

Comments to “Treatment for Acute Pain: An Evidence Map”

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I write as a technically trained non-physician subject matter expert on public policy for regulation of prescription opioid analgesics. I have 22 years experience as a research analyst, moderator and webmaster for online chronic pain communities, supporting tens of thousands of patients, with over 70 papers published in a mixture of professional medical journals and popular media. In 2018, I addressed public meetings of the FDA Opioid Policy Steering Committee and the HHS Inter Agency Task Force on Best Practices in Pain Management.

While there can be constructive purpose in gathering recent practice standards and systematic outcomes reviews to assess the strength of evidence for acute pain, the manner in which AHRQ contractors have performed this task raises serious questions concerning research integrity and methods.

1. We are made aware that this research was guided by a named group of “Key Informants”; summaries are provided of their telephone conference calls. But qualifications and current employment of these informants do not appear in the report. While the study investigators declare that they have no personal or professional conflicts of interest, we do not know if this assertion also applies to the Informants upon whom the investigators relied.
2. The scope of review is initially restricted to 2016-2018, with selective research to earlier years for areas of practice where new guidelines do not appear. Medical practice in 2016-2018 has been profoundly and negatively influenced by the 2016 CDC guidelines on prescription of opioids to adults with chronic pain. However, CDC guidelines are presently undergoing a process of reconsideration and repudiation -- not only by CDC but also by FDA and multiple medical professional associations.
3. The American Medical Association has declared that Morphine Milligram Equivalent Daily Dose - a centrally important “metric” of the CDC guidelines – should not be considered relevant in assessing practice standards for prescription of opioids. This measure is rendered moot by the wide range of variation in opioid metabolism between individuals, due to genetic polymorphism in expression of key enzymes in the human liver.

4. By restricting scope of study to 2016-2018, earlier pertinent outcomes reviews are excluded. One key document is the Cochrane Review of 2010 which found evidence of addiction in only 0.27% among ~4800 patients treated with opioids for chronic non-cancer pain.ⁱ

The combination of these factors must prompt a significant reassessment of the rigor and medical evidence of any trials embraced by the Draft Comparative Effectiveness Review.

Evidence of Systematic Reporting Bias

Many areas of the proposed "Evidence Map" reflect an uncritical and scientifically unsupported systematic bias against opioid analgesic therapy. No opportunity seems missed to amplify on widely prevalent anti-opioid hype and hysteria which assigns responsibility for the US public health problem with opioid addiction and mortality to doctors "over-prescribing" opioid pain relievers to their patients. This casual bias is signaled in part by reference to "press reports" as if they establish an association between rising rates of opioid related mortality versus rising rates of prescription in the first decade of the 21st Century. This association is unproven and in fact conclusively contradicted by the medical and statistical evidence.

We now know beyond any reasonable contradiction that there is no cause and effect relationship between rates of opioid prescribing by healthcare providers, versus rates of overdose-related mortality from all sources – legal or diverted prescriptions and illegal street drugs. This lack of relationship is conclusively established from data published by the CDC itself. Figures below are constructed from 17 years of data in the CDC Wonder database and Annual Drug Surveillance Report. Cause and effect association of opioid-related mortality to physician prescribing is directly contradicted by CDC data on prescribing rates, mortality, and demographics in patients versus those of addicted populations [ⁱⁱ]

