Preventive Medicine 118 (2019) 171–175

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Review Article

Clinical solutions to chronic pain and the opiate epidemic

Matthew Murray[a], Alexander Stone[b], Virginia Pearson[a], Glenn Treisman[a,*]

[a] Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, USA
[b] Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, USA

ABSTRACT

The current opiate epidemic has caused tens of thousands of deaths annually and hundreds of billions in economic losses. From 1979 to 2015, accidental opiate-related deaths increased by 4250%. Despite its magnitude, the driving forces remain poorly understood. A narrow understanding by physicians, administrators and policy makers has resulted in a clinical approach to chronic pain treatment misguided by expediency, shortsighted cost reduction, pharmaceutical profit, and patient satisfaction. Until the broken elements are well understood, effective policy solutions will remain elusive. In this review, we describe the first comprehensive timeline of significant contributing factors between 1979 and the present. To address the complexity of treating patients with chronic pain and its contribution to opiate overuse, we outline an alternative clinical and health systems approach to chronic pain therapy. Addressing the underlying drivers will require empowering physicians to use clinical judgment over guidelines and algorithms to provide holistic, high-quality healthcare to individual victims of the opiate epidemic.

1. Introduction

The use of opiates for pain was liberalized starting in the 1980s with a corresponding increase in addiction, illicit use, overdose deaths and disability, without improvement in overall perception of pain (Compton et al., 2016). The faddish postulate that "pain medications" can treat all pain resulted from the confluence of consumerism in medicine, cost reduction, an emphasis on profits and the over-simplification of medical practice. The response of policies to decrease opiate prescribing has been equally simplistic, resulting in a shift to heroin and other illicit drugs with a corresponding increase in fatalities (Compton et al., 2016). An understanding of the factors that drive the epidemic is needed for a successful solution.

Opiate agonists are addictive (Ewan and Martin, 2013; Treisman and Clark, 2011). While there is little evidence that chronic opiate therapy improves function or outcome for patients with chronic pain (Chou et al., 2015), there is strong evidence for opiate use in acute pain. Withholding appropriate opiate therapy for acute pain in patients with a high "opiate risk score" is medically unacceptable, and chronic opiate therapy for chronic pain in patients with a low "risk score" will often be unhelpful. Patients with greater risk for opiate misuse require greater vigilance (as with any medications with high risk). There is some evidence that a subset of patients with chronic pain do benefit from chronic opiate therapy, supporting the need for physician judgment.

Treatment of patients with chronic pain is complicated, expensive, and takes time and expert evaluation. Inadequate education and support for the medical community has hampered the effective treatment for chronic pain. In this paper, we describe the history and causes of the current opiate epidemic, give an alternative approach to the treatment of chronic pain, and suggest a coherent solution to the problem of opiate overprescribing.

2. The crisis of opiate misuse and addiction in the U.S.

The United States is suffering from an opiate epidemic that has been attributed to pharmaceutical companies, prescribers, "drug addicts," and bad doctors. Less often mentioned are the roles of the Joint Commission on Accreditation of Healthcare Organizations (the "Joint Commission"), hospital administrators, insurance providers, government regulators, and the recent emphasis on patient satisfaction in medicine. While assigning blame is unproductive, fully understanding the broken elements is essential for an effective solution.

The recent rise in opiate use began in the 1980s based on legitimate criticism of inadequate pain control in palliative cancer care and postoperative pain (Fig. 1). As part of the debate, a 1980 letter in the New England Journal of Medicine reported that among 11,882 patients prescribed opiates, only four developed addiction (Porter and Jick, 1980). This one-paragraph letter has been cited over 1000 times and is widely used as an argument for increased use of opiates to treat pain. Another highly influential paper published in 1986 concluded that chronic opiate therapy was safe for non-cancer pain in a case series of 38 patients (Portenoy and Foley, 1986). Neither of these reports claimed to be more than observations, but they were widely misused to support a fundamental shift in medical practice. An article in Scientific American titled "The Tragedy of Needless Pain" also had a significant impact on both the medical and lay community (Melzach, 1990). The

