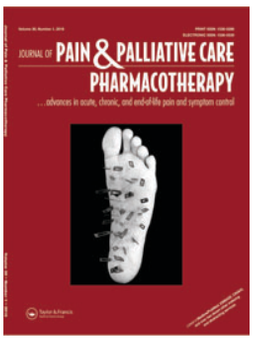

Taylor & Francis
Taylor & Francis Group

Journal of Pain & Palliative Care Pharmacotherapy

ISSN: 1536-0288 (Print) 1536-0539 (Online) Journal homepage: http://www.tandfonline.com/loi/ippc20

Negative outcomes of unbalanced opioid policy supported by clinicians, politicians, and the media

Willem Scholten & Jack E. Henningfield

To cite this article: Willem Scholten & Jack E. Henningfield (2016) Negative outcomes of unbalanced opioid policy supported by clinicians, politicians, and the media, Journal of Pain & Palliative Care Pharmacotherapy, 30:1, 4-12, DOI: 10.3109/15360288.2015.1136368

To link to this article: http://dx.doi.org/10.3109/15360288.2015.1136368

JOURNAL OF PAIN & PALLIATIVE CARE PHARMACOTHERAPY
2016, VOL. 30, NO. 1, 4–12
http://dx.doi.org/10.3109/15360288.2015.1136368

Taylor & Francis
Taylor & Francis Group

ARTICLE

Negative outcomes of unbalanced opioid policy supported by clinicians, politicians, and the media

Willem Scholten and Jack E. Henningfield

ABSTRACT

Harmful and nonmedical use of prescription opioids has increased precipitously in the United States and some other countries in recent years, but not everywhere around the world. Addressing this problem requires attention to scientific data and to objective and balanced consideration of factors driving the problems. Unfortunately, the situation has been blurred by some politicians, health professionals, and the media by their using inadequate concepts, misrepresenting and exaggerating facts, and demonizing pain patients. In this article, we analyze what has occurred and present what we believe to be a balanced view of the problems. We advocate comprehensive drug control policies implemented in a way to reduce harmful use and diversion problems balancing the public health benefits and risks of opioid medications. We make recommendations for responsible prescribing, including implementing the World Health Organization (WHO) policy guidelines and similar United Nations Office of Drug Control (UNODC), which we believe can contribute measurably to the prevention of diversion of prescription opioids while ensuring patient access to the most appropriate medicines. Measures to reduce the risks of nonmedical use of opioid medicines should be based to the greatest extent possible on accurate evaluation of the mechanisms leading to such use, including diversion activities.

ARTICLE HISTORY
Received 12 December 2015
Accepted 31 December 2015

KEYWORDS
access; controlled substance; media; misuse; opioid; overdose; policy; public health; regulation

Introduction

The 21st century has been marked by increasingly frequent and dramatic headline news and the attention by U.S. politicians, health professionals, and the public on the harmful outcomes from opioid analgesic use. Much of this attention questioned the benefits of opioids and sensationalized their risks.[2] On the positive side, this attention focused leading U.S. public health agencies and institutions, including the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and the National Institute on Drug Abuse (NIDA), as well as Congress, prompting them to work together in efforts to control harmful use of opioids while addressing the needs of patients. This is delineated in the FDA summary timeline.[3]

Balanced consideration of benefits and risks should be a foundation for all treatment decisions and policy. However, public health responses often fail to achieve the delicate balance between the benefits of these medicines for large numbers of patients and the harm that these medicines can do if not used as intended. Conclusions often are based on questionable evidence as this paper describes. Efforts by politicians, the media, and some health professionals have produced policy and regulations that have been—and will continue to be—adopted with the potential to prevent persons in chronic pain from receiving medications that they legitimately need without contributing substantially to the prevention of harmful use.

