

NATIONAL PBM COMMUNICATION • December 17, 2008

Methadone-Related QTc Prolongation and Torsades de Pointes

In November 2006, PBM issued a [national bulletin](#) informing VHA providers about the potential for death, overdose, and serious cardiac arrhythmias during methadone therapy. The purposes of this present communication are to inform VHA providers about (1) risks of methadone-associated QTc prolongation and torsade de pointes (TdP); and (2) the Physician Clinical Support System for Methadone.

Methadone-related QTc Prolongation and Torsade de Pointes

Based on a recently published review of the subject,¹ the PBM considers the following items to be the salient points on methadone-related QTc prolongation and TdP:

1. QT dispersion, QTc prolongation, QTc interval fluctuation, and TdP have been reported in patients treated with methadone for opioid dependence or pain management.
2. The incidences of QTc prolongation and TdP during methadone therapy are unknown.
3. A dose-dependent effect on QTc prolongation has been shown in some studies.
4. Overall, prolonged QTc or TdP has been observed at a wide range of methadone doses from 10 to 1200 mg daily.
5. Drugs that inhibit metabolism of methadone, drugs that prolong QTc intervals or induce TdP, and genetic variation in metabolism of methadone may increase risk of methadone-related prolongation of the QTc interval. Drugs that can increase methadone levels most notably include the CYP3A4 inhibitors, such as protease inhibitors (e.g., ritonavir, nelfinavir, indinavir), macrolide antibiotics (e.g., clarithromycin, erythromycin), azole antifungals (e.g., ketoconazole, itraconazole), and selective serotonin reuptake inhibitors (e.g., fluvoxamine, fluoxetine, sertraline). (For an extensive list of drugs that have been associated with prolonged QTc interval or TdP, go to www.torsades.org.)
6. There is a lack of consensus on when to do ECGs, with recommendations varying from never necessary, to screening at-risk patients, to screening all patients prior to starting methadone.
7. Risk factors for QTc prolongation or TdP include elderly women, advanced heart disease, congenital and acquired long-QT syndromes, concomitant use of drugs associated with QTc prolongation or TdP, family history of sudden death, hypokalemia, and hypomagnesemia.
8. General recommendations use QTc intervals longer than 430 ms in males and 450 ms in females as the thresholds for increased risk for TdP, and a QTc interval longer than 500 ms as the cutoff for a definite risk for TdP. QTc intervals longer than 500 ms or more than 40 ms over baseline measurements warrant strong consideration of stopping the offending drug.
9. Further recommendations on ECG monitoring with methadone therapy are expected from The Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2009.

Physician Clinical Support System for Methadone

CSAT has funded the Physician Clinical Support System for Methadone (PCSS-M). This is a free, nationwide program through which health care providers needing information and mentoring on methadone treatment for opioid addiction and/or pain can connect with experts in the field. [PCSS-M MENTORS](#) provide telephone, email, and on-site support. They come from across the country and work in licensed opioid treatment programs, pain clinics, primary care, and other practice settings. The PCSS-M is coordinated by the [American Society for Addiction Medicine \(ASAM\)](#) in conjunction with other leading medical societies. Within 6 months they will have a mentoring network with 30 mentor physicians, 3 national clinical experts, a medical director, co-medical director, and senior advisor. The steering committee consists of 20 other organizations including the VA, AMA, the American Academy of Pain Medicine, the American Pain Society, the American Psychiatric Association, and the American Academy of Addiction Psychiatry. The PCSS-M will be fully operational in the first quarter of CY 2009.

REFERENCES

- ¹ Cruciani RA. Methadone: To ECG or Not to ECG...That Is Still the Question. *J Pain Symptom Manage* 2008;36:545-552.

ACTIONS

- **Facility Director (or physician designee):** Forward this document to the Facility Chief of Staff (COS).
- **Facility COS:** Forward this document to all appropriate providers who prescribe this medication (e.g., **primary care providers, pain specialists, neurologists, substance abuse specialists, palliative care specialists, heme-onc providers, and cardiologists**, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).