Stephen Martin, MD, EdM
A rural family physician and Associate Professor at the University of Massachusetts Medical School ...
Sep 7 · 20 min read

Neat, Plausible, and Generally Wrong:
A Response to the CDC Recommendations for Chronic Opioid Use

Stephen A. Martin, MD, EdM;
Ruth A. Potee, MD, DABAM; and
Andrew Lazris, MD

. . .

Abstract

The American crisis of opioid addiction and overdose compels our strongest efforts toward successful prevention and treatment. Recommendations from the Centers for Disease Control and Prevention (CDC) for chronic opioid use, however, move away from evidence, describing widespread hazards that are not supported by current literature. This description, and its accompanying public commentary, are being used to create guidelines and state-wide policies.

These recommendations are in conflict with other independent appraisals of the evidence—or lack thereof—and conflate public health goals with individual medical care. The CDC frames the recommendations as being for primary care clinicians and their individual patients. Yet the threat of addiction largely comes from diverted prescription opioids, not from long-term use with a skilled prescriber in a longitudinal clinical relationship. By not acknowledging the role of diversion—and instead focusing on individuals who report functional and pain benefit for their severe chronic pain—the CDC misses the target.

We provide here a review of the evidence regarding long-term opioid use for chronic pain in order to a) better point public health efforts, and b) reduce harm from consequent restriction of these medications for patients who have substantial benefit in their use.

. . .

Introduction

The Centers for Disease Control and Prevention (CDC) has had historical credibility with the medical community, generally making judicious use of evidence for public health benefit. That is why it is disconcerting to read its recommendations [1] on opioids for chronic pain and accompanying descriptions in the media. With these new recommendations concerning the use of opioids, the CDC has taken available data and developed a narrative that H.L. Mencken would generally have described as "neat, plausible, and wrong." [2]

The narrative is as follows: People in chronic, severe pain are readily provided unproven opioids in ever-increasing doses, get easily addicted and die of overdose either from the opioids prescribed to them or from a switch to lethal heroin.

Neat? Yes. Plausible? Yes. Wrong? Unfortunately, yes.

. . .

People in chronic, severe pain are readily provided unproven opioids in ever-increasing doses …

Patients with chronic, severe pain in 2016 have often tried available first-line options of physical therapy, behavioral treatment, NSAIDs, acetaminophen, anticonvulsants, tricyclic antidepressants, etc. prior to beginning an opioid medication. Indeed, the general outcome for many patients in pain is ever-increasing hardship in finding skilled prescribers who are willing to provide such treatment. [3–6]

Long-term opioid medication is intended to help address intractable suffering. Here the CDC makes a striking set of exceptions; its recommendations are exclusive of "active cancer treatment, palliative care, and end-of-life care." Why is cancer privileged over other debilitating conditions? Sickle cell anemia, severe arthritis, spinal stenosis, inoperable kidney stones, chronic pancreatitis, and other conditions also have high levels of pain that can be successfully mitigated by opioids.

In addition, the exception "palliative care" is notable. In defining people to be served by palliative care, the National Consensus Project notes that "serious or life-threatening illness is assumed to encompass populations of patients at all ages within the broad range of diagnostic categories, living

with a persistent or recurring medical condition that adversely affects their daily functioning or will predictably reduce life expectancy." [7] Chronic pain, when controlled for sociodemographic factors, has been found to reduce life expectancy by ten years. [8] It doubles rates of suicidal ideation, attempts, and completion [9] while quadrupling rates of depression and anxiety. [10] When people look for some relief of chronic suffering, they are doing so relative to a situation of misery. Given the impact of chronic severe pain, it appears to meet the definition for palliative care itself.

Can people in chronic pain expect meaningful relief from long-term opioid use? Not according to the CDC. The recommendations state there is no evidence for such use and only evidence of harm. While it is certainly true there is an absence of longer-term data, the CDC defined chronic pain as lasting longer than three months, but included only studies that lasted over one year. An independent systematic review [11] finding evidence of benefit was thus excluded.

Absence of evidence is not evidence of absence, and the CDC's claim is also belied by direct reports from patients using long-term opioid treatment who report substantial pain and functional improvements. The CDC, in telling patients that "the benefits are transient and generally unproven," [12] is essentially telling patients they are wrong about their pain and function. When conventional evidence is limited and suffering is high, use of clinical ethics for individual patients has been proposed as a worthwhile decision-making model. [13]

Another model is finding what safely works for each patient. [14] While acknowledging the limitations of current evidence, the 2014 National Institutes of Health "Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain" concluded that:

> *Patients, providers, and advocates all agree that there is a subset of patients for whom opioids are an effective treatment method for their chronic pain, and that limiting or denying access to opioids for these patients can be harmful.*

> *[O]ur consensus was that management of chronic pain should be individualized and should be based on a comprehensive clinical assessment that is conducted with dignity and respect and without value judgments or stigmatization of the patient. [15]*

> *… Biased media reports on opioids also affect patients. Stories that focus on opioid misuse and fatalities related to opioid overdose may increase anxiety and fear among some stable, treated patients that their medications could be tapered or discontinued to "prevent addiction." [16]*

