The Agency for Healthcare Research and Quality Labors Mightily To Produce a Mouse

By

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On August 31, 2020, the US Agency for Healthcare Research and Quality (AHRQ) announced availability of a draft systematic outcomes review on **"Treatments for Acute Pain".** The report is intended to support revision and expansion of the 2016 CDC guidelines for prescription of opioids to adults with chronic non-cancer pain, by inclusion of new guidelines for acute (short term) pain treatment. In this intention, the draft report hugely fails.

I have downloaded, reviewed and commented on this draft via the AHRQ in-house gateway:
https://effectivehealthcare.ahrq.gov/products/treatments-acute-pain/draft-review

ABSTRACT:

In its year-long effort to assess the trials literature pertinent to treatments for acute pain, the Agency for Healthcare Research and Quality has labored mightily to produce a mouse. The resulting report is clearly biased by an anti-opioid agenda, drawing conclusions that are largely unsupported by the 115 trials they extracted from an identified literature of over 20,000 reports. Missing is any evidence of participation by patients or their advocates. Also missing is acknowledgment of the abysmal state of rigor and depth in the trials literature. The report demonstrates no credible basis for its top-level claims that Tylenol and NSAIDs are superior to opioids in the treatment of acute pain in medical disorders such as kidney stones.

This report should be withdrawn for a major reconsideration in light of findings of both the American Medical Association Opioid Task Force, and the HHS Interagency Task Force on Best Practices in Pain Management.

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MY COMMENTS AS SUBMITTED

Section 1. Comments on the Evidence Summary of the draft report

Main Points (Bullet Points quoted from the Report)

· • Opioids are probably less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) for several acute pain conditions (postoperative pain, surgical dental pain, and kidney stones) and might be similarly effective to NSAIDs for low back pain.

My response:

One of the more subtle reporting biases found in this report is that opioids are rarely a treatment of first choice in low back pain not associated with surgery. It is thus to be expected that NSAIDs will be a default first treatment in mild to moderate low back pain. The inclusion of single-dose trials in the data review introduces a bia against opioids, in that no opportunity is offered for appropriate dose titration to reach effective levels of medication.

· • Opioids might be and NSAIDs are probably more effective than acetaminophen for surgical dental pain, but opioids are probably less effective than acetaminophen for kidney stone pain.

My Response:

Again, the anti-opioid bias is evident in any connection between this “main point” and single-dose trials. Having myself been treated on multiple occasions for kidney stones -- with both acetaminophen and low-dose prescription opioids -- I can attest that acetaminophen is far less effective or immediate in moderating pain in some patients. More fundamentally, this assessment is widely reflected in patient reports from social media.

· • An opioid might be more effective than Gabapentin for acute neuropathic pain.

My Response:

This is one of the few areas of the report in which “might” is appropriately used. During 24 years of online support group moderation as a non-physician subject matter expert in chronic neuropathic face pain, I have observed that Gabapentin is widely used off-label in management of such pain. Some patients respond positively to titrated/divided doses over 1200 mg/day; others receive no pain relief from this medication; some are initially relieved only to have pain recur within weeks or months for no explained reason. A few display allergic reactions to the med. “Brain fog” (cognitive disorganization) and word finding difficulty are common side effects in many.

For significant numbers of patients, opioids offer improved outcomes for both effectiveness and fewer side effects.

· • Opioids are probably associated with increased risk of short-term adverse events versus non-opioid pharmacologic therapy for acute pain, including any adverse event, study withdrawal due to adverse events, nausea, dizziness, and somnolence, but serious adverse events are uncommon in randomized trials.

My Response:

Although serious short term adverse events may be uncommon in randomized trials, withdrawal by patients placed on placebo is common due to uncontrolled breakthrough pain. Moreover, many adverse events associated with non-opioid pharmacologic therapy are not observed in hospital settings, but instead occur later in re-admissions for liver toxicity, cardiac irregularities, ulcers or colitis reactions. Failure to acknowledge this obvious confound compromises the integrity of the observation.

· • Being prescribed an opioid for acute low back pain or postoperative pain might be associated with increased likelihood of use of opioids at long-term follow-up versus not being prescribed.

My Response:

This assertion is almost certainly an example of the post hoc ergo propter hoc fallacy. Prevailing medical practice looks upon prescription opioids as an option for relatively severe pain that is unresponsive to other interventions. Initial high severity and protracted duration of pain are associated with later emergence of chronic pain syndromes. Since opioids are used in more severe or intractable pain, we would expect continuing use during long-term follow-up compared to cases where pain is less severe and opioids are not initially tried.

Large-cohort studies (not referenced by the AHRQ report) of post surgical pain are also available that demonstrate rates of long-term prescription (>90 days continuous renewals) in opioid-naïve post-surgical patients on the order of 1% or less. Within this 1%, some proportion reflects not exposure to opioids in any habituating sense, but rather the failure of a surgical procedure to fully address the original cause of pain. This distinction is not acknowledged in the AHRQ report as a confound, and it should be.

