

Review Article

The Prescription Opioid Crisis — A Problem of Chronic Pain Management

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Abstract

The steady rise in prescription opiate mortality has led to recommendations by the CDC to sharply curtail use of opiates in treatment of chronic nonmalignant pain, limit opioid dosage to extremely low levels, and replace opioid treatment with alternatives. These recommendations ignore extensive scientific evidence of the efficacy of opioids, even in chronic pain management. They overestimate the prevalence of side effects. They vastly overestimate the prevalence of addiction in the clinical setting, likely confusing it with patient requests for dose changes motivated by persistent pain. They strongly recommend the use of alternatives to opioid management that are not supported by sufficient clinical trial evidence to justify translation to the clinic. They do not consider suffering to be sufficient motivation for treatment. They focus on total opioid mortality, rather than defining it as a quantifiable risk (approximately 1%/year) that should be considered in medical decision making, and implicitly assume that chronic pain is a minor problem that could not possibly justify the incursion of significant risk. Guidelines have failed to emphasize key principles of opioid management (e.g., individualized dose titration; treatment of depression; and utilization of control of pain, rather than an analog scale of pain magnitude, as a guide to treatment). By and large, the development of guidelines has failed to even consider the reasons for opiate deaths and how better management of chronic pain could both reduce risk of death and improve pain control. In this review, I consider means to these ends in some detail.

Keywords

- Opioids
- Chronic pain management
- Opioid effectiveness
- Opioid mortality

ABBREVIATIONS

CDC: Centers for Disease Control; MED: Morphine Equivalent Dosage; FDA: Food and Drug Administration

INTRODUCTION

At least some of us who work in the trenches caring for patients with chronic non-malignant pain view with considerable alarm emerging approaches to the prescription opioid overdose death crisis, including new CDC guidelines [1,2] and FDA plans [3]. We also feel that a wonderful opportunity to both reduce opioid overdose deaths and improve treatment of chronic pain is being squandered. It is our sense that the solutions being proposed are often simplistic, ignore important existing science, and emphasize opioid regulatory approaches over creative, scientifically founded approaches to chronic pain.

The CDC study [1], is remarkable for its thoroughness and transparency. Nevertheless, the choice of studies to be included, their interpretation, and the ultimate conclusions of the document inevitably reflect the climate of our times, which overwhelmingly favors the view that chronic nonmalignant pain is a modest problem that warrants no treatment risks and that opioids are ineffective for chronic pain and fraught with enormous hazard

(e.g., Franklin [4]). In the CDC report, as in other reviews, there is frequent conflation of statistical association with causation [e.g., in the claim that co-prescription of benzodiazepines magnifies opioid risk]. Because the effect of optimally titrated opioid treatment, provided in the context of a comprehensive pain management plan, can be very large [5], individual practitioner experience is eminently relevant to the discussion. I can think of no other field of medicine in which the divergence between expert opinion, as in the CDC study, and clinical practice experience is so vast and in which expert opinion seems to overlook so many key issues [see below]. Finally, and most crucially, the intense focus on opioids and opioid dose limitations represents preoccupation with a symptom rather than the deeper problem: developing safer and more effective approaches to chronic pain management.

A number of assertions have been repeated either without scientific evidence or in spite of strong countervailing evidence. For example

There is no evidence that opioids are effective in the long-term management of chronic pain: Assertions of opioid ineffectiveness are at great odds with clinical experience, the results of well-designed randomized trials testing effectiveness [6], and open trials demonstrating long-term stability of

effectiveness [7-10]. Yet, they are repeated so often and with such authority that they are now widely believed by health care practitioners and patients alike and define public policy. An alternative reading of this charge is that there exist no phase III trials of long-term use of opioids for chronic nonmalignant pain. This is true, but for obvious reasons: it would be unethical to conduct such trials because equipoise could not be established, and such a trial would be logistically impossible because nearly all patients in the placebo group would drop out [6].

The side effects of opioids commonly exceed their beneficial effects: This assertion ignores the evidence that side effects are accentuated by over-rapid titration [11], as well as the evidence that intolerable side effects are highly idiosyncratic [12,13] and can usually be largely avoided by switching to a different opioid.

Many Americans are now addicted to opioids [3]: If a patient has intolerable pain 24/7, how would one know whether a request for escalation of dosage reflected pursuit of euphoria, relief from withdrawal-related dysphoria, or seeking of an acceptable level of pain control? Most likely, this perception of prevalent addiction reflects the fact that many patients with chronic nonmalignant pain are inadequately managed, perhaps under-dosed, and understandably seek relief.

There are many proven alternatives to opioid treatment of chronic nonmalignant pain that, if used widely, would substantially address the problem: In fact, clinical trials of alternative chronic treatments scarcely suggest enough efficacy to establish equipoise in head to head trials with opioids. Thus, an ethical trial design might involve testing the extent to which alternative treatments can enable reduction in opioid dosage.