The CDC, in contrast, highlights that prescription opioids are "really dangerous medications which carry the risk of addiction and death." [12]

Though it found, as did the CDC, a lack of long-term evidence for opioid use, the American Geriatrics Society still determined them to be a potentially "indispensable" treatment for selected patients. [17] British geriatric guidelines are similar. [18] While advocating their judicious use, Canadian guidelines note that "opioids can be an effective treatment for chronic non-cancer pain (CNCP) and should be considered." [19] In the month preceding the CDC recommendations, the *Lancet* published an editorial titled "Increasing worldwide access to medical opioids," describing how 80% of the world's population lack access to morphine, part of the World Health Organization's essential medicine list since its inception. [20] Disproportionate use of opioids in the US is an expression not only of American supply and demand, but near-complete restriction on opioid access for 5 billion people. [21]

Potential side effects from appropriately-dosed opioids include constipation, fatigue, and lower libido. As with other medication side effects, patients and their clinicians can develop ways to ameliorate them or discontinue treatment should the side effects be too troublesome. Much has been made of opioid-induced hyperalgesia. But even the most recent reviews of this phenomenon are unable to determine its prevalence, and studies have generally been experimental in nature or with unusual administration of opioids (e.g., intrathecal). [22,23] Whether it is clinically important for patients with chronic pain on standard opioid medication is unclear. [24] As to concern for dose escalation, a recent cohort study found it occurred in fewer than one in ten opioid-naïve patients. [25]

First-line interventions advised by the CDC are limited in their effectiveness. Acetaminophen was recently found to have no impact on osteoarthritis pain. [26] NSAIDs had their FDA warning strengthened in 2015 regarding heart attacks or strokes [27] and their risks of kidney injury and gastrointestinal bleeding have long been recognized. [28,29] Anticonvulsants or tricyclic medications for neuropathic pain have a number needed to treat of 5, meaning 4 patients do not have a benefit. [30] Perhaps "multidisciplinary biopsychosocial care with a prominent component of self-management,

generally accepted as the gold standard of care for chronic pain"? According to a pain specialist, its availability has "all but disappeared in the United States." [31]

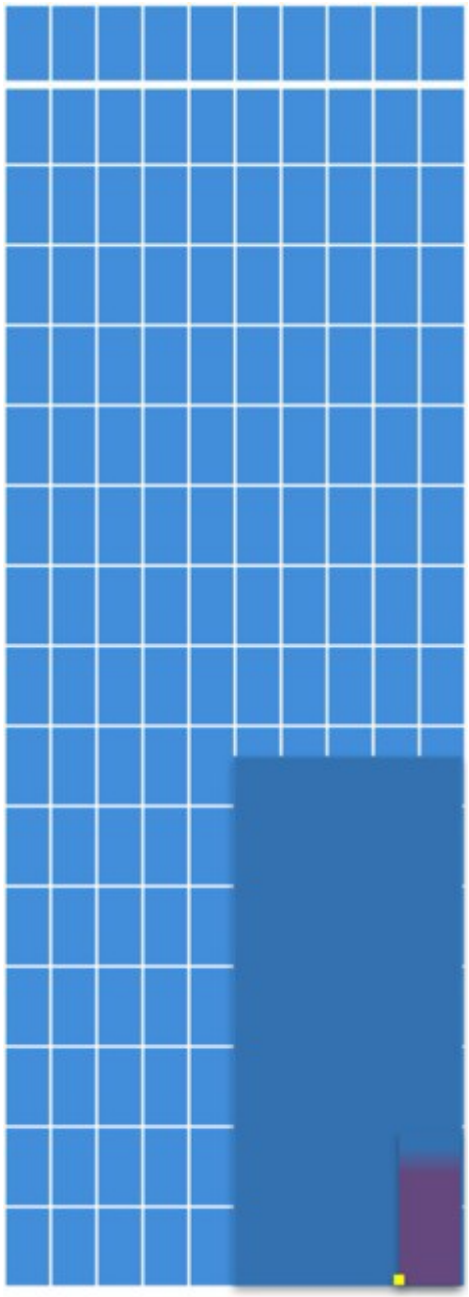
Ultimately, for the individual patient, the choice to use opioids is not made in a vacuum. The decision is made in comparison with the status quo of chronic, intractable pain despite other medical interventions. As a comparison, chemotherapy for cancer treatment also has severe side effects, even toxicity. People make the choice to use such treatments because they are choosing against the alternative.