* Corresponding author at: 600 N. Wolfe St., Suite 119, Baltimore, MD 21205, USA.
E-mail address: glenn@jhmi.edu (G. Treisman).

https://doi.org/10.1016/j.ypmed.2018.10.004
Received 5 April 2018; Received in revised form 30 September 2018; Accepted 8 October 2018
Available online 11 October 2018

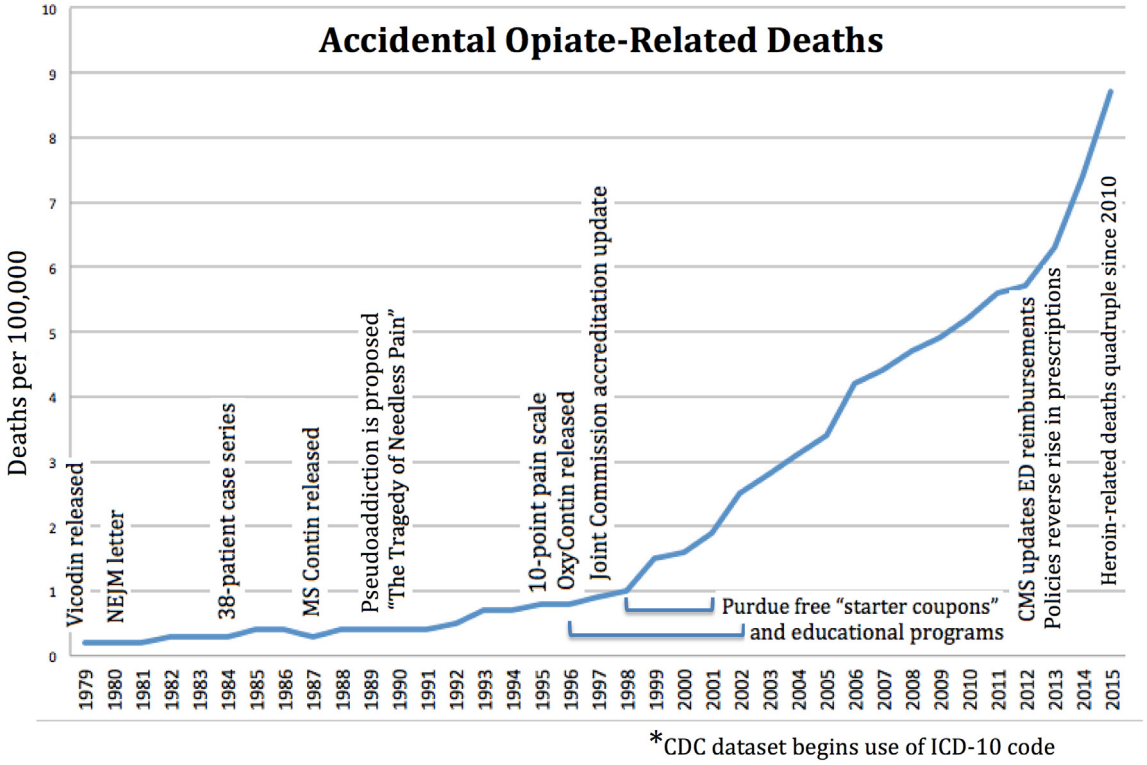

Fig. 1. Accidental opiate-related deaths from 1979 to 2015. Deaths per 100,000, with significant contributing factors annotated.

paper claimed, "When patients take morphine to combat pain, it is rare to see addiction." The article also referred to the 38-patient case series as "something in medicine that is akin in aeronautics to breaking the sound barrier".

In 1995, the American Pain Society (APS) announced a "quality improvement initiative" to measure pain using a 10-point scale on a vital signs sheet (Committee APSQ of C, 1995). The following year the president of the APS announced in his annual speech that pain must be regarded as the "fifth vital sign," launching a campaign to promote pain management with equal importance to other vital signs such as blood pressure or body temperature (Committee APSQ of C, 1995). Within a year of the campaign, the Veterans Administration (VA) developed a toolkit to promote this approach, and the Joint Commission began to focus on pain assessment as part of their accreditation criteria (Pain as the 5th Vital Sign Toolkit, 2000). In 1997, the American Academy of Pain Medicine and the APS released a consensus statement for expanding opiate prescribing, stating that pain is managed inadequately and that the accepted principles of practice for opiates "…should be promulgated" (The use of opioids for the treatment of chronic pain, 1997). The consensus statement cited no studies. In 1998 the Federation of State Medical Boards issued a policy recommendation that physicians not be subject to regulatory action for prescribing opiates, even for adverse effects or death from chronic high-dose therapy (Position Of The Federation Of State Medical Boards, 1998). No distinctions were made between acute and chronic pain.