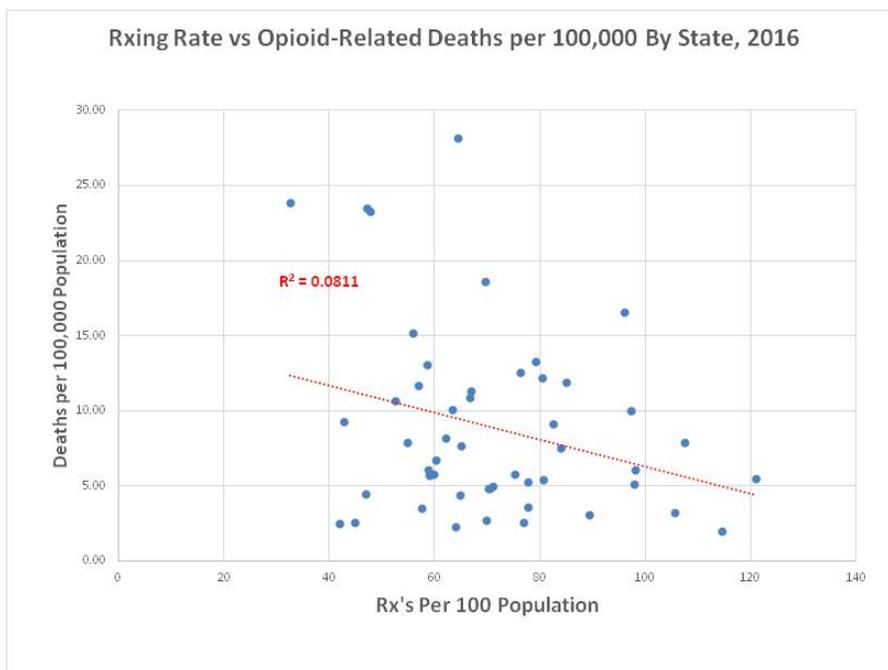


Figure 1: US Prescribing Rates Vs Mortality – CDC Wonder Database

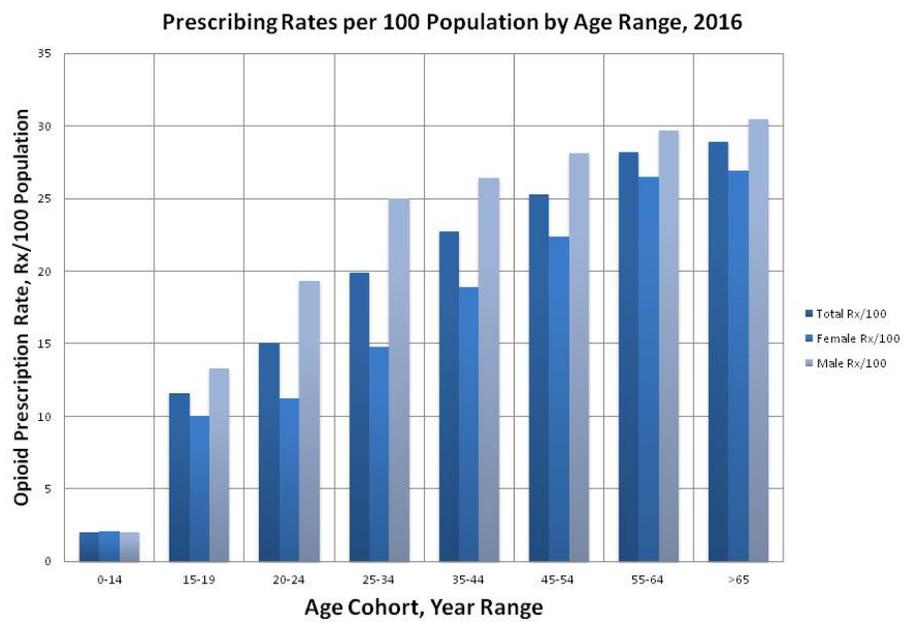


Figure 2: Prescribing Rates by Age Cohort

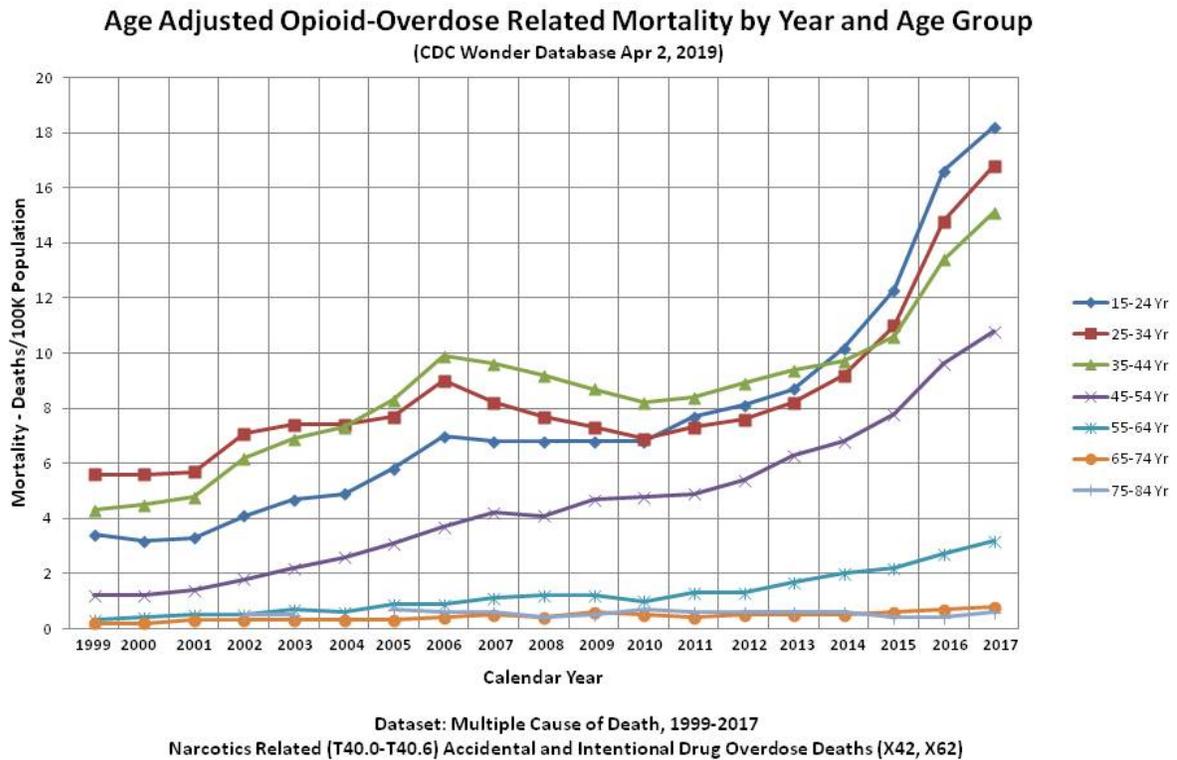


Figure 3: Age-Adjusted Opioid Overdose Mortality by Year and Age Group

As noted from Reference 1, overdose-related mortality is six times higher in youth and young adults than in seniors age 55 and older. Yet seniors are prescribed opioids two to three times more often than young people. Moreover, rates of overdose mortality in seniors have remained relatively stable over 17 years at the lowest levels in any age group, while skyrocketing in young adults to levels now six times higher than in seniors.

The typical chronic pain patient is a woman in her 40s or older, while the typical initiating addict is a young male with a family history of substance abuse, alcoholism, economic dislocation and/or family trauma. Women whose lives are stable enough to see a doctor regularly for pain are almost never found to be substance abusers.

Demographics profoundly contradict exposure to medical opioids as a significant cause of opioid addiction. As noted by Dr Nora Volkow, Director of the National Institute On Drug Abuse, and a co-author:

“Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of persons who are exposed to opioids — even among those with pre-existing vulnerabilities. [iii]

Findings of a 2018 study reported in the British Medical Journal [iv] reinforce this observation for issues of acute pain practice addressed in this Evidence Map. Investigators examined health insurance records to establish outcomes among more than 586,000 patients prescribed opioids for the first time after surgery. Less than one percent continued renewing their prescriptions longer than 13 weeks. 0.6% were later diagnosed with Opioid Abuse Disorder, during follow-up periods averaging 2.6 years between 2008 and 2016.

