Research Article ISSN 2639-9474

Nursing & Primary Care

Revising the US CDC Guidelines on Opioid Prescription A Commentary

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Received: 21 October 2020; **Accepted:** 17 November 2020

Citation: Lawhern RA. Revising the US CDC Guidelines on Opioid Prescription A Commentary. Nur Primary Care. 2020; 4(6): 1-6.

ABSTRACT

The US Centers for Disease Control and Prevention (CDC) have begun a major review and revision to their 2016 Guidelines on prescription of opioids to adults with chronic non-cancer pain. Stakeholder comments were solicited in April 2020, in the US Federal Register concerning management of acute and chronic pain. Among comments received was a 17-page letter from the President and CEO of the American Medical Association.

If acted upon, the AMA comments would almost entirety redirect the logic and practices recommended in 2016, and invalidate most core assumptions of the CDC writers. This paper summarizes the substance of AMA-recommended changes affecting the practice of nursing. Recommendations are offered for further evolution of these changes, to address weaknesses in supporting research and clarification of intent.

Keywords

Diseases, Prevention, Nursing, Patient suicides.

Introduction

This paper is written from the perspective of a 24-year advocate for people in pain. For some nursing practitioners, the message may seem difficult. Summarized here is the nature of changes that may occur in medical and nursing practice for the treatment of pain. Some of these changes represent an almost revolutionary reversal of public health policies put in place during the last ten years.

For nurses, nurse practitioners and physicians, pain is the most frequent presenting symptom that brings patients into medical care. Nurses may be the first medical professionals whom a pain patient sees in either private practice or hospital.

The US Centers for Disease Control and Prevention 2016 guidelines on prescription of opioids to adults with chronic non-cancer pain [1] have been a major recent influence in the work of all nurses. However, these guidelines are increasingly recognized as fatally flawed by errors of science, lack of transparency for internal CDC processes, failures of medical ethics and misdirection of public health policy.

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* This paper was originally prepared as a scripted presentation for the Virtual Conference on Nursing and Nursing Practice, Hyderabad, India (Session: Nursing Care and Nursing Practice), August 28, 2020. A shorter article summarizing main points of the material was published as "The American Medical Association Takes on the CDC Opioid Guidelines" on the Blog of Dr Lynn Webster at https://www.lynnwebstermd.com/2020/10/10/american-medical-association-takes-on-cdc/

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In December 2019, the CDC announced formation of an Opioid Workgroup, to oversee review, revision, and possibly expansion of their 2016 guidelines, with an intended release late in calendar year 2021. [2] In April 2020, CDC released a call in the US Federal Register for stakeholder comments on treatment of acute and chronic pain. Over 5400 comments were received from individual patients, caregivers, doctors and professional organizations. Many of those comments were highly critical of CDC errors.

It is appropriate to focus particularly on comments of the American Medical Association, as directed to the 12 top-level recommendations of the 2016 CDC Guidelines [3].

Key Events in CDC Guideline Development

The 2016 guidelines on opioids were the culmination of a multi-year process of reconsideration for the desired roles of opioid therapies in medical practice.

- 2014 – US FDA rejects petitions to restrict availability of opioid prescriptions, citing lack of medical evidence.
- 2014 – US Agency for Healthcare Research and Quality (AHRQ) issues report on opioid effectiveness and safety.
- 2015 – US House Oversight Committee directs CDC to open its guideline development process to public input for longer than three days.
  - ~5,000 comments received in the US Federal Register -- largely ignored.
- CDC Guideline published March 2016
  - Immediate widespread controversy is generated, with concerns for patient and doctor impacts [4,5].
  - 35 US States legislate restrictions on opioid prescribing dose and/or duration.
  - Insurance providers and chain pharmacies impose restrictive policies and pre-authorization requirements.
  - US DEA, Department of Justice and State drug enforcement organizations mount campaigns against physicians who prescribe opioids to their patients.
- November 2018 - AMA repudiates MMEDD thresholds and opposes "high prescriber" letters as a violation of legal due process.
- March 2019 - CDC acknowledges Guidelines were widely "misapplied."
- December 2019 - CDC invites volunteers for a new Opioid Work Group.
  - Federal Register calls for "stakeholder comment" April-June 2020
  - 5400 comments received, many sharply critical of effects of policy in desertions by physicians.

