed opioids is urine drug testing (UDT). UDT may help identify patients engaging in aberrant drug-related behaviors and who may benefit from restructuring of their opioid therapy or treatment of underlying addiction or opioid misuse. Although no study has evaluated optimal UDT intervals in patients prescribed methadone or other opioids, the panel suggests that clinicians obtain a baseline UDT, including specific testing for methadone, in all patients prescribed methadone for opioid addiction and in all patients prescribed methadone for chronic pain that have risk factors for drug abuse. Subsequent UDT should be performed periodically if justified based on the patients' assessed risk for drug abuse or diversion. The APS-AAPM guideline on use of opioids for chronic noncancer pain suggests that clinicians use the risk assessment to help guide UDT monitoring intervals.[16] Patients treated for opioid addiction are at high risk for opioid abuse and misuse and generally warrant frequent monitoring. Patients prescribed methadone for chronic pain who may need more frequent or intense monitoring include those with a prior history of substance use disorder, patients with an unstable or dysfunctional social environment, and those with comorbid psychiatric conditions. In patients treated for chronic pain at low risk for adverse outcomes and on stable doses of opioids, the APS-AAPM guideline also suggests that clinicians consider UDT monitoring, as evidence indicates that a substantial minority of patients who engage in aberrant drug-related behaviors do not have identifiable risk factors.[48,54] In such patients, repeat testing every 6 to 12 months may be sufficient, though clinic follow-up every 3 to 6 months is generally suggested.

Medication Interactions

- The panel recommends that clinicians use methadone with care in patients using concomitant medications with potentially additive side effects or pharmacokinetic or pharmacodynamic interactions with methadone (strong recommendation, low-quality evidence).

Evidence on the magnitude of clinical harms associated with the concomitant use of methadone plus potential interacting medications is limited, and most trials were not designed to evaluate serious harms. However, several types of drug interactions can increase risk in patients using methadone and therefore require attention and care in prescribing (Table 1). These include use of drugs that

- alter methadone absorption, metabolism, and/or excretion, thereby changing methadone blood levels;
- have additive or synergistic sedative or respiratory suppressant effects; and/or
- prolong QTc intervals.

Like other opioids, methadone is primarily metabolized in the liver and gastrointestinal tract[25] by cytochrome P450 (CYP) enzymes including CYP2B6, CYP3A4, CYP 2C19, CYD2D6, and CYP1A2.[62,104] Many other medications can affect the metabolism of methadone and other opioids because they are CYP inhibitors (leading to increased opioid levels)[63] or CYP inducers (leading to decreased opioid levels).[36] CYP inhibitors may increase risk for sedation and respiratory depression at a specific opioid dose, and CYP inducers may reduce effectiveness of methadone at a specific dose or precipitate withdrawal.

In addition, like other opioids, methadone has sedating and respiratory depressant effects that may be augmented by use of medications and drugs (such as alcohol) with similar effects. In particular, a high proportion of cases of overdoses involving methadone occurred in patients with benzodiazepines in their system at the time of death.[12,37,90,94,103] The panel suggests that clinicians generally avoid benzodiazepines in patients prescribed methadone because of the possible association with increased overdose risk. However, in stable patients on long-term low doses of a benzodiazepine plus methadone, the panel found insufficient evidence for or against routine discontinuation of the benzodiazepine, though a careful consideration of potential risks relative to benefits is warranted.

Finally, care is needed when combining methadone with other drugs that may prolong QTc intervals. In spontaneously reported cases of methadone-associated arrhythmia, antiretroviral drugs for human immunodeficiency virus were the most common coadministered drugs.[51] The ECG should be carefully monitored and doses of methadone and/or other drugs adjusted to keep the QTc within a safe range, as discussed elsewhere in this Guideline.

The panel recommends that clinicians review patient medications prior to initiation of methadone and consider discontinuation or dose reduction of medications with potential interactions or additive side effects (Table 1). If methadone is initiated, the panel recommends close monitoring following methadone initiation. In patients on methadone, clinicians should review new medications for potential interactions before starting them, monitor for interactions if they are used, and make appropriate methadone dose changes when a CYP inducer or inhibitor is discontinued or when the dose is adjusted. For example, discontinuation of a CYP inducer in a patient prescribed methadone could result in high methadone levels, potentially increasing the risk for overdose.

Methadone Use in Pregnancy

- The panel recommends monitoring of neonates born to mothers receiving methadone for neonatal abstinence syndrome and treatment for neonatal abstinence syndrome when present (strong recommendation, moderate-quality evidence).

Neonatal abstinence syndrome occurs in three-quarters or more of infants exposed to methadone prenatally.[20,43,49,50,64,75,81,82,86,87,110] Evidence on

comparative risk of neonatal abstinence syndrome associated with different opioids is limited but may be higher with methadone than buprenorphine.[33,46] Although most studies have evaluated the incidence of neonatal abstinence syndrome following maternal use of methadone for treatment of opioid addiction, methadone has also become frequently used for treatment of chronic pain in women of childbearing age.

Opioid agonist treatment with methadone is the current standard of care for opioid addiction during pregnancy in order to improve both maternal and fetal outcomes.[19] Detailed guidance regarding management of addiction during pregnancy is beyond the scope of this Guideline but is available from the American Congress of Obstetrics and Gynecology.[19] For women with chronic pain, clinicians should weigh the benefits and harms of methadone and other opioids when considering its use during pregnancy and inform women of the potential risks to the newborn, as well as the risk of opioid withdrawal with discontinuation of methadone during pregnancy. The panel recommends monitoring of all newborns born to mothers receiving methadone for neonatal abstinence syndrome and provision of appropriate treatments when it occurs.