Numerous authors have blamed Purdue Pharmaceuticals for initiating the opiate epidemic, but when OxyContin was released in 1996 prescriptions for hydrocodone had already quadrupled since 1979 (CDC and NCHS, 2015). Despite this, the role played by pharmaceutical companies in promoting opiate use was dramatic. OxyContin was marketed as a safer, less-addictive opiate based on the idea that its slow release formula produced less of a "high" and therefore had less abuse liability (Van Zee, 2009). The marketing of OxyContin was aggressive. A report by the U.S. Government Accountability Office (GAO) noted that Purdue Pharmaceuticals funded over 20,000 pain-related educational programs before termination in July 2002 (GAO, 2003). These programs urged primary-care physicians (PCPs) to prescribe OxyContin as first-line treatment to patients with non-cancer pain. The FDA later cited these marketing claims as false, for example that opiate analgesics cause addiction in less than 1% of patients (GAO, 2003). Purdue tracked physicians who prescribed the most OxyContin and built a wide network of sales representatives who received bonuses of up to $240,000 for promoting prescribing. Between 1998 and 2001, Purdue sales representatives provided "patient starter coupons" to physicians, which gave patients a free trial of OxyContin for up to 30 days. Roughly 34,000 patient starter coupons were redeemed. By 2002, PCPs wrote half of all OxyContin prescriptions, the majority of which were for non-cancer pain. Ultimately, criminal charges were brought against Purdue for misleading physicians, patients, and regulatory agencies about the risks of OxyContin. In total, Purdue paid $635 million in one of the largest criminal prosecutions of its kind. These fines pale in comparison to Purdue's profit from OxyContin, peaking at over $1 billion per year (GAO, 2003). Although the opiate epidemic began before OxyContin was released, pharmaceutical marketing played a central role in expanding opiate use for chronic pain.

As the evidence for opiate overuse grew and physicians raised concern, some defenders of chronic opiate therapy promoted the idea of "pseudoaddiction," a supposed iatrogenic syndrome from undertreating pain (Weissman and Haddox, 1989). The belief was that patients treated with insufficient analgesics would seek additional treatment, mimicking the behavior of an addict. Therefore, the clinical solution for pseudoaddiction was additional opiates. The underlying assumption of pseudoaddiction was that opiates are not addictive. A 2015 review on pseudoaddiction showed no studies validating the concept and that only 33 of 224 papers on pseudoaddiction contained any data at all (Greene and Chambers, 2015).

The Joint Commission denies playing a role in the opiate epidemic on their website despite requiring pain assessment tools and protocols for pain treatment since 2001. The Joint Commission requirements were even used as a marketing tool by Purdue. Pain ratings and opiate

therapy became entrenched in hospital administrations in fear of Joint Commission action. Terms such as “pain emergency” were introduced into hospital policies to make certain that pain complaints were met with an “adequate response.” In the Joint Commission standards published in 2001, numerous statements focus on the need for standardized assessment and response to pain. An example was “Pain intensity scales are enlarged and displayed in all areas where assessments are conducted.” Also required were public postings such as, “Statement on Pain Management: All patients have a right to pain relief” (Joint Commission Resources, 2001). According to physicians, this significantly affected their practice regarding opiate use and continues to be an issue even now (Kelly et al., 2016). While the Joint Commission website states that it never advocated pain as a vital sign, David Baker, Executive Vice President for the division of Health Care Quality Evaluation for the Joint Commission, wrote a cogent piece about the lessons learned from this opiate epidemic by the Commission. In response to the criticisms over time, he wrote: “The Joint Commission made multiple changes. The 2001 example of implementation that said “Pain is considered a ‘fifth’ vital sign in the hospital's care of patients” was changed in 2002 to say “Pain used to be considered the fifth vital sign,” and by 2004 this phrase was deleted from the accreditation standards manual” (Baker, 2017).