· • Heat therapy is probably effective for acute low back pain, spinal manipulation might be effective for acute back pain with radiculopathy, massage might be effective for postoperative pain, and a cervical collar or exercise might be effective for acute neck pain with radiculopathy.

My Response:

Radiculopathy pain is associated with nerve pinch or lesions. Spinal manipulation in such cases must be administered with profound caution to avoid further damaging nerves that may already be compressed or damaged. Studies which mix patient populations with and without radiculopathy introduce potential confounds that should be acknowledged and assessed before drawing any general conclusions on effectiveness or treatment risks.

· • Research is very limited on the comparative effectiveness of therapies for sickle cell pain, acute neuropathic pain, neck pain, and management of postoperative pain following discharge.

My Response:

These research limitations are no less applicable for other categories of pain addressed by the AHRQ report and have in fact been highlighted in a Cochrane Review of the 2016 CDC Guidelines on prescription of opioids to adults with chronic non-cancer pain. In fact, the current AHRQ review unintentionally offers significant support for an assessment that the current state of medical trials literature lacks methodological rigor to such a degree that generalizations drawn by AHRQ writers are clearly inappropriate and should be withdrawn outright.

TECHNICAL EXPERT PANEL

Quoting from the report:

"In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts."

My Response:

If these important defining elements of the study do not represent the views of individual technical and content experts, then whom DO they represent? And precisely how were they arrived at? In areas of research where conclusions may be controversial, it is customary to entertain a "minority report". However, the AHRQ report instead opts for an effort to create the illusion of collegial unanimity.

Treatments for Acute Pain Systematic Review [Structured Abstract]

My Response:

Remarks on the Key Points apply equally to the structured abstract.

Section 2. Comments on the Introduction section of the draft report.

"Opioids, traditionally considered the most potent analgesics, are frequently used for acute pain. Therefore, acute pain management must be considered within the context of the current opioid crisis. Opioid prescribing quadrupled from 1999 to 2010; concurrently, the number of opioid analgesics deaths and opioid use disorder cases similarly rose sharply. 17 In 2017, an estimated 47,600 Americans died from opioid overdose (approximately 17,000 from prescription opioids 18)."

My Response:

As offered in the AHRQ report, this phrasing is another example of the post hoc ergo propter hoc fallacy. It is now known from multiple published sources that there is no cause-and-effect relationship between rates of opioid prescribing by doctors to their patients, versus rates of opioid overdose-related mortality. Seniors over age 62 have the highest rates of opioid prescription for pain and the lowest rates of overdose mortality – for the most part stable for the past 17 years. Youth under age 19 have the lowest rates of prescription but demonstrate mortality rates three to six times higher than seniors. This demographic inversion cannot be explained by any medical model that posits prescribing as a substantial cause of either opioid addiction or overdose deaths.

It is also known that there is no correlation between prescribing rates versus mortality on a US State-by-State basis. Data published in the CDC Wonder database for 2017 inform us that the trend line for opioid mortality versus prescribing rates is for lower

mortality in US States where prescribing is highest. Multiple demographic studies and published reports of US CDC itself also confirm that the major driving factors in the current “opioid crisis” are illegal fentanyl, heroin, and Methamphetamine -- not prescription drugs. When a prescription opioid is found in postmortem drug toxicity screens, it is almost always found in association with multiple illegal substances and alcohol. At least one published estimate of the proportion of overdose deaths attributable to a single prescribed opioid alone is on the order of 2.5%.

As confirmed by the AMA in its recent comments to CDC, to represent the US opioid crisis in prescription-centric terms is a profound and fallacious mischaracterization.

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“The 2016 Centers for Disease Control and Prevention (CDC) guideline focused on chronic pain, but included one recommendation to limit opioids for acute pain in most cases to 3 to 7 days. This recommendation was based on evidence indicating an association between use of opioids for acute pain and long-term use. 35”

My Response:

This earlier recommendation has likewise been challenged by the AMA in its recent comments concerning needed revisions to the 2016 guidelines.

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“In the last several years, over 25 states have passed laws restricting prescribing of opioids for pain; nearly half of the states with limits specify that they apply to acute pain.20,36 Although data indicate some effects of policies in reducing opioid prescribing, studies on clinical outcomes are lacking.”

My Response:

June 2020 AMA comments to the CDC likewise challenge CDC to actively advocate for repeal of these laws.

As a final observation on this section of the AHRQ draft report, I note that the introduction is remarkable not only for what it says, but for what it doesn’t. The report ignores well established contradictions to its own politically pre-determined messages.