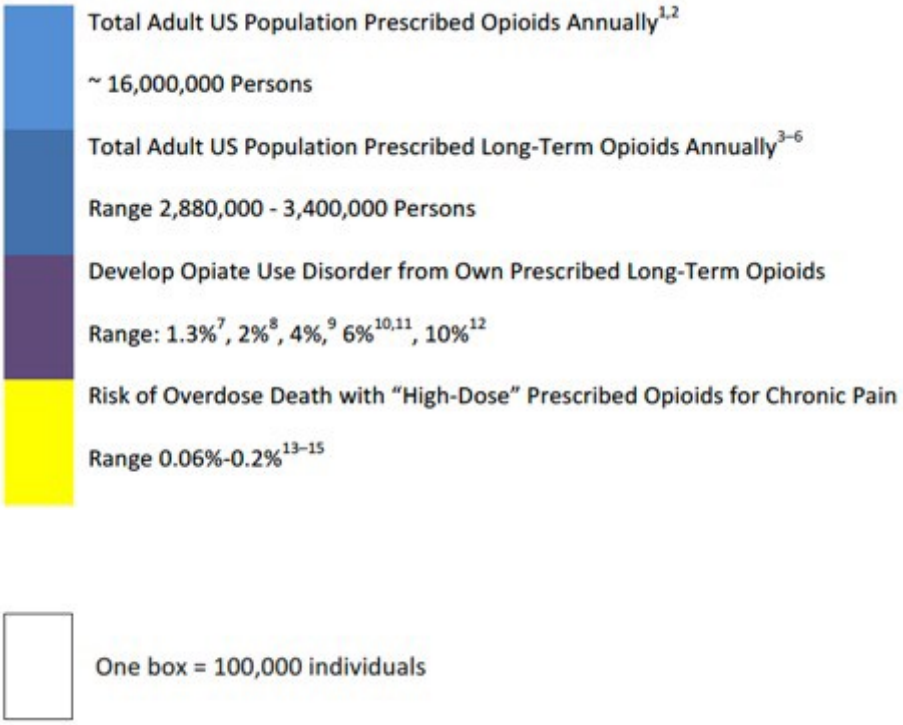
. . .

… get readily addicted and die of overdose of either the opioids prescribed to them or from a switch to lethal heroin.

The CDC states that "prescription opioids are just as addictive as heroin." [32] Others call them "heroin pills." [33] But a full year after after major surgery, only "0.4% of older opioid-naive patients continued to receive ongoing opioid therapy." For chronic opioid treatment, studies show rates of developing an opiate use disorder to be in the range of 2% to 10% (Figure 1a). Even then, as others [34] have noted, the complexities of chronic pain and addiction behaviors make the outright diagnosis of opiate use disorder a challenge. Unfortunately, recent publications have included "pooled studies with widely differing definitions, outcome variables, and populations," which detract from their conclusions. [35] Concerns about such misleading data and definitions come from a wide variety of sources. [36–38] The term "prescription opioids" itself is problematic as the adjective does not distinguish how the drug was actually obtained by the user.

Figure 1a
Annual Total and Long-Term Prescriptions of Opioids, with Risks of Opiate Use Disorder and Overdose Death