Consumerism and patient satisfaction also play a role in amplifying the existing problem. Despite growing evidence of a dramatic increase in opiate-related deaths, in 2012 the Center for Medicare and Medicaid Services (CMS) launched an updated value-based payment scheme that linked 30% of ED reimbursements to patient satisfaction surveys. The Hospital Consumer Assessment of Healthcare Providers and Systems survey has a designated subset of questions for pain, which are: “During this hospital stay, did you need medicine for pain? How often was your pain well controlled? How often did the hospital staff do everything they could to help you with your pain?” (HCAHPS Survey, 2012) This financial incentive to satisfy patients led hospital administrators to put even greater pressure on physicians to prescribe opiates. Pressure to satisfy patients does not leave room for judgment about the appropriate use of opiates nor misuse by patients. The launch of the CMS program to link payment to patient satisfaction began seven months after a landmark study showed higher patient satisfaction is correlated with increased mortality in a nationally representative sample (Fenton, 2012). A 2016 study reported that 40% of surveyed ED physicians or a colleague they knew had been formally disciplined for not prescribing opiates, and 71% perceived pressure from administrators to prescribe. They attributed this pressure to both reimbursements and Joint Commission's standards. Because patient satisfaction scores often affect personal compensation, these scores put physicians' self-interest in direct conflict with the needs of their patients. In one study, 98% of physicians opposed the use of patient satisfaction scores as part of quality care assessment (Kelly et al., 2016).

Between 1999 and 2011 the number of opiate prescriptions nearly quadrupled, coinciding with a tripling of opiate-related deaths across the U.S. (Jones, 2013; Chen et al., 2014) Drug-related deaths have become the number one cause of accidental death in the U.S., surpassing motor vehicle crashes, gun-related deaths, and HIV-related deaths during the peak of the HIV epidemic (Berge and Burkle, 2014; CDC, 2017a). In 2013 alone, the economic impact of the opiate crisis was estimated to be $78.5 billion, with only 4% of these costs spent on rehabilitation programs (Florence et al., 2016). From 1979 to 2015, accidental opiate-related deaths increased by 4250% (CDC and NCHS, 2015).

3. What is known about opiates and chronic pain?

Pain can be divided into two distinct categories: acute pain and chronic pain. The difference is not simply duration. While acute pain helps protect the damaged tissue during the healing process, chronic pain represents a change in the nervous system such that pain signals are dissociated from tissue injury (Treisman and Clark, 2011). These differences in underlying pain mechanism suggest that treatment may be different as well. A systematic review in 2008 identified 4209 relevant citations and reported no randomized controlled trials addressing opiates in the treatment of chronic non-cancer pain. Observational data showed that patients on long-term opiates had an increased risk of abuse, fracture, myocardial infarction, and overdose in a dose-dependent manner. The majority of studies assessing long-term opiate therapy for chronic pain lasted under six weeks, with zero studies lasting more than one year (Chou et al., 2015). Different types of chronic pain have been characterized but research has been limited in this area. The treatment of chronic pain often requires expert evaluation and both physical and pharmacologic therapies. While more expensive than simply prescribing opiates, these treatments are often highly effective in a variety of outcome measures (Swedish Council on Health Technology Assessment, 2006).

The phenomenon of increased pain sensitivity caused by opiate therapy is known as opiate-induced hyperalgesia (OIH). One prospective study suggests that OIH occurs within 1 month of initiating opiate therapy (Chu et al., 2006). Local OIH to electric shock is seen within 90 min after high-dose fentanyl therapy (Chu et al., 2011; Mauermann et al., 2015). The mechanisms underlying OIH are unclear, but appear to involve pain facilitating mechanisms, and may overlap with opiate receptor desensitization seen in tolerance, in which the pain system becomes more sensitized to noxious stimuli and is ineffectively modulated by opiates (DuPen et al., 2007). One explanation used to help patients understand OIH is conceptually simple: just as light sensors in the eye adapt to become more sensitive with reduced light, pain sensors become more sensitive when pain transmission is blocked by opiates.