Such measure can be seen worldwide, and they have been present since the introduction of drug control policies in the early 20th century. A prime example was the banning of cannabis tincture in the United States in the middle of the last century, an action that was gradually adopted by other countries, including the United Kingdom in the 1960s. Following this, the Single Convention on Narcotic Drugs came into being 50 years ago. As a result of unbalanced policies, over 5½ billion people worldwide lack adequate access to opioid analgesics.[4,5] This extends to other classes of controlled medicines as well and continues today, exemplified by efforts by China at the United Nations Commission

Willem Scholten, PharmD, MPA, Consultant – Medicines and Controlled Substances, Willem Scholten Consultancy, Lopik, The Netherlands. Jack E. Henningfield, PhD, is Adjunct Professor of Psychiatry and Behavioral Sciences at The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, and Vice President for Research Health Policy and Abuse Liability at Pinney Associates, Bethesda, Maryland, USA.
CONTACT Willem Scholten Consultant – Medicines and Controlled Substances at Willem Scholten Consultancy, PharmD, MPA, Wielsekade 64, 3411 AD Lopik, The Netherlands.
Color versions of one or more figures in the article can be found online at www.tandfonline.com/ippc

on Narcotic Drugs to ban the anesthetic and essential medicine ketamine. That would deprive people in low-resource settings from access to essential surgery because it is the only available anesthetic for essential surgery in most rural areas of developing countries, home to more than 2 billion of the world's people.[6]

For decades, emphasis has been placed preventing harm from opioids and other controlled substances without acknowledging that many psychoactive substances are truly essential medicines. These include opioids for the treatment of pain and dependence, and anesthetics that in resource-poor settings cannot be replaced by other anesthetics.

The epidemic of harmful use of opioids

Nonmedical use of opioids carries substantial risks, including dependence, overdose, and death. The extensively reported increase in opioid consumption in the United States has been accompanied by a notable increase in overdose deaths involving prescription opioids.[7,8] The term "prescription opioid" was initially used to distinguish between opioid medications and illicitly trafficked substances such as powdered heroin. However, what constitute prescription opioids (which may include stolen and illicitly trafficked medications) soon became unclear and was considered to be synonymous with prescribed opioids. Consequently, without much analysis of what actually contributes to nonmedical use, measures were taken to limit the availability of such medicines that could be prescribed to patients with pain. Similarly, there often is little distinction made between harms *involving* opioids and harms *caused by* opioids. Epidemiologists and public health officials should acknowledge the critical difference between these terms. Opioid-related harms can be influenced by numerous concurrent factors, including polydrug use, administration by routes for which the formulations were not intended, progression of pathological conditions, physical and mental comorbidities, and prescription of methadone, including for pain.[9,10] Efforts to reduce harmful use, diversion, and mortality without impairing access to opioids indicated for patients include risk evaluation and mitigation strategies (REMS). Other risk management efforts, along with the development of increasingly abuse-deterrent medications, are beginning to show evidence of progress.[11–14]

Efforts to more stringently regulate pain management practices that deny or substantially impair opioid access by people with chronic pain make sense only when there is good evidence that such effects are occurring disproportionately among people with chronic pain and if there is a proposed mechanism on how a specific measure can curb the problem. But what is the evidence that chronic pain patients are the problem or that restricting access to chronic pain patients will reduce harmful use of opioids and mortality more generally? In fact, many secondary analyses of large-scale databases used to support this contention do not support this claim due to a number of methodological factors. Informed interpretations of associations between prescription data and harmful outcomes are largely possible only in the presence of clinical and other data characterizing those associations. Knowing whether people who have suffered harms received a medication for (1) a legitimate medical purpose and then used it as intended, (2) a legitimate medical purpose and then used it in noncompliance with treatment instructions, or (3) purposes of nonmedical use may call for vastly different interventions.

Certainly, each of these situations needs addressing. However, currently the extent is unclear in how far harms are confined to patients with chronic pain who are using these medications as directed.

There are well-described problems with diversion in a limited number of countries.[15] The U.S. literature clearly shows that those who wish to use prescription opioids for nonmedical purposes can obtain these medications by a variety of methods, including through prescriptions. Although there are insufficient data available to quantify the amounts diverted to nonmedical use from various parts of the drug distribution system, there appears to be significant theft, fraud, and other unlawful conduct.[16–20] For example, an annual, population-based U.S. survey estimates that around 70% of persons who have reported using opioids nonmedically admitted that they obtained the drug for free from friends or family members or through theft or purchase.[21] Correspondingly, large quantities of prescription opioids have been sold by illegitimate pain clinics, contributing to overdoses occurring predominantly in persons obtaining opioids for nonmedical purposes.[19,22,23] Thus, it is puzzling how the authors of a recent JAMA commentary could offer the following observation:

> It is unclear whether these prescriptions [to non-medical users] were issued for therapeutic purposes or originated from unscrupulous prescribers (i.e., 'pill mills'); regardless, the source of opioid use and misuse is often a seemingly legitimate prescription.[24]

Do the authors consider prescribing opioids at a pill mill as a "legitimate prescription" or as corruption?

