

Comments to the Colorado Department of Regulatory Agencies
“Guidelines for the Safe Prescribing and Dispensing of Opioids”
[Revised 3/14/19]

Richard A Lawhern, Ph.D ¹., Stephen E Nadeau, MD,² and Andrea Trescot, MD³

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Abstract

In its present form, the Colorado Department of Regulatory Agencies (CDRA) “Guidelines for the Safe Prescribing and Dispensing of Opioids” is neither safe for patients nor grounded in scientific evidence. The CDRA document replicates the very serious scientific flaws of the 2016 CDC Guidelines on prescription of opioids to adults with chronic non-cancer pain. Pending draft CDC updates and revisions to the guidelines appear to compound the same errors.^{4 5}

The core “measures of merit” around which the entire CDC [and Colorado derivative] opioid guidelines are constructed comprise limitations on doctor-prescribed Morphine Milligram Equivalent Dose (MMED), combined with limitations on length of prescriptions. A June 2021 FDA Workshop, as well as multiple independent published analyses and critiques of the MMED concept reveal this measure to be unsupported by scientific evidence and enormously destructive to both individual patients and to the practice of

¹ Richard A Lawhern PhD is a technically trained patient advocate and healthcare writer with 25 years experience, and ~130+ papers and articles published in a mixture of medically oriented journals and mass media.

² Stephen E Nadeau, MD is affiliated with Research Service and the Brain Rehabilitation Research Center, Malcom Randall VA Medical Center and the Department of Neurology, University of Florida College of Medicine. Positions offered in this paper may not reflect those of the Veterans Affairs Department or the University of Florida College of Medicine.

³ Andrea Trescot MD is a past President of the American Society for Interventional Pain Physicians. Positions offered in this paper may not reflect those of ASIPP.

⁴ NCIPC BSC Opioid Workgroup Report, July 2, 2021, Submitted to the July 16 2021 Public Meeting, available at <https://www.cdc.gov/injury/pdfs/bsc/OWG-Report-of-Recs-1-12-06.30.21-FINAL-508.pdf>

⁵ Pat Anson, “CDC Advisory Panel Warns Revised Guideline Ignores Benefits of Opioids”, *Pain News Network*, July 16, 2021, https://www.painnewsnetwork-org.cdn.ampproject.org/c/s/www.painnewsnetwork.org/stories/2021/7/16/advisory-panel-warns-cdc-revised-opioid-guideline-ignores-risk-of-undertreating-pain?format=amp&fbclid=IwAR14Fwe7C5Sxdri5Oq5NNhWb8ymooMYQ-6qAYne_vLgevR251T93_sgFSA8

pain medicine. The only ethically appropriate response to this scientific reality is outright repudiation and withdrawal of the Colorado guidelines and of the parent US CDC guidelines on which they are based – without replacement.

In keeping with recommendations of the American Medical Association,^{6 7} we believe that CDRA *must* take a public position advocating for repeal of all Colorado legislation that attempts to establish hard limits on opioid prescribing dose or duration. Such a policy is beyond the competency of lawmakers and has been used as an excuse for unjustifiable persecution of physicians and even termination of their practice by State and Federal drug enforcement authorities and the Colorado State Medical Board. The fully predictable consequences have been widespread harms to both physicians and their patients.

Discussion

Comments which follow are organized by sections of the March 2019 revision of the CDRA “Guidelines for Safe Prescribing and Dispensing of Opioids”. Many of the references herein have separately been made available in comments submitted by one of the authors, Richard A Lawhern, for inclusion in the minutes of the July 16 public meeting of the Board of Scientific Counselors of the National Center for Injury Prevention and Control. ⁸ However all authors jointly support comments below.