Likelihood of diagnosis increased with the length of prescriptions, but rose only modestly as dose levels rose from under 20 to over 120 MMED. It is plausible that this incidence estimate represents a maximum, in that diagnosis of OAD was frequently made by general practitioners lacking current training in Opioid Abuse Disorder. A hostile regulatory environment has created incentives for discharge of patients being managed on opioids – whether or not their actual behavior fits profiles for substance abuse.

Also pertinent, is a 2016 study reported in the Journal of the American Medical Society [v] which tracked long-term opioid prescription renewals in non-surgical patients and compared prescription rates to 642,000 patients who underwent one of eleven common types of surgery. Opioid prescriptions were defined as “chronic” when 10 or more scripts were written in one year or a prescription was renewed continuously for more than 120 days.

In this study, the rate of chronic prescriptions of opioid analgesics among millions of non-surgical patients was estimated at 0.136 percent. For four of 11 surgical procedures, the same rate of prescriptions occurred after surgery as before. For seven remaining procedures, long-term opioid prescription renewals rose only marginally -- to 0.174% for caesarean delivery, and a maximum of 0.69% for total knee replacement. It seems plausible that much of this increase reflected emergence of chronic pain from failed procedures, rather than misuse of medical opioids.

Finally, attention must be drawn to the June 2018 AHRQ systematic outcomes review for non-pharmacological, non-invasive therapies in chronic pain. Although this report attempted to put a positive interpretation on outcomes, details of the report significantly contradicted its summary conclusions.

Buried deep in the report was admission of a major weakness in the literature for techniques such as acupuncture, rational cognitive therapy, and others – some of which are also addressed in the present Evidence Map. Trials for these techniques almost uniformly failed either to fully define “usual therapy” or to account for an assumed but

undocumented continuation of such therapies in parallel with trials of non-pharmacological alternatives. Unsurprisingly, the strength of medical evidence was found to be weak in almost all of the trials literature for alternative techniques in chronic pain. It will be highly surprising if the same trend is not found by a deep quality review of the same techniques applied in acute pain.^{vi}

Recommendations

1. Withdraw the draft AHRQ Evidence Map for an independent internal review of process and findings in quality reviews of non-opioid therapies applied in acute pain practice.
2. Explicitly address whether weaknesses of the trials literature for non-opioid therapies in chronic pain may also apply in the assessment of acute practice guidelines.
3. Re-direct the process and text of the Evidence Map to remove the scientifically unsupported assumption that prescription opioid analgesics are inherently addictive and dangerous under appropriate medical supervision.
4. Fully identify the professional qualifications and employment of all “Key Informants.”

ⁱ Merideth Nobel, Jonathan R Treadwell, Stephen J Treger, et al, “Long Term Opioid Management for Chronic Non-Cancer Pain” Cochrane Systematic Review, 20 January 2010. <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006605.pub2/full>

ⁱⁱ Richard A. Lawhern, “[Over-Prescribing Did Not Cause America’s Opioid Crisis](#)”, Dr Lynn Webster blog, Updated April 5, 2019

ⁱⁱⁱ Nora D Volkow, MD, and Thomas A McLellan, Ph.D., “Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies” . *NEMJ* 2016; 374:1253-1263 [March 31, 2016](#)]. <http://www.nejm.org/doi/full/10.1056/NEJMra1507771>

^{iv} Gabriel A Brat, Denis Agniel, Andrew Beam, Brian Yorkgitis, Mark Bicket, Mark Homer, Kathe P Fox, Daniel B Knecht, Cheryl N McMahill-Walraven, Nathan Palmer, Isaac Kohane, “Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study”, *BMJ* 2018;360:j5790 <http://www.bmj.com/content/360/bmj.j5790.long>

^v Eric C. Sun, Beth D. Darnall, Laurence C. Baker, Sean Mackey, “Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period”, *JAMA Internal Medicine* 2016;176(9):1286-1293.

<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2532789>

^{vi} Richard A Lawhern, Ph.D., and Stephen E Nadeau, MD, “Behind the AHRQ Report -- Understanding the limitations of “non-pharmacological, non-invasive” therapies for chronic pain.” *Practical Pain Management*, V18, Issue 7, October 2018.