In one of the most descriptive studies of unintentional overdose fatalities, in West Virginia, 63.1% of the decedents had used pharmaceuticals with no documented prescriptions, and 55.6% of the decedents were never prescribed opioid analgesics. In addition, 79.3% of the decedents had used multiple substances, both illicit and prescription drugs ("polydrug use"), which may well have contributed to their deaths, and 21.4% of the decedents received controlled substances from multiple prescribers ("doctor shopping").[25] This study did not determine, whether decedents from the latter group were "real" pain patients, or people seeking drugs for illicit purposes.

Another American study, describing 9940 cases of overdose deaths, described 51 persons for whom dosages of 100 mg/day or higher of morphine equivalents were prescribed during the first 3 months of a prescription episode, showing an increased risk for this group.[26] A 24-month case-control study (2009–2010) reported 932 opioid-related overdose deaths in Tennessee for a mean rate of 7.4 deaths per 100,000 population per year. Of those, 592 (63.5%) of the patients were in the Tennessee Controlled Substances Monitoring Program, corresponding to a mean rate of 15.1 prescription opioid–related overdose deaths per 100,000 patients per year. The authors of that study found an overrepresentation of patients were prescribed methadone.[10] Although there is no doubt that opioid agonist prescribing and dispensing to pain patients, to a certain level, contributes to morbidity and mortality in the United States, these studies show that many of these tragedies appear to involve opioids that have been diverted or obtained through unlawful activities, including those of nonpatients.

Although the foregoing is focused on the harmful use of opioids, it is important to provide some perspective about the magnitude of the potential need for opioids by people with serious and chronic pain, which is often referred to as "a lot of pain" or in medication labeling as "moderate to severe pain." In the United States, an estimated 25.5 million adults (11.2% of the population) experienced pain every day for the past 3 months. A "lot of pain" was reported by 23.4 million adults (10.3% of the population), and severe pain by 14.4 million adults (6.3% of the population.[27] By contrast, in 2012, the U.S. National Survey on Drug Use and Health reported past-month use of heroin by persons aged 12 or older by 335,000 (0.1% of the population), and past-month users of "pain relievers" without a prescription by 4,862,000 (1.9% of the population).[28] Globally, in 2013, opioid use disorders caused a loss of 8,136,200 disability-adjusted life years (DALYs). Low back and neck pain are associated with 106,665,500 DALYs and neoplasms with 197,093,500 DALYs. The sum of the latter two is 303,759,000 DALYs, or 37 times as many DALYs as are associated with the disease burden from opioid use disorders. The DALYs for opioid use disorder take into account 51,000 deaths globally from this cause, corresponding to 2,286,648 years of life lost (YLL).[29,30] These estimates do not in any way suggest that harmful use of opioids, whether due to illicitly obtained or distributed pharmaceuticals, or heroin, is not a major public health problem, but provide the perspective that an equally important public health issue is ensuring appropriate access to opioid pain relievers for the millions of people in the United States and globally who suffer pain.[31]

Symptoms of ill-considered policies

A recent editorial in this journal reads in part "Of particular concern is the fact than many of our elected leaders, including politicians and prosecutors, are among the most vocal advocates of simplistic—and usually unsuccessful—attempts to define simple solutions for this complex problem."[32] The media and politicians often are eager to enter the debate over restriction of opioids without much nuance. Examples are recent tweets by the President of the United States in which the information was presented inaccurately (Figure 1). In reality, the 2012 annual consumption of opioids in the United States was 7.4 defined daily dosages per capita.[33] This includes the full mu-opioid agonists morphine, oxycodone, hydromorphone, fentanyl, methadone, and pethidine (meperidine).

