An Open Letter to the New England Journal of Medicine  
(Wake Up and Smell the Coffee!)  

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As a healthcare writer, I read a lot of medical literature. Among other publications, I’m subscribed online to one of the preeminent sources in American healthcare: the New England Journal of Medicine (NEMJ). Thus I saw a recent paper by Nora D Volkow, MD, and Thomas A McLellan, Ph.D., affiliated with the National Institutes on Drug Abuse, titled “Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies” [NEMJ 2016; 374:1253-1263 March 31, 2016].

I found several useful observations in this article, which partially dispel prevailing misconceptions held by doctors and government bureaucrats.

"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 preexisting vulnerabilities (Table 3). 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."

This being acknowledged, I found other elements of the piece disturbing. Thus I wrote to the authors via the NEMJ comments gateway, requesting that my comment be published by the journal. The following is an extract from my letter.

".... I would offer several contrary or qualifying points pertaining to your assertions concerning opioid analgesics, summarized in [an] introductory paragraph:

"However, two major facts can no longer be questioned. First, opioid analgesics are widely diverted and improperly used, and the widespread use of the drugs has resulted in a national epidemic of opioid overdose deaths and addictions. More than a third (37%) of the 44,000 drug-overdose deaths that were reported in 2013 (the most recent year for which estimates are available) were attributable to pharmaceutical opioids; heroin accounted for an additional 19%. At
the same time, there has been a parallel increase in the rate of opioid addiction, affecting approximately 2.5 million adults in 2014.[9] Second, the major source of diverted opioids is physician prescriptions.[10,11] For these reasons, physicians and medical associations have begun questioning prescribing practices for opioids, particularly as they relate to the management of chronic pain. Moreover, many physicians admit that they are not confident about how to prescribe opioids safely,[12] how to detect abuse or emerging addiction, or even how to discuss these issues with their patients.[13]

After summarizing my background and previous publications, I offered the following counterpoints to the authors.

1. The present "epidemic" of opioid-related deaths was not created by actively managed prescriptions made by doctors to people in pain. It was instead fueled by drug diversion from home medicine closets in burglaries and by family members stealing or being given medications unused by those for whom they were prescribed. Millions of doses also hit the street yearly from pharmacy and hospital thefts. There is little or no evidence that rates of drug addiction have risen with the liberalization of prescribing practice in the 1990s, even though the number of deaths in which an opioid is implicated as one of several factors may have done so. Current overdose statistics are dominated by heroin, imported fentanyl, morphine stolen from hospitals, and methadone diverted from treatment programs. Current prescriptions by doctors appear to figure in fewer than a quarter of overdose deaths and are frequently complicated by alcohol abuse or anti-anxiety drugs.

2. Arguably, many dimensions of the present drug epidemic have been substantially worsened by FDA mandating of reformulated "abuse resistant" OxyContin in 2010. In the years since that action, prescriptions of OxyContin have dropped by two-thirds, while deaths involving heroin have tripled. This inverse relationship was not accidental. Addicts formerly using regulated and safe medications found that they could no longer get or afford their drug of choice, and went into the street for less expensive and unregulated drugs.

3. A large majority (possibly 90%) of addicts begin abusing drugs and alcohol in their teens — some as early as middle school. This reality was acknowledged by one of your NIDA colleagues during discussions in the first session of the President's Commission on Combating Drug Abuse and the Opioid Epidemic in June of this year. However, the number of teens who see a doctor for pain severe enough to justify long term use of opioid analgesics is tiny. As suggested by a 2008/2010 Cochrane Review, the number of opioid-naïve pain patients who are later diagnosed with opioid misuse disorder may be on the order of 2% or less (other sources report as small as 0.5% and as large as 5%). The notion that large numbers of actively managed pain patients will fall into addiction is a mythology that begs contradiction.
4. There is ample evidence that the March 2016 CDC opioid guidelines were (as one published paper is titled in part) "Neat, Plausible, and Generally Wrong". The quality of research was so egregiously poor and the distortions and biases so pronounced that even some members of the CDC consultants core group have since disavowed their association with the document.

5. Unintended but horrific consequences of these guidelines have included the involuntary discharge or rapid tapering of tens of thousands of patients for whom opioid analgesics have been the only therapy which has managed their pain and sustained the quality of their lives for many years. These patients' experience exposes as silly, the notion that every opioid user is a potential abuser. They are stable and have displayed none of the … self-destructive behaviors which characterize the DSM-5 diagnosis. They do not suffer from hyperalgesia (a "disorder" for which there is presently no medical consensus on diagnostic signs or appropriate therapies). They may indeed be "dependent" on opioids for pain control, and may suffer withdrawal when forced off pain relievers. But they are not addicts or potential addicts.