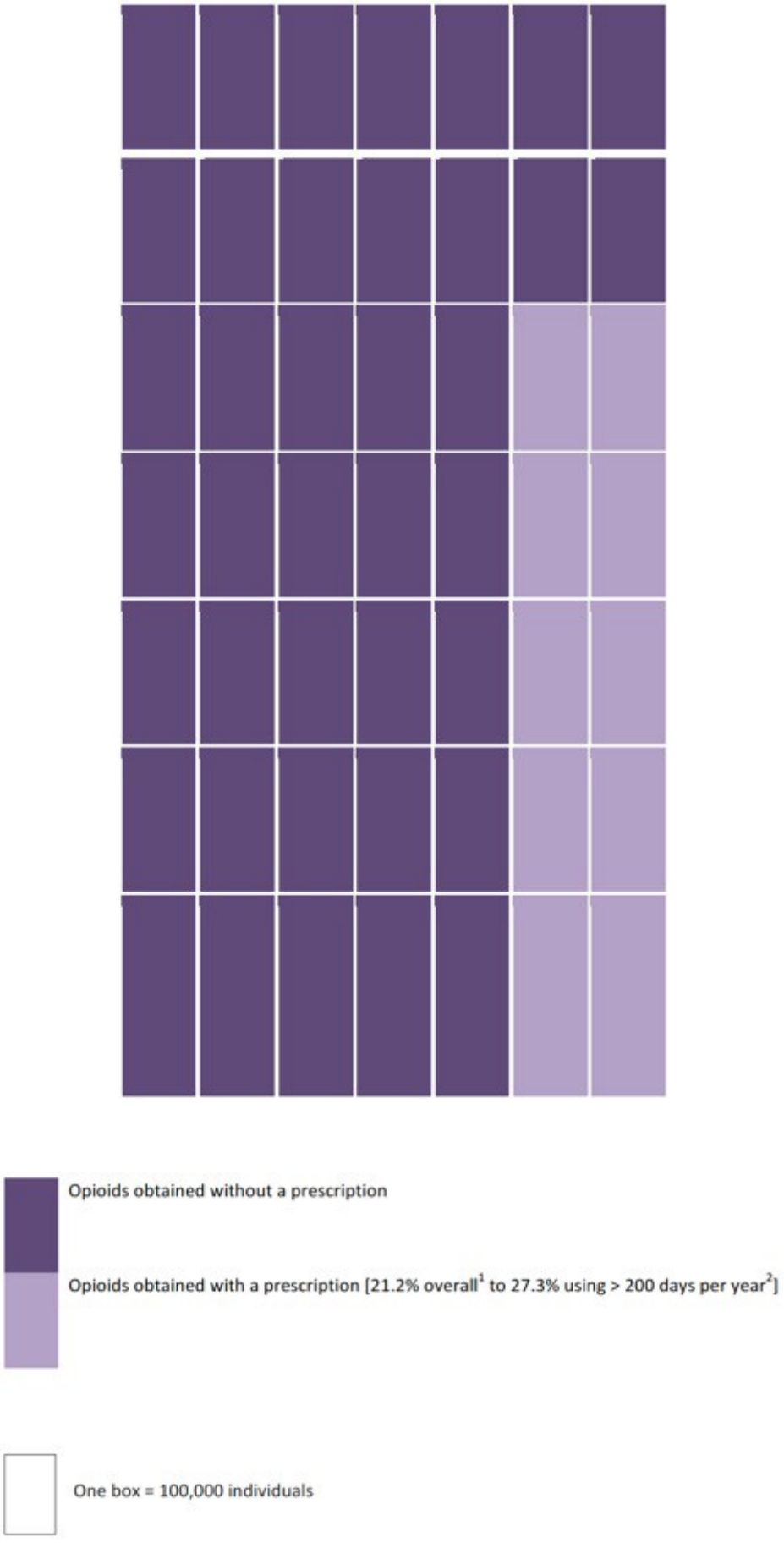


Among those who take opioids long-term for chronic pain, the CDC highlights the potential for overdose ("overdose" is mentioned 144 times in the recommendations) and death. [1] This is certainly an outcome to be feared. The study cited in the CDC's own telebriefing [12], however, found "opiate-related" death to occur in 59 of 32,449 (0.2%) patients taking opioids for more than three months. [39] The context of these deaths was unknown (e.g., whether medications were taken as prescribed or from intentional overdose) and there was no corresponding control cohort of patients in chronic pain without opioid use. The senior author noted that the "generalizability of these findings to other patients is uncertain." A prior study by the same authors put the rate of overdose death at less than 1%, even for "high dose" prescriptions (Figure 1a). [40,41] In its review of a Citizen's Petition to limit doses of chronic opioids, the FDA found that "the scientific literature does not support establishing a maximum recommended daily dose of 100 mg MED [morphine equivalent dose]." [42]

Opioid overdose deaths are generally the result of diverted medications ("diversion" is mentioned 2 times in the recommendations) (Figure 1b), heroin, fentanyl, or a combination of these. Diversion is most often from prescriptions for acute, not chronic, pain. [43] Most West Virginia overdose deaths were associated with diversion. [44] Among Montana overdose deaths, only a third of those on Medicaid had a claim for an opioid prescription during the month before their death. [45] Analysis of recent Massachusetts overdose deaths found "evidence to support an emerging

hypothesis that illegally-obtained substances are the driving force behind opioid-related deaths." [46] Prescription opioids accounted for a minority of 2014 Massachusetts fatal overdoses [47,48], a trend that has also been found nationally. [49] Should prescription opioids be used prior to initiating heroin, the CDC has found that use to be "nonmedical." [50] Heroin is currently the most lethal opioid in terms of people affected (though fentanyl, with or without heroin, is also having an increasingly grave impact). 94% of people in treatment for opioid addiction said they chose to use heroin because prescription opioids were "far more expensive and harder to obtain." [51] The National Institute on Drug Abuse estimates that fewer than half of young people injecting heroin report abusing prescription opioids beforehand. These crucial details are unacknowledged in the CDC recommendations.

Figure 1b
Sources of Nonmedical Opiate Use


Opioids obtained without a prescription
Opioids obtained with a prescription [21.2% overall[1] to 27.3% using > 200 days per year[2]]
One box = 100,000 individuals

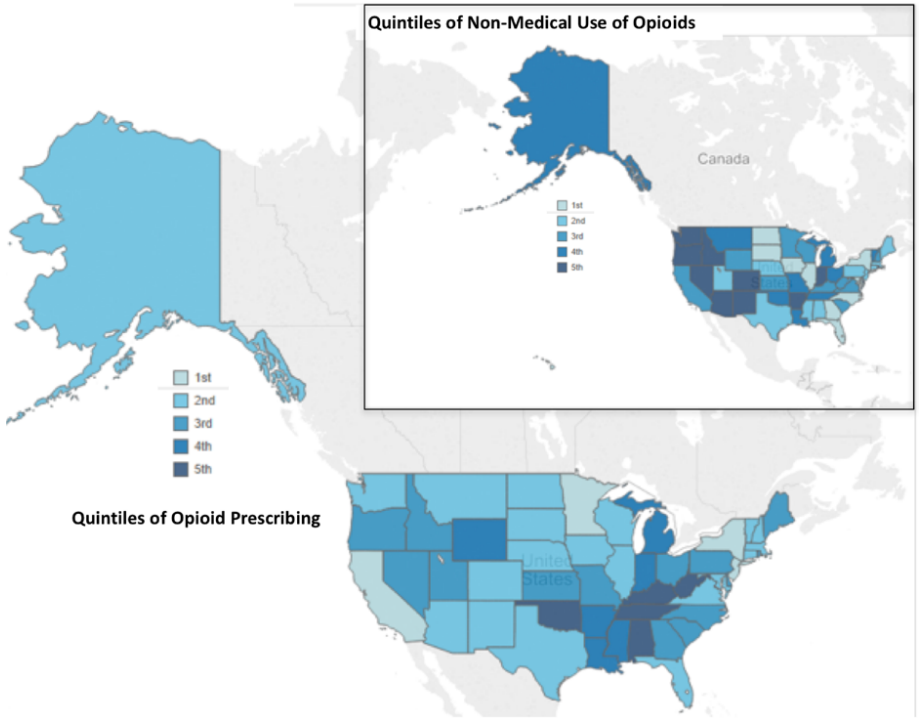
. . .