Preamble:

Authors’ Comments: As written, the Preamble of the Colorado Guidelines is phrased as an apologia for arbitrary and unjustified attempts to “solve” a major opioid-related US public health crisis in addiction and overdose related mortality by restricting patient access to prescription opioids. However, from multiple sources, including the American

⁶ James L. Madera, MD, CEO American Medical Association, public letter to Debra Dowell, MD, “Re:Docket No. CDC-2020-0029”, June 16, 2020, <https://searchf.ama-assn.org/letter/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2020-6-16-Letter-to-Dowell-re-Opioid-Rx-Guideline.pdf>

⁷ Jack Deutsch, “AMA Backs Update to CDC Opioid Prescribing Guidelines”, American Medical Association Press Release, July 22, 2021, https://www.ama-assn.org/press-center/press-releases/ama-backs-update-cdc-opioid-prescribing-guidelines?utm_source=twitter&utm_medium=social_ama&utm_term=5205422460&utm_campaign=Advocacy&utm_effort=FBB009&fbclid=IwAR0MXqGu-9L0lguqSgNu7TgDoLWd4baZRGGLoy2v-rFyK_eV0NyYJ60NE

⁸ NCIPC Board of Scientific Counselors, “Meetings, Minutes, and Documents” last accessed July 30, 2021 <https://www.cdc.gov/injury/bsc/meetings.html>

Medical Association, it is clear that since 2010, there has been no statistical relationship between rates of opioid prescribing and rates of opioid overdose related mortality.⁹,¹⁰

On the basis of extensive literature review and analysis, two of the authors have elsewhere noted, "...As the causes of the opioid crisis have come into focus, it has become clear that the crisis resides predominantly in the streets and that efforts to curtail it by constraining opioid treatment in the clinic are unlikely to succeed."¹¹ In 2019, there were 49,860 opioid deaths, 13,501(27%) from prescription opioids and 36,359 (73%) from illicit opioids¹². Thus it must be immediately obvious that restrictions on opioid prescribing will not "solve" our US public health crisis in overdoses caused by illegal street drugs.

The Preamble of the Colorado Guidelines also suggests that "strategies are needed to increase healthcare providers' use of the Prescription Drug Monitoring Program (PDMP)." However, we must point out that there is considerable evidence that such programs have not been effective in reducing opioid overdose mortality, and may instead be implicated in driving both substance abusers and chronic pain patients into unsafe street markets after desertion by their physicians.¹³

Finally, the Preamble states "This Policy provides guidelines and represents the Board's current thinking on this topic. It does not set a standard of care for prescribers or dispensers." Unfortunately, as we have learned since the issuance of the CDC Guidelines, there is great risk that recommendations by authoritative agencies will translate into de facto standards of care. The CDC "guideline" has been and will continue to be used by State drug enforcement authorities and Medical Boards as a criterion for sanctions and legal prosecution against doctors who are deemed to "over-prescribe".

⁹ Richard A Lawhern, Ph.D. "Stop persecuting doctors for legitimately prescribing opioids for chronic pain", STAT News, June 28, 2019, <https://www.statnews.com/2019/06/28/stop-persecuting-doctors-legitimately-prescribing-opioids-chronic-pain/comment>

¹⁰ Jeffry Singer, MD, "Evidence Pours More Cold Water on the False Narrative that Prescriptions Caused the Opioid Crisis", *Cato at Liberty*, November 20, 2019, <https://www.cato.org/blog/evidence-pours-more-cold-water-false-narrative-prescriptions-caused-opioid-crisis>

¹¹ Steven E Nadeau, MD, Jeffry K Wu, and Richard A Lawhern, PhD, "Opioids and Chronic Pain: An Analytic Review of the Clinical Evidence", *Journal of Medicine*, National College of Physicians, March 1, 2021.

¹² Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis NL. Trends and geographic patterns in drug and synthetic opioid overdose deaths — United States, 2013-2019. *MMWR Morbidity and Mortality Weekly Report*. 2021;70(6):202-7).

¹³ Jacob James Rich and Robert Capodilupo "Prescription Drug Monitoring Programs: PDMP Effects on Opioid Prescribing and Drug Overdose Mortality." *Reason Foundation*, July 2021, <https://reason.org/wp-content/uploads/prescription-drug-monitoring-programs-effects-on-opioid-prescribing-and-drug-overdose-mortality.pdf>

Executive Summary of the Colorado Guidelines

Prescribing Safeguards: “**Dosage** - When prescribing a dosage above 50 mme/day, **STOP:** 1) Ensure the patient’s condition warrants the higher dose; 2) Ensure the benefits of a higher dose outweigh the risks; and, 3) Ensure additional risk mitigation strategies are in place.”