Factors that are known to increase the likelihood of developing chronic pain have been extensively described including the type of injury, the degree of pain control at the time of injury, psychological factors and the cultural understandings of pain and healing. Psychiatric co-morbidities such as major depression, addiction, personality disorder, and poor coping skills increase the risk for chronic pain (Clark, 2009). Catastrophizing, a maladaptive coping method associated with the development of chronic pain and disability, has been described and can be effectively treated. It is influenced by negative affectivity and illness misinformation which leads to pain-related fear, avoidance of activities, and finally disuse, depression and disability (McLean et al., 2005). One study determined that the level of catastrophizing at baseline was an independent predictor of pain 8 weeks later (Haythornthwaite et al., 2003). Many of these factors can be made worse by chronic opiate therapy. Opiates reinforce behaviors associated with their administration, and when individuals take opiates in response to their distress, catastrophizing or extroverted temperaments can increase (Treisman and Clark, 2011).

4. Prescription for a cure

Limited understanding of chronic pain and the opiate epidemic has resulted in detrimental policies to reduce prescriptions rather than improve the quality of patient care for those suffering. Patients already dependent or addicted are being injured by the sudden unavailability of opiates. In Florida, for example, efforts to strictly limit oxycodone prescriptions in 2010 led to a 50% reduction in oxycodone-related deaths, but a resultant increase in heroin use caused total overdose deaths in 2014 to increase by 22.7% (Johnson et al., 2014; CDC, 2017b). Even excessively prescribed opiates are less dangerous than illicit opiates obtained by patients when their prescribed drugs are discontinued. Heroin is also far cheaper than illicitly obtained prescription opiates: one 80-milligram OxyContin pill has a street value of roughly $80, while a comparable dose of heroin costs only $10 (Berge and Burkle, 2014). This transition from prescribed opiates to IV heroin has led to concurrent epidemics in needle-transmitted infections, such

as hepatitis C and HIV, particularly among young Americans (Suryaprasad et al., 2014; Peters et al., 2016).

A comprehensive response to the opiate epidemic would involve several elements. The first is better clinical care for chronic pain, addiction, opiate dependence, and vulnerable populations. Careful evaluation to look for treatable causes of pain is an essential first step. Many patients have not had adequate evaluation for their pain. Rehabilitative care is expensive but is less costly than the current opiate epidemic with accompanying overdose deaths and loss of human potential, increased admissions for addiction, emergency room visits, disability, crime, jail time, and continued medical care. The second component is education. Because of the scope of the current problem, clinicians widely need education or re-education about appropriate use of opiates, pain types, as well as recognition and initiation of treatment for addiction, depression, and other psychological vulnerabilities. Clinicians in practice seek this education. Patient education will also be necessary to reverse the commonly held belief that prescription drugs are necessary for good medical care. The U.S. is one of only two countries in which direct-to-consumer advertising of pharmaceuticals is legal; reversing this law could address this emphasis on pharmaceuticals while strengthening the doctor-patient relationship. The third element is research. Chronic pain treatments are poorly studied and research is inadequately supported. A better understanding of model care and effective healthcare delivery is also essential to achieve the necessary clinical outcomes. All interventions, whether to clinical practice, health systems or research funding, should be supported by high quality data. This must include both new policies and old policies that are not supported by new data. The misuse of the NEJM letter and the 38-patient case study serve as a lesson in moving too quickly to change medical practice without adequate data.

Insurance companies and other funders of healthcare promote formulaic approaches and reflexive treatments that are inexpensive and straightforward, such as guidelines or algorithms, rather than a holistic approach in the evaluation and treatment of patients. The use of checklist diagnoses such as “chronic low back pain” and “fibromyalgia” grossly underestimate the multifactorial nature of these conditions, and lead to generalized treatment recommendations. Insurers also often apply co-pays to effective but expensive treatments such as physical therapy while offering inexpensive treatments (such as opiates) in their place. This phenomenon is amplified by financial pressure and time constraints on clinicians. Burdensome “prior authorizations” and other barriers influence the choices of treatment made by clinicians and patients, and while they may save money in the short term, they shift the cost to loss of function, disability payments and decreased productivity for people who could be rehabilitated. Physical therapy, while costly at first, helps prevent re-injury by altering biomechanics, and allows patients who have ongoing pain to continue treatments free of charge for years after learning effective techniques.