Relief of suffering is an insufficient goal of pain treatment: The consistent omission of relief of suffering as a legitimate goal for opioid treatment implicitly [and successfully] licenses omission from the opioid dialogue of the millions of people with chronic nonmalignant pain who are able to enjoy quality lives thanks to effective pain relief - unarguably a long-term benefit. Patients with chronic nonmalignant pain report a health-related quality of life as poor as patients dying of cancer [14].

The steady rise in prescription opiate-related deaths is sufficient reason to avoid or sharply constrain opiate use [e.g., to ≤ 50 mg MED/day]: Medical decision-making should involve a careful discussion with the patient of benefits and risks. Two recent studies, both population-based, provide a basis for estimating risk of death. In a study of 22,912 patients on long-acting opiates, the excess risk of death associated with opiates was 0.59%/year [15]. In a study of 32,449 Canadians receiving opiates through public assistance, annual risk of death [as defined by a coroner's finding of plausible tissue concentrations] was approximately 0.06%/year in those on low-dose therapy and approximately 1.4%/year in those receiving >200 MED/day [16]. These risks would almost certainly be perfectly acceptable to nearly all patients with severe chronic pain.

A considerable body of scientific evidence and its implications are being ignored. For example

Opioid dosage needed to achieve adequate control of pain

varies by a factor of at least 15 [17-20], in part because of differences in pain intensity, but in very substantial part because of allelic and splice variants of the mu-1 (OPRM1) receptor gene [21]. The result is that many patients require and tolerate very high doses of opioids and there is a high probability that, on average, their physicians will be unwilling to titrate dosage adequately to achieve satisfactory control. Failure to recognize this science undoubtedly provides some basis for claims that clinicians are prescribing opioids far in excess of clinical need [3].

The prevalence of depression, arguably the single most important comorbidity in chronic pain because it is such a potent amplifier of suffering, is almost certainly vastly underestimated. Even in studies testing the influence of opioid dosage on related morbidity and mortality have found that in high dose groups, the prevalence of depression is only about 12-27% [22,23]. In my own 30-year experience, the prevalence of depression in this population is close to 100% and treatment of depression often provides a remarkably effective alternative to opioid dose titration in improving pain control. It is also fair to ask, what fraction of opioid overdose deaths represent suicides [24,25].

There is good reason to believe that our current standard of pain measurement, a visual analog scale of pain intensity, is inappropriate in the management of chronic pain [26,27], and that instead, we should be assessing adequacy of pain control [5].

The rise in opioid-related deaths is cause for great concern, but little attention has been directed to the reasons for this rise. These likely include insufficient expertise by practitioners; inadvertent double dosing by patients because of failures of attention and memory; concurrent use of alcohol; and Armageddon-like perspectives in chronic pain patients hopeless about ever achieving relief, hopelessness compounded by depression [5]. Clearly science must be brought to bear on these issues, but in the meantime, we have enough clues to take some first steps.

Treatment of patients with chronic pain is complex, challenging, time consuming, requires considerable practitioner expertise, precision, discipline, and commitment, and makes heavy demands on office staff. This is not care that, at least for patients with more severe problems, can be achieved with our current general medical practice infrastructure. How might the problem be approached?

1. Educate practitioners, from medical school, through residency, and in postgraduate medical education, in the basics of maximally safe and effective chronic pain management, with all its complexities, subtleties, tricks of the trade, and potential pitfalls; when to refer; and how to work hand in hand with specialists. Such education must be comprehensive, sophisticated, balanced, detail oriented, and take into full account that effective treatment of chronic pain enables millions of people to work and enjoy family life, even as treatment with opioids incurs serious risks.
2. Organize a tiered system of care, in which general practitioners either refer patients to pain specialists, or continue responsibility for day-to-day management but get regular periodic advice and back-up from pain

specialists. Incentivize general practitioners to participate in such a system.

3. Incentivize the extraordinary burden of care essential to adequate care of patients with chronic pain. Physicians are unlikely to spend the necessary 30-60 minutes for a return visit when they are only reimbursed for 15 minutes of care.
4. Dignify rather than vilify the pain specialists who would provide the vital hub of any definitive solution to the prescription opioid problem. At present, these specialists are routinely the target of repeated inquiries by their boards of medicine; subject to enormous pressures, including threatened loss of clinical privileges by hospital executives; decried by pharmacists as quacks and drug pushers, even as most pharmacists refuse to fill prescriptions; and obliged to spend hours each week dealing with pharmacists and insurance companies.
5. Replace the humiliation and other forms of psychological abuse routinely dealt patients with chronic pain by health care professionals at all levels with compassion and respect.
6. Educate patients and family members about opioid risks, benefits, and alternatives, and about the distinctions between tolerance, dependence, genuine need for higher dosage, and addiction.
7. Bring pharmacists into full partnership with physicians in the care of patients with chronic pain, including copying them on clinic notes.
8. Develop technological approaches to preventing inadvertent double dosing.
9. Formalize strategies for increasing the number of well-qualified pain specialists.
10. Avoid regulatory strictures that only hamstring physicians, particularly pain specialists, in the provision of care. In fact, it is a highly dubious proposition that the opioid problem can be regulated away. Far more creative solutions are needed.