Authors’ Comments: The Colorado guidelines, as well as the CDC 2016 opioid “guidelines” -- and the present CDC draft rewrite – seek to constrain the availability of medically prescribed opioid analgesics, employing threshold values of Morphine Milligram Equivalent Daily Dose (MMED) as the major criteria.

We now know from multiple sources that MMED at best provides a very rough guide to clinicians who are switching a patient from one opioid to another.^{14, 15, 16} Data from multiple studies, including patients on long-term opioids and opioid-naïve patients treated for post-operative pain, reveal that opioid dose requirements differ from patient to patient by a factor of as much as 15.

Published studies reveal the pivotal role of individual genetically mediated variations in opioid metabolism. Taken in combination, these references effectively invalidate all efforts to generalize standardized criteria for opioid dose across general patient populations or specific disease entities.^{17 18 19 20} This literature brings new urgency to the observation of the 2019 HHS Task Force on Best Practices in Pain Management that there is no one-size-fits-all pain patient or therapy plan.

¹⁴Jeffrey A. Singer, MD, “If Lawmakers Really Want to ‘Follow the Science’, They Will Repeal Codified Opioid Guidelines”. *Cato At Liberty*, May 24, 2021. <https://www.cato.org/blog/lawmakers-really-want-follow-science-they-will-repeal-codified-opioid-guidelines>

¹⁵ Josh Bloom, PhD, “Comments to the FDA – Opioid Dosing Based on Milligram Morphine Equivalents is Unscientific”, *American Council on Science and Health*, May 24, 2021, <https://www.acsh.org/news/2021/05/24/comments-fda-opioid-dosing-based-milligram-morphine-equivalents-unscientific-15561>

¹⁶ Sally Satel, MD, “The Truth About Painkillers” *National Affairs*, Nr 47, Spring 2021. <https://nationalaffairs.com/publications/detail/the-truth-about-painkillers>

¹⁷Tom Lynch, Amy Price, “The Effect of Cytochrome P450 Metabolism on Drug Response” *Am Fam Physician*. 2007 Aug 1;76(3):391-396. <https://www.aafp.org/afp/2007/0801/p391.html>

¹⁸ Donna J. Belle and Harleen Singh, “Genetic Factors in Drug Metabolism”, *Am Fam Physician*. 2008 Jun 1;77(11):1553-1560 <https://www.aafp.org/afp/2008/0601/p1553.html>

¹⁹ Andrea M. Trescot, MD, and Semyon Faynboym, MD “A Review of the Role of Genetic Testing in Pain Medicine”, *Pain Physician* 2014;17 ISSN 1533-3159

²⁰ Bhushan A Kapoor, Prateek Lala, Julie L.V. Shaw, “Pharmacogenics and Chronic Pain Management” *Clinical Biochemistry*, 2014. <http://dx.doi.org/10.2016/j.clinbiochem.2014.05.065>

As acknowledged in July 16, 2021, discussions between the CDC National Center for Injury Prevention and Control, Board of Scientific Counselors and Opioid Work Group members, the 50 mg/90 mg MMED thresholds established in CDC guidelines have no support in either data or science. It is entirely plausible that these specific numbers are artifacts of the dose range conventions used widely in published papers on hospital admissions. Such thresholds have no plausible or validated relationship to patient benefit or risks of harm, other than a weak association of higher dose levels with protracted prescribing and elevated rates of mortality. Multiple studies have estimated that annual mortality associated with >100 MMED is on the order of 0.25% per year (see below).

Often ignored in considerations of the association between opioid dose and case-fatality rate is the fact that higher prescribing doses tend to be associated with more severe pain and more complex underlying medical conditions. For these conditions, mortality may derive from the medical condition itself, rather than the use of opioids in managing pain. This potential confound is rarely examined in medical literature and is not acknowledged in the Colorado Guidelines.