Effective treatments exist for the various subtypes of chronic pain, such as central or peripheral sensitization, de-afferentation pain, and complex regional pain syndrome. Each of these pain syndromes requires expert evaluation and diagnosis with targeted therapy. Pharmacotherapy includes SNRI antidepressants, anticonvulsants, calcium-channel blockers, alpha-2 receptor modulators, neuromodulators such as tricyclic antidepressants, and numerous others that have shown great benefit to particular patient populations. Pain interventions such as nerve blocks, trigger point injections, Botox injections, and local anesthesia for rehabilitative treatments are often essential for success. Non-pharmacological interventions such as mindfulness, physical therapy, biofeedback, relaxation, massage, acupuncture, and acupressure have all shown efficacy for certain chronic pain types. Even treatments with weak evidence for chronic pain have better evidence than opiates and have not resulted in an epidemic of fatalities. Lastly, some patients do appear to benefit from chronic opiate therapy for chronic pain. Risk of the treatment compared to potential benefit needs to guide clinician judgment rather than the reflexive algorithms and policies currently promoted in patient care.

Treatment of chronic pain should involve an interdisciplinary team of physicians, nurses, physical therapists, and occupational therapists working together to address all factors contributing to chronic pain, including mental health, addictions, and rehabilitation (Gatchel et al., 2014). Treatment should be tailored to the individual patient so that all of the patient's conditions are addressed. A thorough medical and psychiatric history and physical exam helps to unveil factors that may be sustaining pathological behaviors such as relief from responsibilities or financial rewards for illness (Treisman and Clark, 2011). Occult psychiatric diseases such as depression need aggressive medical management. Problems in the patient's life, such as marital discord, family dynamics, and living situations can be barriers to recovery. Personality factors such as focusing on the present, feelings or rewards as opposed to the future, function, and avoidance of consequences can make patients difficult for doctors to understand and successfully treat. Patients with cognitive limitations, deeply held cultural beliefs about medical care, or the feeling of victimization may need support and education to encourage their participation in a treatment. Lastly, preexisting or iatrogenic addiction disorder makes it difficult for patients to consider treatment without opiates.

Support for clinicians treating patients currently receiving opiates should assist in evaluation, gradual tapering of opiates, rehabilitative treatments, specialized management with alternative pain therapies, and adequate time for the process to take place. A hierarchy of expertise from PCPs to tertiary centers with outpatient, inpatient, and high-level integrated specialty care must be developed.

5. Conclusion

A simple focus on relief of discomfort rather than longer-term recovery is the product of both hopelessness in patients and lack of resources for clinicians. Systemic change is required to fix the current epidemic and avoid repeating past failures. The simplistic policies of restricting opiate prescriptions have failed. There is an existing expertise in the evaluation and treatment of chronic pain to provide education and training. To counter the pressure to prescribe opiates, physicians need support for ongoing frequent evaluation, holistic hands-on treatment and an investment in rehabilitation, rather than a focus on algorithms and guidelines. Appropriate evaluation and treatment of patients may take months for individuals to recover and years for financial returns, but will result in better outcomes and vastly reduced expense with time.

Labeling patients as “high cost utilizers” masks the failure of our healthcare system to provide effective rehabilitative care for patients with chronic illnesses. Such patients require innovative and collaborative care. The extraordinary advancements in treatment for HIV, hepatitis C, cancers, infections, and bipolar illness were driven by the desire to save patients, and this epidemic will also be solved by the desire to treat its individual victims. Therapeutic optimism is the engine of medical progress.

Declaration of interests

G.T. reports having been a consultant for Gilead Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Author contributions

All authors contributed to the writing and editing of the manuscript, and have approved the final version. Fig. 1 was created by MRM.