CONCLUSION

In sum, the solution to the prescription opioid problem lies in improving our management of chronic nonmalignant pain. The National Pain Strategy recently published by Office of the Assistant Secretary for Health at the U.S. Department of Health and Human Services (https://iprcc.nih.gov/National_Pain_Strategy/NPS_Main.htm) incorporates many of the points made here and is likely to constitute a far more effective and less burdensome approach to the prescription opioid crisis than the opioid-specific approaches being recommended by the CDC and the FDA.

REFERENCES

1. Dowell D, Haegerich T, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, MMWR Recomm Rep. 2016; 65: 1-49.
2. Frieden TR, Houry D. Reducing the risks of relief -the CDC opioid prescribing guideline. N Engl J Med. 2016; 375: 1501-1504.
3. Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. N Engl J Med. 2016; 374: 1480-1485.
4. Franklin GM. Opioids for chronic noncancer pain. A position paper of the American Academy of Neurology. Neurology. 2014; 83: 1277-1284.
5. Nadeau SE. Opioids for chronic nonmalignant pain. To prescribe or not to prescribe—what is the question? Neurology. 2015; 85: 646-651.
6. Hale ME, Ahdieh H, Ma T, Rauck R, Oxymorphone ER Study Group 1. Efficacy and safety of OPANA ER [oxymorphone extended release] for relief of moderate to severe low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. J Pain. 2007; 8: 175-184.
7. Milligan K, Lanteri-Minet M, Borchert K, Helmers H, Donald R, Kress H-G, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain. 2001; 2: 197-204.
8. Mystakidou K, Parpa E, Tsilika E, Mavromati A, Smyrniotis V, Georgaki S, et al. Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. J Pain. 2003; 4: 298-306.
9. Portenoy RK, Farrar JT, Backonja M-M, Cleeland CS, Yang K, Friedman M, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain. 2007; 23: 287-299.
10. Roth SH, Fleischmann RM, Burch FX, Dietz F, Bockow B, Rapoport RJ, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain. Arch Intern Med. 2000; 160: 853-860.
11. Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag. 2011;16: 337-351.
12. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. J Clin Oncol. 2001; 19: 2542-2554.
13. Quang-Cantagrel N, Wallace MS, S.K. M. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. Anesth Analg. 2000; 90: 933-937.
14. Fredheim OM, Kaasa S, Fayers P, Saltnes T, Jordhøy M, Borchgrevink P. Chronic non-malignant pain patients report as poor health-related quality of life as palliative cancer patients. Acta Anaesthesiol Scand. 2008; 52: 143-148.
15. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA. 2016; 315: 2415-2423.
16. 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: 1-11.
17. Beeton AG, Upton PM, Shipton EA. The case for patient-controlled analgesia. S Afr J Surg. 1992; 30: 5-6.
18. Cepeda MS, Carr DB. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. Anesth Analg. 2003; 97: 1464-1468.
19. Leitao MM, Malhotra V, Briscoe G, Suidan R, Dholakiya P, Santos K, et al. Postoperative pain medication requirements in patients undergoing computer-assisted [“robotic”] and standard laparoscopic procedures for newly diagnosed endometrial cancer. Ann Surg Oncol. 2013; 20: 3561-3567.
20. Okutomi T, Saito M, Mochizuki J, Amano K, Hoka S. A double-blind randomized controlled trial of patient-controlled epidural analgesia

- with or without a background infusion following initial spinal analgesia for labor pain. *Int J Obstet Anesth.* 2009; 18: 28-32.
21. Pasternak GW. Opioids and their receptors: are we there yet? *Neuropharmacol.* 2014; 76: 198-203.
22. Braden JB, Russo J, Fan M-Y, Edlund MJ, Martin BC, DeVries A, et al. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med.* 2010; 170: 1425-1432.
23. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose. *Ann Intern Med.* 2010; 152: 85-92.
24. Madadi P, Persaud N. Suicide by means of opioid overdose in patients with chronic pain. *Curr Pain Headache Rep.* 2014; 18: 460.
25. Cheatle MD. Depression, chronic pain, and suicide by overdose: on the edge. *Pain Med.* 2011; 12: S43-S48.
26. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Breivik Hals EK, et al. Assessment of pain. *Br J Anaesth.* 2008; 101: 17-24.
27. Kim J, Lee KS, Kong SW, Kim T, Kim MJ, Park S-B, et al. Correlations between electrically quantified pain degree, subjectively assessed visual analogue scale, and the McGill Pain Questionnaire: a pilot study. *Ann Rehabil Med.* 2014; 38: 665-672.

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