Published CDC data reveal that there is no relationship between rates of opioid prescribing and rates of opioid-related overdose mortality on a US State-by-State basis. Age cohort demographics also directly contradict any medical model for cause and effect between prescribing and overdose mortality. Seniors over age 62 are prescribed opioids three to six times more often than youth under age 19. However, in 2017, overdose related mortality was 13-22 times as high among youth as in seniors over age 64 and it had doubled over the previous five years among those under age 64 whereas it had increased by only 33% in those over age 64. Mortality in seniors has remained relatively stable at the lowest levels in any age group, while opioid-associated mortality has skyrocketed in youth..^{21 22}

Continuing from the text of the Colorado Guidelines:

Formulation- When prescribing a long-acting or extended relief formulation, **STOP:** 1) Ensure the patient's condition warrants this formulation; 2) Ensure the benefits of this formulation outweigh the risks; 3) Consider concurrent medications that may potentiate the effects of the formulation; 4) Ensure the

²¹ Richard A. Lawhern, PhD, "Tracking Down the 'Research' Behind The CDC's Opioid Prescribing Guidelines", National Pain Report, August 10, 2016.
<http://nationalpainreport.com/tracking-down-the-research-behind-the-cdcs-opioid-prescribing-guidelines-8831122.html>

²² Richard A. Lawhern, "The Opioid Crisis in Three Charts" – May 2021,
<http://face-facts.org/lawhern/the-opioid-crisis-in-three-charts/>

patient has been treated with immediate release opioids for at least one week prior to prescribing or dispensing this formulation; and, 5) Ensure additional risk mitigation strategies are in place.

Authors' Comments: Buried deeply in the June 2018 AHRQ Systematic Outcomes Review for Non-Pharmacological / Non-Invasive Therapies,²³ is an acknowledgment that should be taken to heart by the Colorado Department of Regulatory Agencies. There are presently no validated patient profiling instruments that accurately predict which patients are “at risk” or under what conditions they are at risk for iatrogenic opioid dependence, addiction, or overdose mortality.^{24 25}

The roles of long-acting and short-acting opioids in pain management are completely different. Long-acting opioids are prescribed on a scheduled basis, e.g., twice daily at the same times every day, in order to achieve constant suppression of pain. Short acting opioids are prescribed for use as needed for breakthrough pain. One could argue that use of short-acting opioids might actually be riskier because it is not precisely scripted and it is easier for patients to forget that they recently took a dose and thereby, overdose. In fact, the precise causes of opioid-associated death have received very scant scientific attention²⁶.

The only “risk assessments” we presently have are grounded upon patient narratives and the experience of the attending medical doctor, augmented by medical records, urine and blood testing for non-prescribed substances. Urine testing is notoriously subject to false positives and inaccurate physician interpretations. Thus the predictable outcome of the process outlined in the Colorado guidelines will be to drive even more doctors out of pain management and even more Colorado chronic pain patients into medical collapse and possibly suicide because of untreated and unsustainable pain.

²³ Skelly AC, et al. Noninvasive nonpharmacological treatment for chronic pain: a systematic review. Prepared for AHRQ, HHS, Publication No.18-EHC013-EF, Rockville, MD, June 2018.

<https://effectivehealthcare.ahrq.gov/products/nonpharma-treatment-pain/research-2018>

²⁴ Richard A Lawhern, PhD and Steven E Nadeau, MD, “Behind the AHRQ Report - Understanding the limitations of “non-pharmacological, non-invasive” therapies for chronic pain.” *Practical Pain Management*, Vol 18, Issue #7, October 3, 2018.

²⁵ Jeffrey A Singer MD, Jacob Z Sullum, Michael E Schatman PhD, “Today’s nonmedical opioid users are not yesterday’s patients; implications of data indicating stable rates of nonmedical use and pain reliever use disorder” *Journal of Pain Research*, V12:617-620, https://www.researchgate.net/publication/330922982_Today's_nonmedical_opioid_users_are_not_yesterday's_patients_implications_of_data_indicating_stable_rates_of_nonmedical_use_and_pain_reliever_use_disorder

²⁶ Nadeau SE. Opioids for chronic nonmalignant pain. To prescribe or not to prescribe—what is the question? *Neurology*. 2015;85:646-51)

For numerous medical conditions and individual patients, long-acting opioids are an essential element of therapy for avoidance of sleep disturbance due to under-medication.²⁷

Continuing from the text of the Colorado Guidelines:

“Duration-

When treating acute, non-traumatic or non-surgical pain, **STOP:** 1) Ensure the amount of medication prescribed or dispensed does not exceed the expected duration of the pain, typically 3-7 days, and complies with Colorado law.