As one published paper phrased the issues, the CDC guidelines were almost immediately recognized as ""Neat, Plausible, and Generally Wrong". [4].

2020 AMA Observations on the 2016 Guidelines [op cit, 3]

- "We can no longer afford to view increasing drug-related mortality through a prescription opioid-myopic lens"
- "…Some patients with acute or chronic pain can benefit from taking prescription opioid analgesics at doses that may be greater than guidelines or thresholds put forward by federal agencies."
- A CDC Guideline only focused on "opioid prescribing" will perpetuate the fallacy that by restricting access to opioid analgesics, the nation's overdose and death epidemic will end."
- The CDC Guideline has been misapplied as a hard policy threshold by states, health plans, pharmacy chains, and PBMs."
- *It is clear that the [2016] CDC Guideline has harmed many patients — so much so that in 2019, the CDC authors and HHS issued long-overdue … clarifications that states should not use the CDC Guideline to implement an arbitrary threshold.** (**emphasis* by the author).

Guideline Revisions Recommended by AMA

AMA Recommendation #1: Non-Opioid and Non-Pharmacological Therapy are Preferred for Chronic Pain

In its first recommended change to the 2016 CDC guidelines, the AMA states that "Non-opioid and non-pharmacological therapy are preferred for patients with chronic pain." They also advocate that public and private payer policy must be realigned to provide coverage, more medical evidence must be developed and more doctor training is needed on use of such protocols

Recent reviews of the trials literature reveal that the state of rigor in trials for non-pharmacological pain therapy is abysmal. An Agency for Healthcare Research and Quality (AHRQ) Systematic Outcomes Review (2019) surveyed 5,000+ trials. Only 220 trials survived quality review. Medical evidence was found to be weak, with only marginal improvements in pain and quality of life. Trials did not directly compare opioid vs. non-opioid therapies [5,6,7].

Despite these findings, many legislators and policy makers are still proposing substitution of such therapies for opioid analgesics as 2020 draws to a close. In the author's view, non-pharmacological alternatives in chronic pain are presently best viewed as adjuncts, ***not*** replacements for a program of NSAIDs, anticonvulsants, anti-depressants, seizure meds used off-label in neuropathic pain, or opioid pain relievers.

The author believes that the AMA has stopped short of speaking the full truth on this issue. Their motivation is quite apparent: many doctors have turned so-called "alternative" therapies of doubtful efficacy into a cash cow. AMA flinched from confronting its own members concerning less effective and not yet FDA-approved therapies.

AMA Recommendation #2: Opioid Therapy Should Continue Only If There Is Clinically Meaningful Benefit In Achieving Treatment Goals

The AMA recommends that, "clinicians should continue opioid therapy only if there is clinically meaningful benefit [or] improvement in achieving treatment goals for *improving or maintaining levels of pain and function* that outweighs risks to patient safety." They also note that "treatment options [should be] accessible to the patient based on their health condition, social determinants of health (e.g. transportation, employment, childcare responsibilities, race, gender, age) and insurance coverage" (**Emphasis* by the author).

There are presently no published trials demonstrating benefits from mandated tapering of opioid therapy in otherwise stable patients. [8] The medical evidence for "opioid induced hyperalgesia" is very weak. [9] And AMA comments make clear that "risk" must be assessed by the attending physician for each individual patient.

Thus far, the AMA has not addressed some well-known difficulties in deciding whether a practitioner is seeing "clinically meaningful benefit" that outweighs "risks" of opioids. There are no trials data demonstrating benefits to patients from forced tapering, despite

the practice being common in the presently hostile regulatory environment. Likewise, no biological mechanism has ever been identified for what is called "opioid induced hyperalgesia", and there is widespread doubt in patient communities that such a medical entity is even real.

Also important in this context, is that AMA comments make clear that "risk" to patients from opioids cannot be generalized. Risks and benefits must be assessed on an individual and collaborative basis between doctor and patient. This is a major redirection of the logic of the 2016 CDC guidelines.

