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POSITION STATEMENT

ACMT Position Statement: The Use of Methadone as an Analgesic

American College of Medical Toxicology[1]

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Use of Methadone as an Analgesic

The position of the American College of Medical Toxicology (ACMT) is as follows:

> *Use of methadone as an analgesic*
> It is the position of ACMT that providers exercise caution when prescribing methadone as an analgesic and preferably avoid this use. Methadone should not be prescribed on an as-needed basis. Clinicians should recognize the risk of overdose (e.g., dose stacking) during the initial induction period for chronic use and titrate very slowly. Patients should be educated on potential risks of methadone at the time of initiation of therapy. Clinicians should obtain a baseline ECG before methadone treatment is initiated in patients with risk factors for QT prolongation such as use of other medications that prolong QT interval, structural heart disease, or a history of arrhythmia. In such higher-risk patients, a follow-up ECG should be obtained approximately 30 days after starting therapy. ACMT supports the FDA's decision to require a Risk Evaluation and Mitigation Strategies program for extended-release/long-acting (ER/LA) opioid medications, including methadone. It is the position of ACMT that the FDA assess the value of this program and make adjustments to ensure reaching the goal of improved safety balanced with effective pain relief.

While individual practitioners may differ, these are the positions of the ACMT at the time written, after a review of the issue and pertinent literature.

Use of Methadone as an Analgesic

The use of methadone as an analgesic (not for treatment of opioid dependence) has grown dramatically in recent years [1]. Nationally, methadone-related deaths have mirrored prescriptions trends, increasing nearly sevenfold between 1996 and 2006 [2]. When comparing data from individual US states, higher rates of methadone prescribing have correlated with increased frequency of opioid-related deaths [3]. While these trends suggest that increased mortality is a function of increased drug availability, some studies implicate methadone in a disproportionate share of overdose events. Investigations of opioid overdose deaths have reported methadone accounting for up to 35 to 40 % of cases [4, 5]. This proportion is striking since sales of other opioids such as codeine and hydrocodone exceed that of methadone. Methadone accounts for a relatively small proportion of opioid prescriptions, but is responsible for a disproportionate number of opioid-associated fatalities [3].

Methadone's pharmacology is responsible in part for the apparent excess mortality risk. Volunteers achieve maximum serum methadone concentrations approximately 4 h after oral dosing [6]. In contrast, maximum serum concentration of hydrocodone occurs approximately 90 min after ingestion [7]. Patients with methadone prescribed on an as-needed basis might take multiple doses, perceiving a lack of efficacy due to

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delayed analgesic onset. This behavior, in combination with the drug's prolonged elimination, may lead to excessive methadone accumulation and toxicity. The duration of methadone's analgesic effect also appears to be significantly shorter than its elimination half-life, which could also prompt too-frequent patient dosing and excessive drug accumulation [8].

Methadone's cardiovascular effects also contribute to toxicity. Methadone's (*S*)-enantiomer (dextromethadone) inhibits the potassium-dependent, delayed rectifier current in cardiac cells. This inhibition risks QT prolongation and the development of torsades de pointes (TdP) [8, 9]. The risk of dysrhythmia is likely to be higher when combined with other drugs that have similar ion channel effects on the heart. Methadone was the second most frequently mentioned drug in cases of drug-induced TdP in a 4-year analysis of FDA Adverse Event Reporting System data [10]. In a community-based series of sudden cardiac death cases in which a therapeutic blood level of methadone (less than 1 mg/L) was detected at autopsy, among 22 total subjects, 17 cases (77.3 %) lacked any evidence of structural heart disease such as ventricular hypertrophy, coronary artery disease, etc. [11]. In contrast, among 106 control cases of sudden death without detectable methadone post-mortem, 60 % had significant structural heart disease. These data "strongly suggested" to the study's authors a causative role for methadone in the development of sudden cardiac death. Actual estimates of QT prolongation in individuals taking methadone have varied depending on populations studied as well as study design. Two cross-sectional studies of patients receiving methadone maintenance therapy (MMT) found frequencies of prolonged corrected QT (defined as greater than 500 ms) of 2.2 and 4.6 %, respectively [12, 13]. Corrected QT prolongation was seen only in patients taking more than 120 mg methadone daily. A much higher prevalence has been noted in other retrospective and prospective studies. Retrospectively evaluated hospitalized patients with a history of IV drug use receiving MMT had a 16.2 % rate of QTc >500 ms (29.9 % had QTc >460 ms) [14]. Corrected QT exceeding 500 ms was observed at methadone doses as low as 30 mg daily. Only 10 % of non-methadone patients had QTc >460 ms, and none had QTc >500 ms [14]. A prospective study evaluated subjects entering a MMT program and compared ECG at baseline to 6 and 12 months later [15]. At both 6 and 12 months, approximately 12 % of patients had prolonged corrected QT (>450 ms in males and >470 ms in females) compared to 5 % at baseline. The authors noted a significant increase in average corrected QT at 6 months compared to baseline which was sustained at 12 months. Frequencies of corrected QT prolongation (>470 ms in males and >490 ms in females) as high as 23 % are reported in patients initiated in MMT [16]. Significant increases in average, corrected QT over baseline were observed after only four weeks of therapy.

A SAMHSA organized expert panel addressed issues relating methadone use and QT prolongation but did not reach a consensus that baseline ECG screening was appropriate for all patients [17]. However, the panel agreed that baseline and 30-day ECGs were recommended for patients with risk factors for QT prolongation, including cardiac arrhythmia, prolonged QT interval, episodes of syncope, dizzy spells, palpitations or seizures, or other clinical features suggestive of risk of dysrhythmia. The panel recommended annual ECGs when methadone dose exceeds 120 mg/day.

In consideration of these risks, experts recommend conservative initial methadone dosing and dose escalation. When converting a patient's pain regimen from high doses of another opioid to methadone, experts in pain management recommend calculating the equianalgesic methadone dose, reducing by as much as 90 %, and dividing into three daily doses [18, 19]. For both pain management and maintenance pharmacotherapy, authors have recommended 30 mg as a maximum initial total daily methadone dose [18–21]. The Institute of Medicine Committee on Federal Regulation of Methadone Treatment recommends raising the daily dose for maintenance pharmacotherapy by no more than 10 mg every week [20]. American Pain Society Guidelines recommend increasing the daily methadone dose by no more than 10 mg every 5–7 days in patients with chronic pain who changed from other opioids to methadone [20].

The FDA's *Information for Healthcare Professionals* also details methadone safety concerns, including both the risk of QT prolongation and the disparity between duration of analgesia, methadone's half-life, and peak respiratory depressant effects [22]. Providers are advised to educate patients not to take methadone more frequently than prescribed.

The Food and Drug Administration Amendments Act of 2007 authorized the FDA to require drug manufacturers to implement a risk evaluation and mitigation strategy (REMS) when necessary to ensure that the benefits of a drug outweigh the risks. The FDA has implemented a REMS for extended-release/long-acting (ER/LA) opioids, including methadone. The main component of the REMS is optional provider education on the potential risks of ER/LA opioids. A blueprint for the education program has been made available [23].

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