When prescribing opioids for subacute pain and the treatment of chronic, non-cancer pain **STOP:** 1) Reassess pain and function within 30 days of initiating therapy to ensure a clear benefit; and, 2) Ensure the benefits of continued opioid therapy outweigh the risks.

If the opioid treatment exceeds 90 days for chronic, non-cancer pain, **STOP:** 1) Ensure the patient continues to show clinical improvement with opioid therapy; 2) Ensure the benefits of continued opioid therapy outweighs the risk; and 3) Ensure additional risk mitigation strategies are in place.

Authors’ Comments:

Guidelines and laws bearing on the opioid treatment of acute pain have been strongly driven by perceived risks that short term opioid treatment will translate to long-term opioid use disorder. A host of studies involving millions of patients have now shown that this concept is invalid. The “risks” of long-term opioid use following surgery are <1% and such use is plausibly related to persisting pain. In fact, there is a serious paucity of science bearing on opioid treatment of post-operative pain and such treatment must deal with the enormous person to person variability in opioid dose requirements, as well as idiosyncratic opioid side effects, which are very common.

At present, the best possible way of dealing with this knowledge gap is to assure that clinicians have full flexibility in addressing the pain of their patients and that they follow patients on a day-by-day basis after surgery to assure that pain is adequately treated (and for sufficiently long) and that there is no evidence of side effects relatable to excessive dosage. Such highly nuanced and individualized treatment relies on clinician judgment and does not lend itself to legislative constraint.

²⁷ Jennifer P Schneider MD, PhD, “Editorial: Why are ER Opioids Out of Favor?” *Practical Pain Management*, Volume 20 Issue #3, June 18, 2020

Optimization of management of chronic pain would best be achieved not by legislative constraint but by assuring far better training of physicians and better re-imbursement of pain management visits, given the magnitude of the challenges posed by these complex patients. Physicians typically receive little or no training in chronic pain management, even as it could be argued that only apprenticeships with pain experts will suffice (and not simply lectures or online courses).

Colorado Guidelines “Diagnose and Evaluate”

Authors’ Comments: Directions provided in the Colorado guidelines (page 2) to medical practitioners are exceptionally deeply detailed. If acted upon and documented in the patient’s medical records, it is doubtful that an initial or updated patient profile can be completed in less than an hour of dedicated time on the part of an examining physician. Unless the State is also prepared to set down “guidelines” on appropriate insurance compensation and billing codes, such standards will predictably drive even more specialists out of pain management practice and discourage General Practitioners from entering the field. Over-regulation has already substantially reduced the number of practitioners in pain management. However, pain is the most frequent single cause that prompts patients to seek a doctor’s help.

Of at least equal concern is the absolute magnitude of perceived “harms” that the Colorado guidelines are ostensibly intended to remedy. For instance, the annual opioid-associated case fatality rate with prescription of >100 MMED has been estimated at 0.25%,²⁸ rising to 0.5% in those receiving >400 MMED.²⁹ There are no scientifically validated predictors of opioid overdose in clinically managed populations. At the same time, absolute dosage is commonly used as a criterion for action against clinicians by regulatory authorities. Given the 15-fold variability in opioid dose requirements, this link between dosage and actions against clinicians only serves to discourage achievement of pain control and to deter clinicians from pain management.

“Consider Alternatives to Opioid Therapy”

Authors’ Comments: The text of this section of the Colorado “guidelines” [Page 4] makes clear that physicians are to first consider non-opioid medical treatments including “acetaminophen, alpha-acting agents, anticonvulsants, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, or topical lidocaine” in preference to opioids in treatment of both acute and chronic pain. Not discussed in the guideline is

²⁸ Bohnert, A.S.B., Valenstein, M., Bair, M.J., Ganoczy, D., McCarthy, J.F., Ilgen, M.A., et al. (2011). “Association between opioid prescribing patterns and opioid overdose-related deaths.” *JAMA* 305, 1315-1321.