AMA Recommendation #3: Open and Honest Doctor- Patient Discussions and Avoidance of Stigma

AMA states that "Clinicians are encouraged to have open and honest discussions with their patients so as to avoid stigmatizing the decision to start, continue, or discontinue opioids or non-opioid therapy. *This discussion also must account for the treatment options accessible to the patient based on their health condition, social determinants of health (e.g. transportation, employment, childcare responsibilities, race, gender, age) and insurance coverage."*

Again, speaking as a patient advocate to nurses who work in hospitals and private practices, the author would pose a polite challenge. How often have you heard -- or yourself applied -- the phrase "drug-seeker" to a chronic patient who requests treatment with an opioid analgesic?

One of the most common complaints heard among the tens of thousands of patients who are active in social media, is that they have been told to their faces that they are drug-seekers looking for a fix -- not people in pain. The author ventures the estimate that hundreds of thousands in the US have been summarily discharged from an ER without treatment, while dealing with a crisis in breakthrough pain. This practice is directly responsible for at least hundreds (possibly thousands) of patient suicides.

AMA Recommendation #4: Preference for Immediate Release Opioids When Beginning Opioid Therapy

"When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/ long-acting (ER/LA) opioids. " [original CDC wording]

"The AMA strongly supports a pharmacist carrying out his or her corresponding responsibility under state and federal law, but the past few years are rife with examples of patients facing what amounts to interrogations at the pharmacy counter as well as denials of legitimate medication."

However, the author must suggest that the prevailing bias against long-acting opioids is not well supported by medical evidence of harms. [10] Indeed and by contrast, long-acting opioids may be helpful in controlling sleep disturbance and related depression.

The AMA also acknowledges that pharmacists have a duty of care to ensure that patients are not exposed to potential overdose. However, in recent years, too many pharmacists have become over-zealous out of a concern for being sanctioned or pursued as criminals if a patient dies or is admitted to a hospital *for any reason* after opioids are dispensed.

AMA Recommendation #5: "Hard Thresholds on Maximum Dose Should Never Be Used."

One of the controversial consequences of the 2016 Guidelines has been State and Medicare imposition of hard limits on opioid dose or duration for both new and legacy patients. These mandates have been attributed to the CDC-recommended dose threshold of 50 Morphine Milligram Equivalent Daily Dose for the conduct of a physician case review. 90 MMEDD was recommended as a maximum limit on prescribing to new patients by General Practitioners, pending transfer of the patient to a pain management specialist who might presumably prescribe at higher doses.

However, on publication of the 2016 guidelines, legislators and State Medical Boards leaped to the unsupported conclusion that the same limits should be applied not only to new patients, but also to existing legacy patients -- millions of whom had been maintained on substantially higher dose levels for years without untoward effects.

By directly challenging the generalization of hard limits on opioid prescribing, the American Medical Association has repudiated the central logic which prompted the CDC Guidelines in the first place. It is now known beyond any rational contradiction, that there is no inherently "unsafe" level of opioid prescribing that can be broadly applied to all pain patients as a limit. Each patient must be evaluated and treated as an individual. And many patients benefit from prescription opioid doses at levels substantially exceeding 90 MMEDD.

AMA Recommendation #6 – Recall of Hard Limits

In their sixth recommendation comments, AMA builds upon Recommendation #5 (above). Not only should CDC avoid stating hard limits on prescription doses, but they should also take steps to advocate for elimination of such limits in existing Federal and State legislation and State Medical Board guidelines that grew from the 2016 guidelines. Such advocacy will comprise an acknowledgement of error that is quite uncommon among governmental organizations.

AMA Recommendation #7 – Evaluate Benefits and Harms At Three Month Intervals

The impact of the wording suggested by AMA is to challenge more frequent evaluation of harms and benefits and to acknowledge that frequent doctor visits create significant patient burdens. Likewise, if a decision is made to taper opioid medication, that decision must entail a candid and detailed exchange between doctor and patient that embraces patient concerns.