Examining this Narrative

Public health interventions are different than clinical interventions. The former are scaled, diffuse and unilateral. The latter are individualized and shared. The CDC recommendations are more focused on public health concerns (such as non-medical use of prescribed drugs) rather than the individual risks and benefits of opioids for actual patients. These guidelines may have, in some form, been helpful in the late 1990s or early 2000s when OxyContin's faulty, criminal formulation made for tragic outcomes for patients and communities alike. [52] In 2016, many regions and prescribers have already taken steps to improve clinical education and prescription monitoring. [53,54] The added constraints of the CDC recommendations and hyperbole that surrounds them serves neither public health nor individual care well.

The CDC recommendations describe a linear relationship between opioid prescribing and nonmedical use. But data on opioid prescribing [55,56] and nonmedical use [57], state by state, tell a more complicated story [Figure 2]. As shown in Figure 2, Colorado is in the lowest quintile of opioid prescribing but the highest quintile of nonmedical use. North Carolina is in the middle quintile of opioid prescribing but the lowest quintile of nonmedical use. CDC data from 2012 shows Florida with the second-lowest quartile of opioid prescribing. But in 2010 Florida physicians bought nearly 90% of all Oxycodone sold in the United States to distribute in more than 1,000 pain clinic "pill mills" [58]; at the time, Floridians themselves were in the lowest quintile of nonmedical use. Just four states—Kentucky, Alabama, Georgia and Arkansas—have 41 of the 50 cities with the highest prevalence of opioid use nationwide [59]; yet these states straddle four quintiles of nonmedical use.

Figure 2
State Comparison of Opioid Prescription Intensity with Nonmedical Use



An international comparison also belies a linear relationship. Between 1997 and 2010, the UK has had a similar trend in increased opioid prescriptions—though at a lower absolute level—but without an increase in overdose deaths. This outcome does not comport with overdose being an inevitable outcome of opioid prescription. [60] Rather than a straightforward infectious model of an epidemic, we need to acknowledge the data show something more complicated, often regional. When it comes to this epidemic, place matters, as the CDC itself reminds us [61], though its new recommendations do not.

. . .

A Different Narrative

Our concern for individual patients is that recommendations and regulatory changes [62] concerning prescribed opioids are increasingly being developed not through evidence, but by a flawed narrative of how addiction develops and overdose occurs. [63,64] The CDC was provided with descriptions of these flaws in the period of public comment, but chose to make only minor revisions. Our concern for public health is that these recommendations do nothing explicitly to address the major source of prescription opioids used in substance use disorders in the United States: diversion. [65] If the actual goal is to reduce the overall reservoir of prescription opioids in order to

reduce diversion, that would be a worthy one. The continued use of graphs that track kilograms of prescription opioids and overdose deaths, however, misleads when many of those "prescriptions" are taking place outside of a skilled, longitudinal, patient-clinician relationship. [66,67]

The data we provide here describe a more accurate narrative: Should other treatments not succeed, people suffering from intractable chronic pain may find that carefully monitored long-term opioids, in combination with other modalities, can help reduce their suffering and improve their function. The evidence indicates they can do so with a low risk of developing opiate use disorder and an exceedingly low risk of overdose death. As with all treatments, the decision to use and continue long-term opioids should be one of ongoing shared decision-making.

Overall, the new recommendations sacrifice accuracy for a fabricated sense of clarity. We support efforts to reduce the scourge of opioid addiction and harm. Indeed, this is much of our own clinical work in primary care. But this goal is better addressed by recommendations that consider both individual patient choice and the impact of prescribed opioids on public health through diversion, two very distinct issues. The outcome might be less neat—yet still plausible—and have the added advantage of being beneficial to the many people struggling with chronic pain.

. . .

Authors

Stephen Martin is a family physician and Associate Professor at the University of Massachusetts Medical School with a special interest in addiction and chronic pain; he is an education/research consultant to CleanSlate Addiction Treatment Centers. Ruth Potee is a family physician and addiction specialist. Andrew Lazris is an internist specializing in geriatric care and in evidence-based medicine. The authors declare no conflict of interest.

Corresponding author:
Stephen A. Martin, MD, EdM
University of Massachusetts Medical School
Barre Family Health Center
151 Worcester Road Barre, MA 01005
stmartin@gmail.com

The authors thank Bonny P. McClain MSc, of Data and Donuts for her graphical contributions.

. . .

References

1. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain-United States, 2016. *JAMA*. 2016;65. doi:10.1001/jama.2016.1464.

2. Mencken HL. The Divine Afflatus. In: *A Mencken Chrestomathy*. A. A. Knopf; 1917: p. 443.

3. Pain Specialist: Many Doctors Underprescribe For Chronic Pain | Here & Now. February 16, 2016. http://hereandnow.wbur.org/2016/02/16/underprescribing-opioids-for-pain.

