



DEC 13 2006

Center for Mental Health Services  
Center for Substance Abuse  
Prevention  
Center for Substance Abuse  
Treatment  
Rockville MD 20857

Dear Colleague:

On November 27, 2006, the Food and Drug Administration (FDA) issued a Health Advisory announcing that it had revised the package insert for methadone because of national concern over a sharp rise in unintentional overdose deaths attributed to prescribed methadone use. The concern relates to the fact that with over 2 million prescriptions written for methadone in 2003, the National Center for Health Statistics reported 2,452 unintentional poisoning deaths with methadone listed as a cause. Although FDA concern has been focused on the increasing use of methadone for pain management, it is important to note that the labeling change, with "black box" warnings, will apply to all methadone medications, including the products used to treat opioid dependence.

Opioid Treatment Programs (OTPs) are encouraged to review the enclosed material, with emphasis on three key points (1) initial dose; (2) black box warning; and (3) patient information sheet.

1. The prior package insert recommendation for methadone used in pain management could have led to a relatively potent first day dose of 80 mg. This could be a particular concern for patients and physicians not familiar with methadone pharmacology.<sup>1</sup> In contrast, the revised package insert for initiation of therapy in opioid non-tolerant patients recommends a usual oral methadone starting dose of 2.5 mg to 10 mg every 8 to 12 hours, which is now consistent with the usual starting dose recommended for patients initiating methadone treatment for opioid dependence.
2. There are now four "black box" warnings in the revised insert:
  - a. with cardiac and respiratory deaths reported during the initiation and conversion of pain patients to methadone treatment from treatment with other opioids, it is critical to understand the pharmacokinetics of methadone when converting patients to methadone. Particular vigilance is necessary during conversion from one opioid to another, and during dose titration.
  - b. Respiratory depression is the chief hazard associated with methadone, with peak depressant effect occurring later and persisting longer than peak analgesic effects. This can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.
  - c. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during methadone treatment for pain management, with most cases involving large, multiple daily doses of methadone. Cases have also been reported in patients receiving doses commonly used for methadone maintenance treatment of opioid dependence.

<sup>1</sup> Current regulation for opioid treatment programs recommends a starting dose for methadone to be no more than 30 to 40 mg on the first day, recommending specific documentation should there be a need to prescribe more.

- d. Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks. This last warning is new to this revised package insert.
3. Finally, the patient information sheet provides new information on pregnancy and may require clarification within the context of opioid assisted therapy. In the information sheet, women who might receive methadone are specifically advised to tell the doctor if they are: 1) pregnant or plan to become pregnant, since, methadone may harm an unborn baby, or 2) breast-feeding, since methadone passes through breast milk and could harm the baby. Women are specifically told to decide on either methadone therapy or breast feeding, but not both.

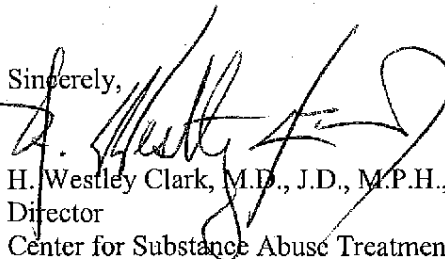
Methadone is considered pregnancy “class C”, like most medications, and safer than some commonly prescribed psychotropic drugs that are class “D”. SAMHSA/CSAT is not aware of evidence that an unborn baby has been harmed from the mother’s use of methadone. Furthermore, neonatal abstinence syndrome (NAS) has been well described and is easily treated with no long-term consequences on child development. Methadone is still considered “probably safe” for lactation (breastfeeding). About 2-3% of methadone might pass through to breast milk, with peak dose 4-5 hrs post administration. The patient information sheet is most applicable to patients who are considering use of methadone for pain management, for whom treatment might be temporary and for whom there might be several alternative treatments. However, for pregnant women and new mothers who are opioid dependent and have adhered to methadone maintenance treatment, the desire to breast feed should be encouraged unless there is another medical or psychological reason that serves as a contraindication to breastfeeding.

The revised FDA package insert is generally consistent with best practice use of methadone already reflected in the CSAT Treatment Improvement Protocols (TIPS).

The FDA health advisory can be found on the web at <http://www.fda.gov/cder/drug/advisory/methadone.htm> and package insert at <http://www.fda.gov/cder/foi/label/2006/006134s028lbl.pdf>. The documents are also enclosed with this letter.

SAMHSA can provide additional information to you on this emerging area of treatment concern. Please contact Kenneth Hoffman, M.D, M.P.H., at 240-276-2701 or [Kenneth.Hoffman@samhsa.hhs.gov](mailto:Kenneth.Hoffman@samhsa.hhs.gov).

Sincerely,



H. Westley Clark, M.D., J.D., M.P.H., CAS, FASAM  
Director  
Center for Substance Abuse Treatment

Enclosures