²⁹ Gomes, T., Juurlink, D.N., Dhalla, I.A., Mailis-Gagnon, A., Paterson, J.M., and Mamdani, M.M. (2011). Trends in opioid use and dosing among socio-economically disadvantaged patients. *Open Med* 5, 13-22.

either absolute effectiveness of these therapies for the conditions that bring patients to a doctor, or risk assessment for untoward side effects.

Certain anticonvulsants, e.g., gabapentin and pregabalin, are beneficial only for neuropathic pain, as with diabetes or shingles. Other anticonvulsants, e.g., carbamazepine and lamotrigine, are beneficial only for neuralgic pain, as in trigeminal neuralgia. Antidepressants can be viewed as an essential (but often under-employed) complement to pain management of any type. The vast majority of chronic pain is musculoskeletal (back, neck, and joint pain) or chronic headache. These types of pain do not respond to these medications. Topicals (e.g., lidocaine, diclofenac gel) may provide significant relief for some patients but rarely is that relief adequate. The recommendation to pursue non-opioid pharmacologic treatment is a reasonable one but it needs to be recognized that, for the vast majority of the 15-20 million Americans with moderate to severe chronic pain, these treatments will not be adequate and opioids are going to be essential.

Non-opioid treatments are not entirely benign. High doses of Tylenol and NSAIDs are associated with hundreds of US hospital admissions for liver toxicity or lower GI bleeds every year. Recent published papers also inform us that the degree of pain relief provided by Tylenol in post-surgical pain may be no better than placebo.^{30, 31, 32, 33}

Also mentioned in the Colorado guidelines are “Non-pharmacologic treatments such as acupuncture, complementary alternative medicine, cognitive behavioral therapy, dry needling, exercise therapy, massage therapy, physical therapy, occupational therapy, osteopathic manipulation, regenerative therapy, trigger point or interventional/targeted injections, electrical stimulation, biofeedback, radio frequency ablation or interventional pain management procedures.”

³⁰ Dominique Mosbergen, “Tylenol Overdose Risk is Staggering; Acetaminophen Safeguards Remain Insufficient” *Huff Post* updated December 6, 2017

³¹ Josh Bloom, PhD., “Need General Surgery? Ignore the Surgeon General”, *American Council on Science and Health*, July 8, 2019 <https://www.acsh.org/news/2019/07/08/need-general-surgery-ignore-surgeon-general-14135>

³² Josh Bloom, PhD, “Tylenol is Not so Safe, but At Least it Works, Right?” *American Council on Science and Health*, September 18, 2017,

“In reality, Tylenol doesn’t work very well at all, and there is plenty of evidence to back this up, especially in systematic *Cochrane Reviews* - highly regarded, evidence-based reviews that carefully evaluate the quality of data in multiple studies.”

³³ Alparslan Turan, MD; Hani Essber, MD; Wael Saasouh, MD et al, “Effect of Intravenous Acetaminophen on Postoperative Hypoxia After Abdominal Surgery – The FACTOR Randomized Clinical Trial” *JAMA*. 2020;324(4):350-358. doi:10.1001/jama.2020.10009

However, a careful reading of the Agency for Healthcare Research and Quality (AHRQ) report on non-pharmaceutical / non-invasive therapy trials³⁴ and the later AHRQ report on treatments for acute pain³⁵ reveals that none of these trials have actually evaluated the effectiveness of alternative non-pharmacological therapies when compared with opioids. AHRQ investigators were forced to “assume” that such therapies were applied as adjuncts to “usual treatments” that were largely undocumented in trial protocols.

It is unlikely that alternative non-pharmacological therapies will be able to supplant opioids in achieving pain control in patients with moderate to severe chronic pain. However, such therapies might enable the use of lower doses of opioids. Comparative effectiveness trials would be essential in providing scientific grounds for recommendations regarding use of alternative therapies. Such trials have not been performed to date.

In general, trials of alternative therapies, as summarized in the AHRQ publications, have lacked scientific rigor. Further, these therapies are often compared with “usual care” but the exact nature of “usual care” is seldom adequately defined. Therefore, claims of effectiveness of such alternatives are weak, at best.³⁶ To our knowledge, none of these treatments has been subjected to the gold standard for medical evidence, a phase III multicenter randomized controlled trial. The availability of alternative therapies, their cost, and the availability of insurance coverage are seldom considered.