Notably, neither the authoritative work of Dr Nora Volkow and the National Institute on Drug Abuse nor the published commentaries of the American Medical Association are discussed.

Specifically, Dr Volkow and a co-author state in the New England Medical Journal:

“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...Older medical texts and several versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) either overemphasized the role of tolerance and physical dependence in the

definition of addiction or equated these processes (DSM-III and DSM-IV). However, more recent studies have shown that the molecular mechanisms underlying addiction are distinct from those responsible for tolerance and physical dependence, in that they evolve much more slowly, last much longer, and disrupt multiple brain processes."

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

Section 3. Comments on the Methods section of the draft report.

Author's Note: With eight key questions, it should immediately have become apparent that many would go unanswered when review of published trials narrowed down the eligible trials set to 151 out of 20,000. However, the review team appears not to have made an effort to refine their focus.

Section 4. .Comments on the Results section of the draft report.

Author's Notes:

Among the 115 trials that survived AHRQ quality review, the assessed strength of medical evidence (SOE) was "low" in 52, "low to moderate" in 3, "moderate" in 15, and "insufficient" in 29. This level of evidence does not engender confidence in generalizations from such results.

The report section on Applicability is worth repeating and parsing (bold emphasis by the author):

Applicability

"A number of issues could impact the applicability of our findings. Most randomized trials were conducted in emergency department or postoperative care unit settings, which might reduce applicability to outpatient management of acute pain. Further, **trials of pharmacologic therapy frequently evaluated a single dose and some trials of nonpharmacologic therapy evaluated a single treatment session, potentially limiting the applicability of findings to a multidose course of treatment.** Trials excluded important patient subgroups, such as persons with a history of substance use disorder, prior opioid use, and psychological or medical comorbidities, or did not report information regarding these factors. In addition, trials were not designed to evaluate how benefits or harms varied in subgroups defined by these factors or others, such as age, sex, and race/ethnicity. **Another limitation to applicability is that most trials—particularly trials of pharmacologic therapy—were designed to assess short-term (<1 week, and often <1 day) effects on pain, with few trials evaluating effects on non-pain outcomes or at longer term followup.** Finally, the applicability of findings for one pain condition addressed in this review to another pain condition in this review, or to acute pain conditions not addressed in this review, is uncertain. For example, opioids were associated with decreased pain versus acetaminophen for dental

pain, but increased pain versus acetaminophen for kidney stone pain. The applicability of findings from one acute pain condition to others may vary depending on the type and nature of the pain. For example, evidence on pharmacologic therapy for low back pain may have high applicability to neck pain, another musculoskeletal condition in the spine, but less applicable to sickle cell pain, neuropathic pain, or abdominal pain."

My Response:

Potential limitations on applicability summarized above seem to fly directly in the face of stated "Key Findings" earlier addressed. It may not be going too far to suggest that these limitations should prompt outright withdrawal of this AHRQ report, in light of the profound weaknesses revealed in medical trials literature.

The many confounds revealed here contradict the top level key findings of the report with respect to comparative effectiveness of opioid analgesics versus NSAIDS or other non-opioid treatments. We simply cannot say from such weak evidence whether non-opioid therapies "probably" or "may" be superior to opioids. Such statements in the report are highly irresponsible and ill-supported.

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Research Gaps

"It is important for future studies on opioids to evaluate longer-term outcomes, including long-term use and potentially associated harms (e.g., opioid use disorder, overdose, impaired social and emotional cognition, and workforce nonparticipation). Well-designed clinical registries that prospectively enroll patients with acute pain prescribed and not prescribed opioids could complement randomized trials evaluating long-term outcomes."

My Response:

Wording of this text reflects an uncritical anti-opioid bias and assumption of harms that is unsupported by medical literature. It also ignores a reality of randomized controlled trials involving a placebo arm. As we are informed by a Cochrane Review, the relative paucity of long-term trials on opioid effectiveness is for the most part a research artifact: many pain patients placed on placebos drop out of conventional randomized trials. To obtain a more balanced trial, it may be necessary to instead perform "enriched enrollment" trials.

See

Baraa O. Tayeb, Ana E. Barreiro, Ylsabyth S Bradshaw, Kenneth K H Chui, Daniel B Carr, "Durations of Opioid, Nonopioid Drug, and Behavioral Clinical Trials for Chronic Pain: Adequate or Inadequate?" *Pain Medicine*, Volume 17, Issue 11, 1 November 2016, Pages 2036–2046.
https://academic.oup.com/painmedicine/article/17/11/2036/2447887

5. Comments on the Discussion section of the draft report

None Offered

6. Comments on the References section of the draft report.

In the report section on Opioid Therapy, the AHRQ team missed or perhaps deliberately ignored a landmark study which contradicts their conclusions concerning the centrality of medical opioids in our public health crisis:

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

In another of the references, AHRQ writers chose to emphasize the appearance of a dose-dependent relationship between initial opioid use in acute pain and long-term use in chronic pain. They ignored the absolute numbers of patients in which such a relationship was inferred. Likewise, they jumped to conclusions on cause and effect that were unsupported by the data offered.