AMA Recommendation #8 – "… no single risk factor should be used as a determining factor in decisions to discontinue or deny care"

Wording of this recommendation and its supporting text directly challenges widely reported abuses of both PDMP findings and urine

test results. Many US patients have been unilaterally discharged by medical practices on the basis of one "failed" urine test or one – often erroneous – indication in a Prescription Drug Monitoring Program that the patient may be seeing multiple physicians to obtain opioid prescriptions.

An even more fundamental issue of science (unmentioned in AMA wording) overshadows this issue. The US Agency for Healthcare Research and Quality has published an updated report on "Opioid Treatments for Chronic Pain". Incidental to other findings, AHRQ stated a key finding that "No instrument has been shown to be associated with high accuracy for predicting opioid overdose, addiction, abuse, or misuse" [11].

The AHRQ report suggests that the Agency attributed their findings to a lack of published evaluations of patient profiling instruments under field conditions. But AHRQ investigators appeared to have ignored a significantly more important confounding factor. A well established literature on genetic polymorphism in liver enzymes that metabolize opioids and most other medications reveals a startling reality: polymorphism in the expression of six P450 enzymes causes wide natural variability in minimum effective doses between patients [12,13].

Some chronic pain patients may benefit from opioid doses as low as 20 MMEDD. But other patients are very poor metabolizers and a third group are "hyper" metabolizers for whom opioids are broken down and pass through the blood-brain barrier in minutes rather than hours. The result of this variability is that some patients benefit from doses that may exceed 2000 (two thousand) MMEDD, without experiencing untoward side effects [op cit 6]. At present, we have no broadly available testing to identify precisely or in advance, in which group a given individual may find themselves.

AMA Recommendation #9: "PDMP reports… should be carefully examined but not used, by themselves, as reasons to discontinue or deny care to the patient."

This AMA comment addresses significant numbers of errors reported from Prescription Drug Monitoring Programs. Such errors can occur even when a patient is referred between members of the same medical practice. Some patients are also seen by both a primary care provider and a specialist in pain medicine. Many patients and some doctors report that their perception of PDMPs is that such databases are primarily used for law enforcement purposes rather than patient care and safety. The author has seen no reports that establish a positive benefit from PDMP reporting in reduced opioid overdose rates, for any US jurisdiction.

AMA Recommendation #10: Urine Testing

While the AMA continues to support use of urine testing as a means of monitoring patient compliance with opioid prescriptions, the wording of their June 2020 comments makes clear that such testing is not a panacea for either patients or physicians. There is wide variability in insurance coverage for testing, and many physicians are not well trained in interpreting test results. Likewise, AMA identifies more general knowledge gaps for test interpretation as an ongoing issue for further research.

AMA Recommendation #11: Co-Prescription of Opioids and Benzodiazepines

AMA comments interject a subtle but meaningful new element into co-prescription issues, by leaving the decision whether to co-prescribe to attending doctors rather than laying down a general standard of care.

"Clinicians should avoid prescribing opioid medication and benzodiazepines concurrently whenever possible, *unless it is clinically indicated and required for optimal patient management"* [emphasis by the author].

Historically, there has been a bias against co-prescribing, on grounds that overdose mortality rates tend to be higher in people who are co-prescribed. However, there are no published trials demonstrating consistent depressed respiration attributable to co-prescribing in live patients. Moreover, cause and effect relationships in any such "association" to elevated mortality are unclear. Mortality where both opioids and benzodiazepine drugs are implicated may be on the order of 0.1 to 0.5% of the treated population [12,13].

Depression and anxiety are frequently co-morbid with chronic pain. Failure to treat both medical issues in a coordinated therapy program appears to be associated with bad outcomes. It is entirely plausible that any increased "risks" of accidental opioid-related mortality may be counterbalanced by improved sleep, reduced levels of patient depression and anxiety, and lower risk of suicide.

AMA Recommendation #12: Treatment of Pain in Patients with Substance Abuse Issues

The AMA basically agrees with the recommendations of CDC in 2016 concerning treatment of substance abuse issues in people who have severe chronic pain. However, their June 2020 comments also take the Insurance industry to task for refusing to embrace parity in coverage for mental health and substance abuse issues.

AMA Recommendation #13: Treatment may include opioids even in patients who have an opioid use disorder.