Bottles exist in many sizes, but the President's message was based on a bottle size of only 7 to 10 pills! Similarly, the organization "Physicians for Responsible Opioid Prescribing," which, inter alia, advocates *against* the availability of opioid analgesics for patients with moderate and severe chronic pain, claims on its website

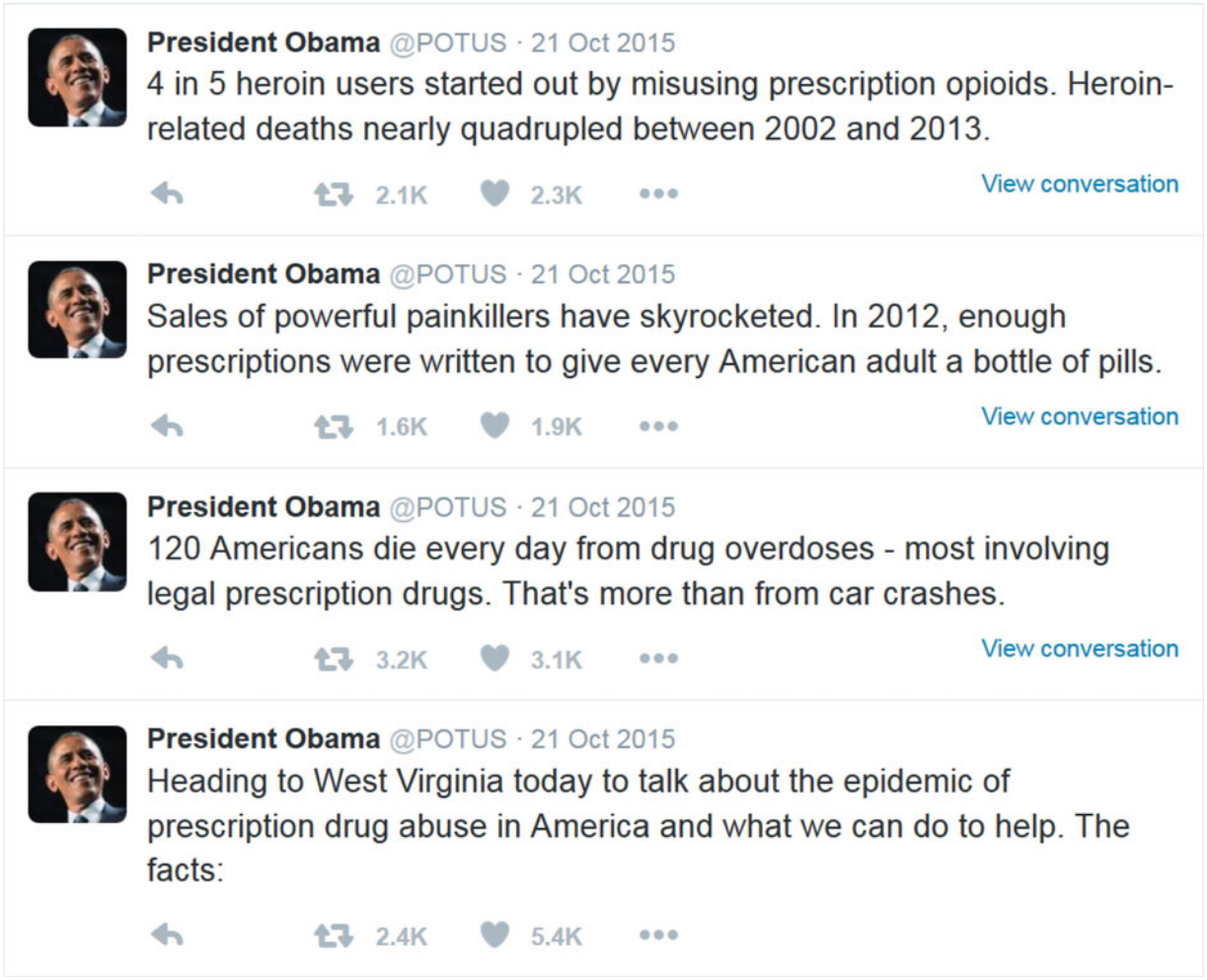

Figure 1. Tweets from President Obama on 21 October 2015.

that "In 2010 doctors prescribed enough pain killers to medicate every American adult around the clock for a month." That website also claims that the United States consumes 80% of all oxycodone and 99% of all hydrocodone, but does not explain that the marketing of these products is largely confined to the United States, especially for hydrocodone, nor that 66% of the world population has no access to opioids for pain relief at all and only 7.5% has adequate access.[5,34]