4. Unger DNS. My chronic pain isn't a crime. The Boston Globe. February 3, 2015 .https://www.bostonglobe.com/opinion/2015/02/03/chronic-pain-isn-crime/hTqwaGVgwX3YpDkXUJMsfI/story.html.

5. Pain Patients Say They Can't Get Medicine After Crackdown On Illegal Rx Drug Trade | Kaiser Health News. August 5. 2015. http://khn.org/news/pain-patients-say-they-cant-get-medicine-after-crackdown-on-illegal-rx-drug-trade/.

6. Freyer FJ. Strict opioids laws hit chronic pain sufferers hard. *The Boston Globe*. June 19, 2016:A1.

7. National Consensus Project for Quality Palliative Care. Clinical Practice Guidlines for Quality Palliative Care, Third Edition. www.nationalconsensusproject.org. Published 2013.

8. Torrance N, Elliott AM, Lee AJ, Smith BH. Severe chronic pain is associated with increased 10 year mortality. A cohort record linkage study. *Eur J Pain*. 2010;14(4):380–386. doi:10.1016/j.ejpain.2009.07.006.

9. Tang NK, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. *Psychol Med*. 2006;36(5):575–586. doi:10.1017/S0033291705006859.

10. Gureje O, Von Korff M, Simon GE, Gater R. Persistent Pain and Well-being. *JAMA*. 1998;280(2):147. doi:10.1001/jama.280.2.147.

11. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane database Syst Rev*. 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2.

12. Transcript for CDC Telebriefing: Guideline for Prescribing Opioids for Chronic Pain | CDC Online Newsroom | CDC. http://www.cdc.gov/media/releases/2016/t0315-prescribing-opioids-guidelines.html. Accessed March 21, 2016.

13. Cohen MJ, Jangro WC. A Clinical Ethics Approach to Opioid Treatment of Chronic Noncancer Pain. *AMA J Ethics*. 2015;17(6):521–529. doi:10.1001/journalofethics.2015.17.6.nlit1–1506.

14. Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ*. 2013;346(may03_1):f2690. doi:10.1136/bmj.f2690.

15. Reuben DB, Alvanzo AAH, Ashikaga T, et al. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. *Ann Intern Med*. 2015;162(4):295–300. doi:10.7326/M14–2775.

16. NIH Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain. September 29–30, 2014. https://prevention.nih.gov/docs/programs/p2p/ODPPainPanelStatementFinal_10-02-14.pdf. Published 2015.

17. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331–1346. doi:10.1111/j.1532–5415.2009.02376.x.

18. Abdulla A, Adams N, Bone M, et al. Guidance on the management of pain in older people. *Age Ageing*. 2013;42 Suppl 1:i1-i57. doi:10.1093/ageing/afs200.

19. Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. Canada: National Opioid Use Guideline Group (NOUGG); 2010. Available from:http://nationalpaincentre.mcmaster.ca/opioid/

20. Cleary JF, Husain A, Maurer M. Increasing worldwide access to medical opioids. *Lancet (London, England)*. February 2016. doi:10.1016/S0140–6736(16)00234–8.

21. Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet (London, England)*. February 2016. doi:10.1016/S0140–6736(16)00161–6.

22. Yi P, Pryzbylkowski P. Opioid Induced Hyperalgesia. *Pain Med*. 2015;16 Suppl 1:S32-S36. doi:10.1111/pme.12914.

23. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011;14(2):145–161.

24. Reznikov I, Pud D, Eisenberg E. Oral opioid administration and hyperalgesia in patients with cancer or chronic nonmalignant pain. *Br J Clin Pharmacol*. 2005;60(3):311–318. doi:10.1111/j.1365–2125.2005.02418.x.

25. Henry SG, Wilsey BL, Melnikow J, Iosif A-M. Dose escalation during the first year of long-term opioid therapy for chronic pain. *Pain Med*. 2015;16(4):733–744. doi:10.1111/pme.12634.

26. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*. 2016;6736(16):1–13. doi:10.1016/S0140–6736(16)30002–2.

27. Center for Drug Evaluation and Research. Drug Safety and Availability —FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. September 9, 2015. http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm.

28. Risser A, Donovan D, Heintzman J, Page T. NSAID prescribing precautions. *Am Fam Physician*. 2009;80(12):1371–1378.

29. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet (London, England)*. 2013;382(9894):769–779. doi:10.1016/S0140–6736(13)60900–9.

30. Kalso E, Aldington DJ, Moore RA. Drugs for neuropathic pain. *BMJ*. 2013;347:f7339.

31. Ballantyne JC, Stannard C. New Addiction Criteria: Diagnostic Challenges Persist in Treating Pain With Opioids. *Pain Clin Updat*. 2013;21(5):1–7.

32. Tavernese S. C.D.C. Painkiller Guidelines Aim to Reduce Addiction Risk. *The New York Times*. March 16, 2016:A1.

33. Doctor: Prescription Painkillers Kill More People Than Heroin | Here & Now. September 9, 2015. http://hereandnow.wbur.org/2015/09/09/heroin-epidemic-overprescribing.