The 2016 CDC guidelines and the current draft rewrite of those guidelines both attempt to address the so-called “opioid crisis” by falsely asserting that non-opioid therapies are “preferable”. In the revised guideline draft, the CDC writers group is essentially proposing **not** to “augment” opioid therapy with non-opioid measures, but rather to replace opioids with a broad class of so-called “alternative” therapies that are highly experimental, supported by very weak medical evidence, and have largely marginal and temporary impact on pain and quality of life. This implicit substitution of experimental therapies for opioid pain relievers known to be effective in millions of patients could be viewed as unethical and irresponsible, the more so because, as of this writing, we know that at least 73% of opioid associated deaths are not related to prescription opioids but rather to illicit drugs, particularly heroin admixed with fentanyl.

³⁴ Roger Chou, et al, “Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review”, *Agency for Healthcare Research and Quality*, June 11, 2018.
<https://effectivehealthcare.ahrq.gov/products/nonpharma-treatment-pain/research-2018>

³⁵ Roger Chou, MD, Jesse Wagner, et al, “Treatments for Acute Pain: A Systematic Review” [Comparative Outcomes Review Number 240] *Agency for Healthcare Research and Quality*, December 2020
<https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-240-acute-pain-review.pdf>

³⁶ Ibid Lawhern and Nadeau, 2018

Discontinuing Opioid Therapy (page 14).

and

Discontinuing /Tapering Opioid Therapy (Appendix Page 2)

The Colorado Guidelines assert:

“The prescriber should consider discontinuing opioid therapy when:

- The underlying painful condition is resolved;
- Intolerable side effects emerge;
- The analgesic effect is inadequate;
- The patient’s quality of life fails to improve;
- Functioning fails to improve or deteriorates;
- The risks of treatment outweigh the benefits;
- The patient overdoses;
- The patient demonstrates suicidality;
- Non-compliance with the treatment plan;
- The prescriber suspects diversion; or
- The prescriber suspects opioid misuse or abuse.”

Authors’ Comments: We offer the following insights based on decades of clinical practice by our two MD co-authors:

- Tapered discontinuation of any medication is accepted practice when painful conditions resolve.
- Side effects are frequently manageable with ancillary medication, particularly for nausea or constipation. Switching to a different opioid may also be effective.
- Inadequate pain relief is not a valid reason for discontinuance of opioid therapy. Most often, inadequate pain relief reflects the 15-fold variability in opioid dose requirement and failure to adequately titrate, possibly compounded by failure to adequately treat crucial co-morbidities.

- As elsewhere noted, there are no reliable predictive risk assessment tools that can establish when risk of treatment outweighs benefits.
- Suicidality may be a reason for referral to counseling, community support, or in-home assistance by a qualified psychological or psychiatric professional. It is NOT a valid reason for forced taper over the patient's objections. In fact, as recent literature is suggesting, inadequately treated pain may drive suicidality.³⁷
- Non-compliance with the treatment plan may be reason for a joint reassessment of that plan by patient and physician. As noted by the American Medical Association, anomalous results of a single blood test or urine test are not a reliable basis for terminating the patient relationship and may be actively harmful.

The actual reasons for noncompliance have not been adequately studied and in fact, the very definition of non-compliance is an unsettled issue. Nevertheless, we accept that agreement between clinician and patient on the treatment plan, in all its details, is essential to management of any medical condition but particularly in the treatment of pain. Apparent noncompliance should always be the occasion for a serious heart to heart talk exploring the reasons for noncompliance and developing strategies for achieving tight control of the medical regimen. Only refractory noncompliance, typically established over the course of several months, should be occasion for discussion of termination of opioid treatment.