Conclusions

Use of methadone for treatment of chronic pain has increased dramatically, in part because of its lower cost relative to other long-acting opioids, despite limited evidence of efficacy for treatment of chronic pain.[15] Methadone maintenance therapy is a mainstay of treatment for opioid addiction and is associated with reduced heroin and illicit drug use, greater retention in therapy, and a trend toward reduced mortality risk.[71] At the same time, overdoses associated with methadone use have increased dramatically, methadone is associated with unique pharmacologic properties that complicate its use, and alternatives to methadone are available for treatment of both chronic pain and opioid addiction. After a review of the available evidence, an expert panel convened by APS, CPDD, and HRS concludes that measures can be taken to promote safer use of methadone. The recommendations presented in this Guideline are based on the underlying assumption that safe use of methadone requires clinical skills and knowledge in assessing and balancing potential risks against potential benefits of methadone, monitoring and management of risks, with the core goal of promoting patient safety and preventing avoidable harms, including serious events such as accidental overdose and fatal arrhythmia. Unlike other Guidelines,[60,70,92] which primarily focused on prevention of arrhythmia, the recommendations in this Guideline also address aspects of patient risk assessment, education and counseling, dose initiation and titration, monitoring, and medication interactions that are directly or indirectly related to risk of respiratory depression, thought to be the primary cause of methadone-associated deaths.

Although these guidelines are based on a systematic review of the evidence on methadone safety, the panel identified numerous research gaps. In fact, the panel only rated 4 recommendations as supported by even moderate-quality evidence. Nonetheless, the panel came to near-unanimous consensus on almost all of its recommendations, including the need to educate and counsel patients on methadone safety, use of ECG to identify persons at greater risk for methadone-associated arrhythmia, use of alternative opioids in patients at high risk of complications related to QTc interval prolongation, careful dose initiation and titration of methadone, and diligent monitoring and follow-up.

The panel acknowledges that implementation of these guidelines has important implications for resource utilization and cost. However, at this time there is insufficient evidence to reliably estimate or model the costs associated with implementation. Given the number of potentially preventable deaths associated with methadone and the availability of alternative treatments, the panel concluded that enhanced efforts to mitigate risks of methadone are justified despite the limited evidence with which to estimate their potential impact. Research is urgently needed to confirm the effectiveness and cost-effectiveness of the recommendations in this Guideline.

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Appendix 1. List of Panel Members With Conflicts of Interest Disclosure

	Conflicts of Interest Disclosed
Cochairs	
APS: Ricardo Cruciani, MD	Received speaking fees from Depomed Advisory Board and Speaker Bureau; Covidean Speaker Bureau; ENDO Pharmaceuticals Speaker Bureau; Ameritox consultant; grant support; Grupo Ferrer consultant (Spain). Received research funding from Ameritrox, New York State.
CPDD: David A. Fiellin, MD	Received honoraria for serving on external advisory panels monitoring the abuse and diversion of buprenorphine for Pinney Associates and Parajuarx.
Panel members	
Roger Chou, MD	No conflicts disclosed.
Peggy Compton, RN, PhD	No conflicts disclosed.
John T. Farrar, MD, PhD	Dr. Farrar has received research grant support (through the University of Pennsylvania) and consulting fees from Purdue Pharma, Forrest Pharma, Endo Pharma, Cephalon Inc, and currently from Teva Pharma.
Mark C. Haigney, MD	No conflicts disclosed.
Charles Inturrisi, PhD	No conflicts disclosed.
John R. Knight, MD	No conflicts disclosed.
Shirley Otis-Green, MSW, ASW	No conflicts disclosed.
Steven M. Marcus, MD	No conflicts disclosed
Davendra Mehta, MD	Consulting fee from St. Jude's and speaker fee from Sanofi.
Marjorie C. Meyer, MD	No conflicts disclosed.
Russell Portenoy, MD	Honorarium received from Spanish company, Grupo Ferrer for teaching conference; honorarium from Pfizer for consulting. Conducts research on the Nabiximols project funded by Otsuka, Inc.
Seddon Savage, MD, MS	No conflicts disclosed.
Eric Strain, MD	Employed as medical director of a clinic that treats patients with opioid use disorders and patients with pain. Consulting for: Transcept Pharmaceuticals, Inc; The Oak Group; and Salfix Pharmaceuticals, Inc. Received National Institutes of Health funding; may receive in next 1 to 2 years pharmaceutical funding for opioid research.
Sharon Walsh, PhD	Received research support from World Meds, Inc, and Catalyst Pharmaceuticals. Served as a paid consultant on abuse liability assessment research and medications development to pharmaceutical companies, including affiliations with Abbot Laboratories, Meda Pharmaceuticals, and Yaupon Pharmaceuticals. Received honoraria and travel support as an invited speaker for Reckitt-Benckiser.
Lonnie Zeltzer, MD	Chair of data-monitoring committee (DMC) for buprenorphine study in children; Purdue Pharma, paid for initial take-off meeting and travel reimbursement, but no patients have completed the study yet and so no DMC reports yet. Received honoraria for lectures on chronic pain and integrative medicine in individuals with Fabry, Pompe, or Gaucher's disease sponsored by Sanofi, Inc.

Appendix 2. American Pain Society Clinical Practice Guidelines Grading System*

	Strength of Recommendation	
Quality of Evidence	Benefits Do or Do Not Clearly Outweigh Risks	Benefits and Risks and Burdens Are Finely Balanced
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or harms	No recommendation	No recommendation

*From the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) work group and adapted by the American Pain Society.