Funding

This research did not receive any specific grant from funding

agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We are grateful for the helpful discussions and editing by Dr. Joyce King, Dr. Edward Treisman, Dr. Catherine DeAngelis, and Alexander Murray.

References

Baker, D.W., 2017. History of the joint commission's pain standards: lessons for today's prescription opioid epidemic. J. Am. Med. Assoc. 317 (11), 1117–1118. https://doi.org/10.1001/jama.2017.0935.

Berge, K.H., Burkle, C.M., 2014. Opioid overdose: when good drugs break bad. Mayo Clin. Proc. 89 (4), 437–439. https://doi.org/10.1016/j.mayocp.2014.02.007.

CDC, 2017a. National Center for Health Statistics: accidents or unintentional injuries. https://www.cdc.gov/nchs/fastats/accidental-injury.htm.

CDC, 2017b. Opioid overdose: drug overdose death data. https://www.cdc.gov/drugoverdose/data/statedeaths.html.

CDC, NCHS, 2015. Underlying cause of death 1999–2013 on CDC WONDER Online Database. http://wonder.cdc.gov/ucd-icd10.html.

Chen, L.H., Hedegaard, H., Warner, M., 2014. Drug-poisoning deaths involving opioid analgesics: United States, 1999–2011. NCHS Data Brief 166, 1–8. http://www.ncbi.nlm.nih.gov/pubmed/25228059.

Chou, R., Turner, J.A., Devine, E.B., et al., 2015. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a national institutes of health pathways to prevention workshop. Ann. Intern. Med. 162 (4), 276–286. https://doi.org/10.7326/M14-2559.

Chu, L.F., Clark, D.J., Angst, M.S., 2006. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J. Pain 7 (1), 43–48. https://doi.org/10.1016/j.jpain.2005.08.001.

Chu, L.F., Dairmont, J., Zamora, A.K., Young, C.A., Angst, M.S., 2011. The endogenous opioid system is not involved in modulation of opioid-induced hyperalgesia. J. Pain 12 (1), 108–115. https://doi.org/10.1016/j.jpain.2010.05.006.

Clark, M.R., 2009. Psychiatric issues in chronic pain. Curr. Psychiatry Rep. 11 (3), 243–250. https://doi.org/10.1007/s11920-009-0037-6.

Committee APSQ of C, 1995. Quality improvement guidelines for the treatment of acute pain and cancer pain. J. Am. Med. Assoc. 274 (23), 1874–1880.

Compton, W.M., Jones, C.M., Baldwin, G.T., 2016. Relationship between nonmedical prescription-opioid use and heroin use. N. Engl. J. Med. 374 (2), 154–163. https://doi.org/10.1056/NEJMra1508490.

Dupen, A., Shen, D., Ersek, M., 2007. Mechanisms of opioid-induced tolerance and hyperalgesia. Pain Manag. Nurs. 8 (3), 113–121. https://doi.org/10.1016/j.pmn.2007.02.004.

Ewan, E.E., Martin, T.J., 2013. Analgesics as reinforcers with chronic pain: evidence from operant studies. Neurosci. Lett. 557, 60–64. https://doi.org/10.1016/j.neulet.2013.08.018.

Fenton, J.J., 2012. The cost of satisfaction. Arch. Intern. Med. 172 (5), 405. https://doi.org/10.1001/archinternmed.2011.1662.

Florence, C.S., Zhou, C., Luo, F., Xu, L., 2016. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med. Care 54 (10), 901–906. https://doi.org/10.1097/MLR.0000000000000625.

GAO, 2003. Prescription OxyContin abuse and diversion and efforts to address the problem. J. Pain Palliat. Care Pharmacother. 18 (3), 109–113. https://doi.org/10.1300/J354v18n03_12.

Gatchel, R.J., McGeary, D.D., McGeary, C.A., Lippe, B., 2014. Interdisciplinary chronic pain management: past, present, and future. Am. Psychol. 69 (2), 119–130. https://doi.org/10.1037/a0035514.

Greene, M.S., Chambers, R.A., 2015. Pseudoaddiction: fact or fiction? An investigation of the medical literature. Curr. Addict. Rep. 2 (4), 310–317. https://doi.org/10.1007/s40429-015-0074-7.