- There are presently no published trials that demonstrate benefits to any patient from mandated or compelled opioid tapering over their objections. Attempts by the State of Oregon to mandate tapering to zero for all Oregon Medicare patients have prompted an open letter from several former Presidents of the American Academy of Pain Medicine to the Governor of that state, identifying the potential for deep patient harms in such a policy.³⁸

An Overall Issue from the July 16th Meeting of the NCIPC BSC and the Opioid Workgroup

³⁷ Janel Miller, "Opioid Tapering Significantly Increases Risk of Overdose, Mental Health Crisis" *Helio*, August 3, 2021.

<https://www.healio.com/news/primary-care/20210803/opioid-tapering-significantly-increases-risk-for-overdose-mental-health-crisis>

³⁸ Sean Mackey MD, Dan Carr, MD, Richard Steig MD, Lynn Webster MD, Chad Kollas MD, Bob Twillman, PhD, "RE Health Evidence Review Commission, Chronic Pain Task Force Revised Proposal", Letter to the Honorable Kate Brown, Governor of Oregon, December 4, 2018.

An expressed concern of the BSC Opioid Workgroup in the public meeting of July 16, 2021 was the large number of references to reports whose principal author was a single individual. The unnamed principal author of several outcome reviews tasked by CDC to the Agency for Healthcare Research and Quality was Dr Roger Chou of the Oregon Health and Science University. Dr Chou was funded to lead research teams on behalf of AHRQ and to generate these reviews. It is reasonable to infer that his influence over their content has been major.

However, Dr Chou also serves on the Board of Scientific Counselors of the National Center for Injury Prevention and Control. This arrangement puts him in the position of being able to lobby for the acceptance of his own work as public policy – a fundamental professional and financial conflict of interest. Dr Chou recused himself from participation in the July 16th meeting during roll call, based on a financial conflict of interest. However, several public meeting participants identified larger issues surrounding this key figure in the opioid guidelines process.

Particularly troubling in Dr Chou's professional history is a close association and co-authorship of papers with individuals who are now or have been affiliated with an anti-opioid advocacy group named "Physicians for Responsible Opioid Prescription (PROP)". It is highly plausible that this association may account for much of the "lack of balance" noted in both the 2016 CDC guidelines and the present attempt to rewrite this fatally flawed document.³⁹

This conflict of interest would be reason enough for suspending any consideration of AHRQ reports as a reference in Colorado Guidelines. However, there are even larger issues in the reports themselves. Comments separately submitted by Richard A Lawhern to the Acting Director of AHRQ explain these issues as follows:

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).

³⁹ Chad Kollas, MD, "PROP's Disproportionate Influence on U.S. Opioid Policy: The Harms of Intended Consequences" *Pallimed – A Hospice and Palliative Medicine Blog*. June 2021.
https://www.pallimed.org/2021/05/props-disproportionate-influence-on-us.html#disqus_thread

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.

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Conclusions of the Authors

Given the lack of scientific support, misinterpretation of the medical literature, anti-opioid bias and selective cherry picking of evidence, we strongly recommend that the Colorado Department of Regulatory Agencies (DORA) “Guidelines for the Safe Prescribing and Dispensing of Opioids” [revised 3/14/19] should be withdrawn in total and not replaced.

We also suggest that DORA should recommend to the Colorado Attorney General that a general judicial review be convened for every court or State Medical Board action to sanction, suspend licensure, or prosecute any doctor for “over-prescription” of opioid analgesics, during the past ten years. In actions where MMED has been a criterion for determining “over-prescription,” convictions should be vacated and an award of financial damages made to any doctor whose practice and professional life have been harmed by application of this gross pseudo-science.

A massive outpouring of data from the CDC has now shown that, while its Guidelines published in 2016 have certainly succeeded in reducing opioid prescriptions across the country, they have had no impact whatsoever on opioid-associated deaths. It has now been shown beyond any shadow of doubt that, since approximately 2012, the opioid crisis has resided in the streets, where it has been propelled by illicit drugs, most particularly heroin admixed with fentanyl. Because the CDC Guidelines of 2016 did not even touch on this street crisis, it has continued to grow to terrible proportions, even as the CDC has created a second crisis, involving the 15 to 20 million Americans with moderate to severe chronic pain. If the State of Colorado is interested in stemming these two opioid crises, it will direct its efforts to stemming the street crisis and it will mitigate, to the extent possible, the enormous harm caused by the 2016 CDC Guidelines and its own.