34. McHugh RK, Nielsen S, Weiss RD. Prescription drug abuse: from epidemiology to public policy. *J Subst Abuse Treat*. 2015;48(1):1–7. doi:10.1016/j.jsat.2014.08.004.

35. Scholten W, Henningfield JE. A meta-analysis based on diffuse definitions and mixed quality literature is not a good fundament for decisions on treatment of chronic pain patients. *Pain*. 2015;156(8):1576–1577. doi:10.1097/j.pain.0000000000000213.

36. Voon P. Further defining and conceptualizing opioid misuse in chronic pain. *Pain*. 2015;156(10):2107. doi:10.1097/j.pain.0000000000000246.

37. Nelson LS, Paulozzi LJ. The toxicology Tower of Babel: why we need to agree on a lexicon in prescription opioid research. *J Med Toxicol*. 2012;8(4):331–332. doi:10.1007/s13181–012–0266–7.

38. Secora AM, Dormitzer CM, Staffa JA, Dal Pan GJ. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. *Pharmacoepidemiol Drug Saf*. 2014;23(12):1227–1237. doi:10.1002/pds.3711.

39. Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, Juurlink DN. Sex Differences in Dose Escalation and Overdose Death during Chronic Opioid Therapy: A Population-Based Cohort Study. Mintzes B, ed. *PLoS One*. 2015;10(8):e0134550. doi:10.1371/journal.pone.0134550.

40. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011;171(7):686–691. doi:10.1001/archinternmed.2011.117.

41. Sullivan MD. Limiting the potential harms of high-dose opioid therapy: comment on “Opioid dose and drug-related mortality in patients with nonmalignant pain”. *Arch Intern Med*. 2011;171(7):691–693. doi:10.1001/archinternmed.2011.101.

42. FDA CDER Response to Physicians for Responsible Opioid Prescribing Partial Petition Approval and Denial. September 10. 2013.

https://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0818-0793.

43. Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain—Misconceptions and Mitigation Strategies. *N Engl J Med*. 2016;374(13):1253–1263. doi:10.1056/NEJMra1507771.

44. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008;300(22):2613–2620. doi:10.1001/jama.2008.802.

45. Fernandes JC, Campana D, Harwell TS, Helgerson SD. High mortality rate of unintentional poisoning due to prescription opioids in adults enrolled in Medicaid compared to those not enrolled in Medicaid in Montana. *Drug Alcohol Depend*. 2015;153:346–349. doi:10.1016/j.drugalcdep.2015.05.032.

46. Massachusetts Department of Public Health. *Assessment of Massachusetts Opioid- Related Deaths: Preliminary Findings*; 2016. July 1, 2016. https://malegislature.gov/Document/Bill/189/Senate/SD2616.pdf.

47. Drug Cocktails Fuel Massachusetts' Overdose Crisis : Shots—Health News: NPR. December 8, 2015. http://www.npr.org/sections/health-shots/2015/12/08/458280574/drug-cocktails-fuel-massachusetts-overdose-crisis.

48. It's Not Just Heroin: Drug Cocktails Are Fueling The Overdose Crisis | CommonHealth. November 13. 2015. http://commonhealth.wbur.org/2015/11/drug-overdose-cocktails.

49. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med*. 2015;372(3):241–248. doi:10.1056/NEJMsa1406143.

50. Jones CM, Logan J, Gladden RM, Bohm MK. Vital Signs: Demographic and Substance Use Trends Among Heroin Users—United States, 2002–2013. *MMWR Morb Mortal Wkly Rep*. 2015;64(26):719–725.

51. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA psychiatry*. 2014;71(7):821–826. doi:10.1001/jamapsychiatry.2014.366.

52. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *Am J Public Health*. 2009;99(2):221–227.

doi:10.2105/AJPH.2007.131714.

53. Alford DP. Opioid Prescribing for Chronic Pain—Achieving the Right Balance through Education. *N Engl J Med*. 2016;374(4):301–303. doi:10.1056/NEJMp1512932.

54. Beauchamp GA, Winstanley EL, Ryan SA, Lyons MS. Moving beyond misuse and diversion: the urgent need to consider the role of iatrogenic addiction in the current opioid epidemic. *Am J Public Health*. 2014;104(11):2023–2029. doi:10.2105/AJPH.2014.302147.

55. Opioid Painkiller Prescribing infographic | VitalSigns | CDC. http://www.cdc.gov/vitalsigns/opioid-prescribing/infographic.html#map. Accessed September 7. 2016.

56. McDonald DC, Carlson K, Izrael D. Geographic variation in opioid prescribing in the U.S. *J Pain*. 2012;13(10):988–996. doi:10.1016/j.jpain.2012.07.007.

57. The NSDUH Report: State Estimates of Nonmedical Use of Prescription Pain Relievers. January 8, 2013. http://archive.samhsa.gov/data/2k12/NSDUH115/sr115-nonmedical-use-pain-relievers.htm.

58. Alvarez L. Florida Laws Shutting "Pill Mills." *The New York Times*. September 1, 2011:A1.

59. Nowak L, Abou Nader J-E, Stettin G. *A Nation in Pain*.; 2014. https://lab.express-scripts.com/lab/publications/~/media/d48ef3ee579848e7bf3f14af536d7548.ashx.