The June 2020 comments of the AMA have added a 13th recommendation to the 12 originally tabled in 2016. This recommendation pushes CDC to recognize and act upon the need to treat pain and substance abuse together in the relatively few patients who present to a physician with both concerns. This may be a long-needed step in the direction of revising US National drug control policy towards harms reduction and away from punitive denial of pain control to patients who also have substance abuse issues.

The supporting text for this recommendation also makes clear that the AMA challenges the unsupported assumption that medically managed prescription opioid therapy is responsible for any significant number of new addicts. This observation is highly pertinent for nurses and other professional medical staff who commonly encounter people in severe pain in an Emergency Room facility.

Summary of AMA Recommendations

The author offers a patient advocate's summary of the positive directions that may be read from the June 2020 AMA comments to the CDC, concerning revision of the 2016 opioid guidelines. As noted earlier, these directions in themselves represent a revolution against prevailing public policy in government regulation of prescription opioid pain relievers and medical practice.

- Recognize the imperative for treating patients as individuals.
- Broaden treatment options and insurance reimbursement to include non-pharmacological therapies as adjuncts to pharmaceuticals.
- Advocate for repeal of State laws and hard limits arbitrarily restricting opioid dose or duration.
- Recognize that the US "opioid crisis" isn't driven by doctors prescribing to their patients -- and never was.
- Stop supporting law enforcement and State Medical Boards that are persecuting doctors out of pain management practice.

Still Room for AMA Improvement

Many positive changes appear in AMA positions concerning treatment of chronic pain by means of medically managed opioid therapy. However, there are also areas where AMA can and should do better in the coming months.

First, the AMA position on non-pharmacological and non-opioid therapies needs to further evolve. AMA emphasis on non-invasive protocols needs to carefully qualify them as adjuncts to a program of medication therapy – not as replacements for opioids per se. There is no support in medical trials literature or evidence-based medicine for such a leap.

Second, the AMA concern for individual treatment needs to be elaborated and clarified. There is sufficient medical evidence to state unequivocally that there can be no one-size-fits-all treatment or dose standard for the use of opioid analgesics. Explicit incorporation of current knowledge on genomics is an essential "nail in the coffin" to repudiate false claims that over-prescribing caused our US public health crisis in the first place – or that continuing restrictions on opioid prescribing will help stem the tide of addiction and overdose mortality. This latter claim is the hinge pin of all US policy on regulation of prescription opioids. And it's simply flat-out wrong.

Third, AMA needs to significantly revise its position on physician-initiated involuntary tapers of opioid dose levels in otherwise stable patients who have benefitted from opioids in the past -- and in new patients as well. Real risks of opioid addiction in medically managed patients are very low and are unrelated to either tolerance or dependence.

In too many cases, physicians who fear that opioids comprise a risk to their patients are actually speaking in code. Their real and unvoiced concern is for possible official sanctions or legal action in the hostile regulatory environment. Doctors are looking for a graceful way to desert their patients and flee from persecution. While this instinct is understandable, patients believe it is past time for physicians to stand up and be counted in opposition to the present misdirection of public policy.

In this context, it is also clear that Morphine Milligram Equivalent Daily Dose is rarely a useful measure of either risk or effectiveness of medically managed opioids. The natural range of minimum effective dose is too broad and unpredictable in individuals. The primary utility of MMEDD may be in temporarily managing transitions between prescription opioids [15,16].

Conclusion

A quotation seems pertinent from Dr Nora Volkow, Director of the US National Institute on Drug Abuse, and her co-author Thomas A McMillan, PhD, in a 2016 paper published by the New England Journal of Medicine. Arguably, this statement should become the guiding principle for completion of pending revisions to the CDC guidelines.

"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" [17].

About the Author *-- Richard A Lawhern Ph.D*

Dr Lawhern is a technically trained non-physician volunteer patient advocate, with 24 years experience as a website developer, moderator and medical literature analyst for online chronic pain communities. He has published over 100 papers, articles, and addresses in a mixture of medical journals and mass media, some with physician co-authors. He sits on two Editorial Boards – the journal of *Practical Pain Management* and the American Council on Science and Health – neither of which has reviewed or approved this paper. Dr Lawhern has no financial or professional conflicts of interest.

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