See

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*

Although the draft report of the HHS Task Force on Pain Management is referenced, its central conclusion that there is no one-size-fits-all pain patient or treatment plan is conveniently ignored.

Also of concern is the inclusion of six references in which Dr Roger Chou is a co-author. Dr Chou has been centrally involved in multiple AHRQ systematic outcome reviews on treatment of pain, as well as being a principal author of the 2016 CDC Guidelines. He has a record of publications co-authored with key figures and founders of the organization "PROP - Physicians for Responsible Opioid Prescribing." PROP and its members have a long history of anti-opioid advocacy and financial self-interest.

If Dr Chou has been a contributor to the current AHRQ report, then I must strongly demand that he recuse himself from any further review of this document, on grounds of professional conflict of interest. His first instinct must be to defend his own body of work, regardless of the consequences to patients or colleagues.

7. Comments on the Abbreviations and Acronyms section of the draft report

None offered

8. Comments on the Appendixes of the draft report.

None Offered

9. General comments on the draft report.

I write and speak as a technically trained non-physician patient advocate for people with chronic pain, with 24 years experience in this field. I have published over 100 papers, articles, public addresses and conference proceedings in a mix of mainstream medical journals and mass media. I sit as an invited participant on two editorial boards, neither of which has reviewed or approved the remarks below.

Overall Observations by the Author:

Use of the terms “are probably” or “might be” to describe outcomes of trials suggests to me a systemic anti-opioid bias throughout the report and its appendices. When reported details of the referenced trials are examined with care, we find no protocols, methods, or analysis to establish either probability or possibility of the claimed outcomes, from the original sources.

What we find instead are assessments of “medical evidence weak” or “no evidence”, describing the majority of 151 randomized controlled trials summarized in the report (from more than 20,000 candidate trials initially flagged from medical literature database search, of which 1871 were subjected to full text review).

It must be assumed that such terms were introduced as opinions by the AHRQ report writers, or peer reviewers, or both. Given that the draft report fails to identify names and affiliations of the writers, it becomes practically impossible to research their professional publications for known biases and predispositions. Likewise important is that there is no evidence of participation in this review process by any patient advocate or representative.

A major shortcoming of this report is its failure to adequately acknowledge confounds in the medical literature and in the analysis of the AHRQ writing team, which significantly compromise any ability to generalize results meaningfully in prescription guidelines or policy.

Specifically, there is no mention of the terms “genetic” or “genomic” anywhere in this report. Yet we now know from other sources that there is high variability in individual responses to prescription opioid medications, due to polymorphism in the expression of six liver enzymes which mediate opioid (and 90% of other medications) metabolism. This medical reality is plausibly a major underlying reason why no currently available patient profiling instrument has demonstrated reliable prediction accuracy for risk of dependence, tolerance, addiction or mortality in medical patients managed on opioid therapy. Lack of such instruments is acknowledged in the report, but no explanation for the reasons associated therewith is offered.

The practical impact of natural patient metabolic variability is that it is literally impossible to generalize conclusions concerning opioid safety or effectiveness, based on any fixed dose or duration criteria. As acknowledged by both the May 2019 report of the HHS Interagency Task Force on Pain Management, and the American Medical Association in

its June 2020 comments to a CDC Call for Stakeholder Comment in the Federal Register, there can be no one-size-fits-all patient or therapy plan. Trying to generalize a single standard of pain care – even for a single disorder – is a fool's errand and very likely to remain so for the foreseeable future.

A clear implication from HHS and AMA findings current as of September 2020 is that fundamental premises and assumptions embedded in the AHRQ systematic review concerning risks or harms must be withdrawn and reconsidered from the ground up. AMA is now on public record challenging the US CDC to undertake nothing short of an across-the-board repudiation and withdrawal of all legislated hard limits on prescription opioid daily dose or duration. This challenge in effect renders much of the AHRQ outcomes review moot.

Also of concern is the process by which this draft report has been issued. AHRQ has circulated it only to their internally managed email distribution lists, with a review period of 30 days. In an outcomes review of this magnitude, a more appropriate venue would be the US Federal Register, for a period of at least 60 days. However, the draft – if it is issued at all – will require major revision and refocus along lines suggested herein, before any public review is announced.

Section 10. Does this report describe both the problem and the evidence in a way that you could understand?

Although the report describes a problem and reviews evidence, its conclusions are biased and substantially divorced from the many confounds revealed in the trials that it purports to review and synthesize.

11. Did you find this report unnecessarily difficult to read?

No comments offered

12. Could you find and understand the results and conclusions?

No comments offered