Haythornthwaite, J.A., Clark, M.R., Pappagallo, M., Raja, S.N., 2003. Pain coping strategies play a role in the persistence of pain in post-herpetic neuralgia. Pain 106 (3), 453–460. https://doi.org/10.1016/j.pain.2003.09.009.

HCAHPS Survey, 2012. Cent Medicare Medicaid Serv. http://www.hcahpsonline.org/Files/HCAHPS V7 0 Appendix A1 - HCAHPS Expanded Mail Survey Materials (English) July 2012.pdf.

Johnson, H., Paulozzi, L., Porucznik, C., Mack, K., Herter, B., 2014. Hal Johnson Consulting and Division of Disease Control and Health Promotion FD of H. Decline in drug overdose deaths after state policy changes - Florida, 2010–2012. Centers Dis. Control Prev. Morb. Mortal. Wkly Rep. 63 (26), 569–574 (doi:mm6326a3 [pii]).

Joint Commission Resources, 2001. Joint Commission on Accreditation of Healthcare Organizations Pain Standards for 2001. https://www.jointcommission.org/assets/1/6/2001_Pain_Standards.pdf (Oak Brook, IL).

Jones, C., 2013. Trends in the distribution of selected opioids by state, US, 1999–2011. In: Safe States Alliance Annual Meeting, (Vol).

Kelly, S., Johnson, G., Harbison, R., 2016. "Pressure to prescribe". The impact of economic and regulatory factors on South-Eastern ED physicians when managing the drug seeking patient. J. Emerg. Trauma Shock 9 (2), 58–63.

Mauermann, E., Filitz, J., Dolder, P., Rentsch, K.M., Bandschapp, O., Ruppen, W., 2015. Does fentanyl lead to opioid-induced hyperalgesia in healthy volunteers?: a double-blind, randomized, crossover trial. Anesthesiology 2, 453–463. https://doi.org/10.1097/ALN.0000000000000976.

McLean, S.A., Clauw, D.J., Abelson, J.L., Liberzon, I., 2005. The development of persistent pain and psychological morbidity after motor vehicle collision: integrating the potential role of stress response systems into a biopsychosocial model. Psychosom. Med. 67 (5), 783–790. https://doi.org/10.1097/01.psy.0000181276.49204.bb.

Melzach, R., 1990. The tragedy of needless pain. Sci. Am. 262, 27–33.

Pain as the 5th Vital Sign Toolkit. Dep Veterans Aff. http://www.va.gov/painmanagement/docs/toolkit.pdf.

Peters, P.J., Pontones, P., Hoover, K.W., et al., 2016. HIV infection linked to injection use of oxymorphone in Indiana, 2014–2015. N. Engl. J. Med. 375 (3), 229–239. https://doi.org/10.1056/NEJMoa1515195.

Portenoy, R.K., Foley, K.M., 1986. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 25 (2), 171–186. https://doi.org/10.1016/0304-3959(86)90091-6.

Porter, J., Jick, H., 1980. Addiction rare in patients treated with narcotics. N. Engl. J. Med. 302 (2), 123.

Position of the Federation of State Medical Boards.

Suryaprasad, A.G., White, J.Z., Xu, F., et al., 2014. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. Clin. Infect. Dis. 59 (10), 1411–1419. https://doi.org/10.1093/cid/ciu643.

Swedish Council on Health Technology Assessment, 2006. Methods of Treating Chronic Pain: A Systematic Review.

The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin. J. Pain 13 (1), 6–8.

Treisman, G.J., Clark, M.R., 2011. A behaviorist perspective. In: Chronic Pain and Addiction, vol. 30. pp. 9–21. https://doi.org/10.1159/000324063.

Van Zee, A., 2009. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. Am. J. Public Health 99 (2), 221–227. https://doi.org/10.2105/AJPH.2007.131714.

Weissman, D.E., Haddox, J.D., 1989. Opioid pseudoaddiction–an iatrogenic syndrome. Pain 36 (3), 363–366. http://www.ncbi.nlm.nih.gov/pubmed/2710565.