6. Medical professionals and families of chronic pain patients are now observing a wave of patient suicides which are the direct outcome of the long shadow cast by CDC guidelines. The guidelines and the current US DEA and State-level witch hunts against doctors who prescribe for pain patients are driving doctors out of pain practice in droves, and patients into disability and agony. This trend may be particularly pronounced among veterans. The trend is no longer arguable. We see reports of fallen pain warriors every week in social media. But US States continue to "pile on" with ever more draconian legal restrictions on doctors trying to treat pain, and patients who experience it.

7. The guidelines are also widely understood to have jumped to medically unsupported conclusions with respect to the long term effectiveness of opioid analgesics in chronic pain. A relative shortage of long term studies of effectiveness appears to have been unfairly conflated with assertions that opioids don't work over the long term. The consultants core group omitted from consideration, any study of opioids less than a year in duration -- but did not impose the same [limit] on studies of non-opioid medications or behavioral therapies. They also failed to explicitly acknowledge such cherry-picking in the published guidelines. A published analysis has demonstrated this unacknowledged bias

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8. The guidelines -- and [this] paper -- also display a particularly glaring and potentially disqualifying omission. Neither addresses the issues surrounding variable opioid metabolism due to genetic polymorphism in expression of liver enzymes. Six enzymes are involved in the metabolism of about 90% of all medications including opioids and
opiates. Polymorphism in the genes which activate these enzymes has created millions of hyper-metabolizers and poor metabolizers in the US population.


9. The natural consequence of genetic polymorphism is that there inherently can be no generalized one-size-fits all threshold of risk in dose levels. Despite a degree of plausibility in assertions that higher dose levels might be associated with higher risks, there is simply no body of published work to establish any precise relationship or a generalized standard of practice. A 90 MMED threshold was proposed in the CDC guidelines as a threshold for physician review of risks and benefits -- interestingly without recommending involuntary tapering of stable patients. However, the Veterans Administration has since mandated involuntary tapering and appears to be implementing a policy of denying opioids outright to all Veterans. Major insurance organizations have piled onto this trend. But because of variable patient metabolism, imposition of such a threshold will condemn millions of patients to therapy failure, who could otherwise be helped by higher managed dose levels which sustain appropriate blood levels of the metabolites crossing the blood-brain barrier.

Our public conversation on chronic pain and addiction is presently dominated by hype and hysteria. Parts of your article seem useful in contradicting some of the circulating misinformation. But I believe it is time for pain patients themselves to be included in this conversation. Policy solutions for addiction cannot be built on the backs of people in agony! I and many others are calling on Congress to direct the CDC to immediately recall their opioid guidelines for a major re-study and revision, to address many unintended and horrendous consequences and to correct biases and errors.

In light of the substantive issues raised in this letter, I hereby request that [it] be published as a comment by NEMJ.

Sincerely,
Richard A. Lawhern, Ph.D.

I have not yet heard directly from the editors of NEJM. However, Dr. Volkow chose to respond by email. Although she did not explicitly authorize the publication of the response, neither did she mark it as privileged. I believe our further exchange can be important in understanding the biases and ethical blind spots of working medical professionals in the issues surrounding opioid analgesics and pain patients. Thus I offer it below:

"Dear Dr. Lawhern:
I appreciate your thoughtful feedback on our article *Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies*. As you describe, the vital efforts to resolve our Nation’s current crisis of opioid addiction and overdose deaths **must also emphasize the safe and effective treatment of patients with chronic pain conditions**. I agree completely with that statement!!!!!!!!! Indeed, NIH recently launched an initiative that will leverage public-private partnerships to accelerate research to develop safe, effective, non-addictive treatments for chronic pain.

“This summer, three cutting-edge science meetings were convened with experts from academia, industry and government to prioritize research efforts to end the opioid crisis; and two of these were devoted to the issue of pain. The first, entitled *Development of Safe, Effective, and Non-Addictive Pain Treatments*, was held on June 16th. The second meeting, held on July 7th, focused on *Understanding the Neurobiological Mechanisms of Pain*. It is our intention that these public-private partnerships will pursue new approaches and recruit additional expertise to develop new safe and effective therapeutics in half the time it currently takes. I’ve attached the publication prepared by Dr. Francis Collins, Director of the National Institutes of Health (NIH), and myself in which we provide a detailed overview of these efforts.

