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August 27, 2014

Suchitra Iyer, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, MD 20850

RE: Draft Report: "The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain"

Dear Dr. Iyer:

The Pew Charitable Trusts applauds the Agency for Health Care Research and Quality (AHRQ) for its work to evaluate the effectiveness and risks of long-term opioid treatment for chronic pain. Pew is an independent, nonpartisan research and policy organization dedicated to serving the public. Our prescription drug abuse project works to develop and support policies that will help reduce the inappropriate use of prescription drugs while ensuring that patients with legitimate medical needs have access to effective pain management.

We appreciate the opportunity to comment on the draft report prepared by your contractor. As the report is revised, we encourage AHRQ to add context regarding harms associated with methadone as a pain therapy and to ensure that qualifications regarding the quality of the evidence are included in the structured abstract.

Harms associated with methadone as a pain therapy

Without additional context regarding the dangers of methadone as a pain therapy, readers could interpret the report to be more positive about the use of methadone than evidence warrants. In the section entitled Key Findings and Strength of Evidence, the authors briefly state that the use of methadone as a pain therapy is associated with a disproportionate share of patient harm. However, the scope and nature of this harm is not fully described in the report. **Pew encourages AHRQ to provide additional details about harms associated with the use of methadone as a pain treatment within the detailed discussion of this therapy.**

Data from the Centers for Disease Control and Prevention (CDC) indicate that methadone accounts for just 2 percent of opioid prescriptions, but 30 percent of opioid-related overdose deaths.[i] According to an analysis of data from 2009 in selected states, methadone was implicated in 40 percent of deaths that involved only one opioid—more than double the deaths attributed to other drugs in its class.[ii]

Methadone's unique properties distinguish it from other opioid drugs. Pain relief from methadone lasts four to eight hours, but its effects on other organs, such as the lungs and heart, can continue for eight to 59 hours.[iii] As a result, patients may put themselves at risk by taking more of the drug before the original dose has been fully metabolized. When taken too often or at too high a dose, methadone can cause life-threatening respiratory depression and heart rhythm or heart rate abnormalities.[iv]Other commonly prescribed drugs, such as anxiety medications, can amplify these effects. Based on this and other information, the Food and Drug Administration (FDA) and professional societies representing pain specialists have recommended against the use of methadone as a first-line treatment for pain.[v] The CDC expands this precaution by stating that insurers should not list methadone as a preferred drug for the treatment of noncancer pain.[vi]

This clarification is especially important given that this systematic review is intended for use by health plans and government programs, as described in the Preface. Given this proposed role in public health policy, it is essential that the report include specific epidemiologic and other information about harms and precautions associated with the use of methadone as a pain therapy. Inclusion of this information would provide readers with appropriate context to support a critical evaluation of the role of methadone in the treatment of chronic pain. It would also be consistent with the approach the authors used in presenting a similar FDA safety warning for buccal fentanyl within this report.

Quality of evidence
The report states that relatively few studies met the inclusion criteria defined for this systematic review. Pew appreciates that evidence limitations frequently prevent the development of strong recommendations or conclusions. It is not our intent to critique the inclusion of specific studies or their outcomes, but rather to ensure that this information is provided with appropriate context. As currently written, some sections of the report do not provide adequate qualifications regarding the limits of the evidence comparing mortality between methadone and morphine. **We encourage AHRQ to ensure that evidence limitations are reinforced throughout the report, including within the Structured Abstract.**

As drafted, the Structured Abstract places strong emphasis on an observational cohort study that found methadone was associated with lower all-cause mortality compared to long-acting morphine. However, the abstract fails to highlight that the authors rated the quality of that evidence as low. There is a statement earlier in the abstract that notes the overall low quality of evidence for the full report, but it is unclear if this statement is applicable to the methadone study or other studies highlighted in the Results section of the Structured Abstract. Other limitations of the methadone study, including the extent to which it is applicable to other populations given the unique characteristics of the Veterans Affairs population that was studied, are described only within the detailed text where they may be overlooked or misinterpreted by some readers. Given the prominent presentation of these study results in the Structured Abstract, it is important to balance that information with a more prominent statement about limitations within that same section.

Conclusion

Thank you for the opportunity to provide comment on the draft report. The Pew Charitable Trusts recognizes prescription drug abuse as a public health crisis in the United States that must be addressed. Comparative effectiveness reviews, such as this draft report, will also play an important role in improving the use of pain management therapies. Should you have any questions or if we can be of assistance with your work, please contact me by phone at 202-540-6916 or via email at creilly@pewtrusts.org.

Sincerely,

Cynthia Reilly
Director, Prescription Drug Abuse
The Pew Charitable Trusts

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[i] Centers for Disease Control and Prevention (CDC), "Vital Signs: Risk for Overdose from Methadone Used for Pain Relief—United States, 1999-2010," *Morbidity and Mortality Weekly Report* 61 no. 26 (2012): 493–97, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6126a5.htm; CDC, "Prescription Painkiller Overdoses: Use and Abuse of Methadone as a Painkiller" (2012), http://www.cdc.gov/vitalsigns/MethadoneOverdoses/.

[ii] CDC, "Vital Signs: Risk for Overdose from Methadone Used for Pain Relief—United States, 1999-2010.

[iii] Food and Drug Administration (FDA), "Public Health Advisory: Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat" (2006), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm124346.htm.

[iv] W. Chen et al., "Benzodiazepine Use and Misuse among Patients in a Methadone Program," *BMC Psychiatry* 11 no. 90 (2011), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3117775/, CDC, "Methadone for Pain Management: The Clinician's Role in Reducing the Risk for Overdose" (2012), http://www.bt.cdc.gov/coca/ppt/2012/08_01_12_Methadone_FIN.pdf.

[v] FDA, "Public Health Advisory: Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat" (2006); The American Academy of Pain Medicine, "The Evidence Against Methadone as a 'Preferred' Analgesic: A Position Statement From the American Academy of Pain Medicine" (2014), http://www.painmed.org/files/the-evidence-against-methadone-as-a-preferred-analgesic.pdf.

[vi] CDC. "Vital Signs: Risk for Overdose From Methadone Used for Pain Relief—United States, 1999-2010.