60. Weisberg DF, Becker WC, Fiellin DA, Stannard C. Prescription opioid misuse in the United States and the United Kingdom: cautionary lessons. *Int J Drug Policy*. 2014;25(6):1124–1130. doi:10.1016/j.drugpo.2014.07.009.

61. Opioid Painkiller Prescribing: Where You Live Makes a Difference. July 2014. http://www.cdc.gov/vitalsigns/opioid-prescribing/.

62. Meier B, Tavernese S. States Move to Control How Painkillers Are Prescribed. *The New York Times*. March 12, 2016:B1.

63. Scholten W, Henningfield JE. Negative outcomes of unbalanced opioid policy supported by clinicians, politicians, and the media. *J Pain Palliat Care Pharmacother*. February 2016:1–9. doi:10.3109/15360288.2015.1136368.

64. Fields HL. The Doctor's Dilemma: Opiate Analgesics and Chronic Pain. *Neuron*. 2011;69(4):591–594. doi:10.1016/j.neuron.2011.02.001.

65. Policy Impact: Prescription Painkiller Overdoses. http://www.cdc.gov/drugoverdose/pubs/index.html. Published 2011.

66. Florida Office of the Attorney General. *Florida's Prescription Drug Diversion and Abuse Roadmap 2012–2015*.; 2015.

67. MGH to Pay $2.3 Million to Resolve Drug Diversion Allegations | USAO-MA | Department of Justice. https://www.justice.gov/usao-ma/pr/mgh-pay-23-million-resolve-drug-diversion-allegations.

. . .

Figure 1a References

1. Frenk SM, Porter KS, Paulozzi LJ. Prescription opioid analgesic use among adults: United States, 1999–2012. *NCHS Data Brief*. 2015;(189):1–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25714043.

2. U.S. Census Bureau. Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States: April 1, 2010 to July 1, 2012 [Internet]. [cited 2016 Mar 27];Available from: http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk

3. Hudson TJ, Edlund MJ, Steffick DE, Tripathi SP, Sullivan MD. Epidemiology of regular prescribed opioid use: results from a national, population-based survey. J Pain Symptom Manage 2008;36(3):280–8.

4. Sites BD, Beach ML, Davis MA. Increases in the use of prescription opioid analgesics and the lack of improvement in disability metrics among users. Reg Anesth Pain Med 39(1):6–12.

5. Prunuske JP, St Hill CA, Hager KD, et al. Opioid prescribing patterns for non-malignant chronic pain for rural versus non-rural US adults: a population-based study using 2010 NAMCS data. BMC Health Serv Res 2014;14:563.

6. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SRB. Characteristics of opioid prescriptions in 2009. JAMA 2011;305(13):1299–301.

7. Ciesielski T, Iyengar R, Bothra A, Tomala D, Cislo G, Gage BF. A tool to assess risk of de novo opioid abuse or dependence. Am J Med 2016;

8. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain 2007;129(3):355–62.

9. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain 2007;8(7):573–82.

10. Pletcher MJ, Kertesz SG, Sidney S, Kiefe CI, Hulley SB. Incidence and antecedents of nonmedical prescription opioid use in four US communities. The Coronary Artery Risk Development in Young Adults (CARDIA) prospective cohort study. Drug Alcohol Depend 2006;85(2):171–6.

11. Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. Clin J Pain 2014;30(7):557–64.

12. Degenhardt L, Bruno R, Lintzeris N, et al. Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study. The Lancet Psychiatry 2015;2(4):314–22.

13. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171(7):686–91.

14. Sullivan MD. Limiting the potential harms of high-dose opioid therapy: comment on “Opioid dose and drug-related mortality in patients with nonmalignant pain”. Arch Intern Med 2011;171(7):691–3.

15. Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, Juurlink DN. Sex Differences in Dose Escalation and Overdose Death during Chronic Opioid Therapy: A Population-Based Cohort Study. PLoS One 2015;10(8):e0134550.

. . .

Figure 1b References

1. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings [Internet]. 2014 [cited 2016 Mar 28];Available from: http://store.samhsa.gov/product/Results-from-the-2013-National-Survey-on-Drug-Use-and-Health-Summary-of-National-Findings/SMA14-4863.

2. Jones CM, Paulozzi LJ, Mack KA. Sources of prescription opioid pain relievers by frequency of past-year nonmedical use United States, 2008–2011. JAMA Intern Med 2014;174(5):802–3.

3. Results from the 2013 national survey on drug use and health: detailed tables: Table 1.54A [Internet]. [cited 2016 Mar 28];Available from: http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2013.pdf.

. . .

Figure 2 References

1. Opioid Painkiller Prescribing infographic | VitalSigns | CDC [Internet]. [cited 2016 Mar 23];Available from: http://www.cdc.gov/vitalsigns/opioid-prescribing/infographic.html#map

2. The NSDUH Report: State Estimates of Nonmedical Use of Prescription Pain Relievers [Internet]. [cited 2016 Mar 23];Available from: http://archive.samhsa.gov/data/2k12/NSDUH115/sr115-nonmedical-use-pain-relievers.htm