“Both meetings opened with remarks from patient advocates, whose perspectives on the toll that chronic pain exacts on patients, their families and their communities served to orient us all to the urgent need for improvements in the medical care available for chronic pain patients. Advances in pain treatment are certainly a vital tool to combat the opioid crisis, but are also required to improve the lives of those suffering with chronic pain. We at NIH are committed to identifying and pursuing the most effective avenues of research to achieve this goal.”

[Bold emphasis in the original.]

I responded in a second round of email exchange as follows:

“Dear Dr. Volkow and Dr McLellan,

While I appreciate your sentiments and personal good will, the central question remains unanswered: given the years-long cycle of development which is common in initial research and later FDA approval of new drugs, what is your position concerning near-term recall and revision of the CDC opioid guidelines published in March 2016? At best, new research may (or may not) offer potential solutions ten years from now. How many chronic pain patients must die in the meantime from suicides due to the arbitrary and capricious denial of opioid analgesics which have worked for years in maintaining the quality of their lives -- with demonstrated and documented minimal actual risk of opioid abuse or addiction? How many US Veterans must be buried before the medical and political establishment wakes up and smells the coffee?
I dislike repeating myself to a professional in your field, but it seems to me that a profound ethical imperative is largely being ignored. It is now widely understood among practitioners, professional associations and patients, that the CDC prescription guidelines are flat-out wrong. They are politically biased, scientifically unsupported, and egregiously incomplete in multiple ways that constitute a clear and present danger to hundreds of thousands of patients. The guidelines are being used as an excuse for discharge of tens of thousands of people in agony and refusal of effective medications to possibly hundreds of thousands more. Doctors are leaving pain management practice in droves, fearful of the ongoing DEA and State authoritarian witch hunt which threatens their licenses. People are dying in totally unnecessary agony. These are practical realities on the ground.

Why will you -- and NEMJ -- not go on public record advocating for a balancing of the scales on this issue? Is this not a classic example of the failure of the principles underlying "first do no harm"?

I repeat my request that the letter [above] be published as a comment by NEMJ, and I ask for your professional support in this request. I look forward to being copied on your further correspondence with the editors of NEMJ.

Dr Volkow's closing response seems to display a major ethical and professional blind spot that I believe is shared with many of her colleagues in Government. She simply misses or ignores the ethical issues I attempted to raise. Thus I offer her words here:

"Dear Dr Lawhern,

I understand your concerns. However, we continue to stand behind the CDC guidelines. The document is intended for primary care providers, not for pain specialists, and it was careful to articulate that the recommended dosages are guidelines; Providers can prescribe higher doses if there is a medical justification for doing so. We are also very aware that implementation of CDC guidelines will require structural changes to the healthcare system to ensure that they provide access to comprehensive pain management interventions to patients and that physicians are properly trained in management of pain in their patients."

[Bold emphasis in the original]

I must ask: how in the world can any medical professional "stand behind" an opioid prescription standard that is injuring and abusing tens of thousands of patients? It seems to me that anyone who would "support" the CDC Guidelines seriously needs to reexamine their own conscience. Congress needs to demand that the Director of CDC withdraw this document for major revision and correction. And this is true regardless of
any parallel efforts to develop safe and effective alternatives to opioid analgesics — an initiative which one must note has been conspicuously absent from American medicine for the last generation.

As a military boss of mine once taught me, policy documents are not written merely for clarity. They are instead written to deny opponents the opportunity to misinterpret them. The Guidelines are an abject failure on this account. They do not explicitly recommend the tapering down or denial of opioid analgesics to patients — but they are widely being misinterpreted as requiring that step. Combined with other CDC errors and omissions, this reality is disqualifying. And the editors of NEMJ need to create space for patient advocates to say so.

About the Author: Richard A ("Red") Lawhern, Ph.D. is a non-physician writer, research analyst, patient advocate, and website moderator for chronic pain patients, families, and physicians. His wife and daughter are chronic pain patients. His 20 years of experience has produced articles and critical commentaries at the US Trigeminal Neuralgia Association, Ben’s Friends online communities for patients with rare disorders, US National Institutes for Neurologic Disorder and Stroke, Wikipedia, WebMD, Mad in America, Pain News Network, National Pain Report, the American Council on Science and Health, the Global Summit for Diagnostic Alternatives of the Society for Humanistic Psychology, Psychiatric News and Psychology Today.