The President also tweeted that heroin-related deaths nearly quadrupled between 2002 and 2013. This is exaggerated, and, more importantly for developing evidence-based policies, it is only half of the truth: heroin-related deaths increased from 2089 deaths in 2002 to 3278 in 2009 (a factor of 1.57), and only when the number of prescription opioid-related deaths stabilized after 2009 did the increase in heroin-related deaths accelerate to 5925 in 2012 (2.83 times the rate in 2002).[35] Another message in the same tweet is that four in five heroin users started out by misusing prescription opioids. However, according to the National Institute on Drug Abuse, "[n]early half of young people who inject heroin surveyed in three recent studies reported abusing prescription opioids before starting to use heroin."[36]

The President was responding to data presented by the U.S. Centers for Disease Control and Prevention (CDC). Those data were apparently interpreted by the President as implying that harmful use of heroin and overdose are caused in part by prescription opioid use and prescribing.[37] In fact, harmful use of heroin and overdose is a decades-long problem in the United States, as well as many other countries that have very low rates of prescription opioid prescribing. Thus, the 2014 World Drug Report when discussing these facts concluded: "the dynamics of misuse of prescription opioids does not necessarily follow making opioids accessible or available for medical purposes.[38]

In the United States, a recent study found that the majority of people in treatment for opioid dependence initiated opioid use with heroin and other illicitly manufactured opioids, not prescription opioids.[39] Nonetheless, the CDC often highlight prescription opioid prescribing as a primary cause of the harmful opioid use and overdoses.[40] Illustrating the complexity of the relationships between harmful use and overdose of prescription opioids with harmful use and overdose of heroin is that when the harmful use of prescription opioids began to decline, as documented by several key measures near the end of the first decade of the 21st century, heroin overdose deaths began to increase. Specifically, as reported by the CDC, the "rate of heroin-related drug overdose deaths was stable at approximately 0.7 per 100,000 from 2002 to 2006, and began to increase gradually through 2009 when the rate was 1.1 per 100,000. Beginning in 2011, the overdose death rate increased sharply, from 1.4 per 100,000 to 2.7 per 100,000 in 2013."[13,37] As discussed by Cicero et al., these trends include demographic, social, geographic, access, and cost factors.[39] This rapid rise in deaths from heroin overdose after the stabilization of prescription opioid overdose deaths suggests that policy approaches focus too narrowly on controlling prescription-opioid risk. This reduces needed medication access to people with pain while not addressing the confluence of factors relevant to the overall problems associated with harmful use of and mortality from opioids.

Demonizing patients

Some research findings are presented in ways that demonize patients to whom opioids are prescribed for legitimate reasons. This section provides a few recent examples.

First, media reports on a recent meta-analysis by Vowles et al. suggested that patients who use opioid analgesics misuse their medicines very often.[41] However, on close reading, the definition used for "misuse" turned out to be identical to what is usually called "patient noncompliance" in medical and pharmaceutical sciences. When Scholten and Henningfield compared the results of this meta-analysis with a meta-analysis on patient noncompliance in the general population of patients who use medicines, noncompliance was not any different between the two groups (21%–29% vs. 24.8%), meaning that patients receiving opioids use their medication as correctly, or inaccurately, as patients receiving any other medications. This case is even more problematic because Vowles et al. included many low-quality studies that were rejected for inclusion in a Cochrane meta-analysis, thereby eroding the scientific validity of their conclusions.[42] Because the authors of the Cochrane systematic review, which was initially intended to be a meta-analysis, did not find one study that met the inclusion criteria, they were limited to publishing it as a literature review. Outcomes of the reviewed studies were incoherent with incidence of opioid dependence among patients following treatment with opioid analgesics for pain relief ranged from 0% to 24% (median: 0.5%) and prevalence ranged from 0% to 31% (median: 4.5%). The authors concluded that the available evidence suggests that opioid analgesics for chronic pain conditions are not associated with a major risk for developing dependence. The most impressive finding of their review is the deficiency of good-quality studies, in contrast to the widespread concern of doctors and authorities relating to the prescription of opioids for pain management.[43]

The low quality of some studies is another problem, and inappropriate analyses on the epidemiology of dependence and harmful use of controlled medicines are omnipresent. This is not unique to this field of study and may reflect what has been termed "surrogate science."[44] Thus, studies that set very low thresholds for categorizing patients as showing dependence or noncompliance may overestimate the rates of dependence and harmful use. Unfortunately, once a study is published, findings from such low-quality studies can acquire equal status and influence as findings from high-quality studies, sometimes even more so when sensationalized by the media.

Another example is the terminology some researchers use to build their case. Some authors qualify patient noncompliance as "aberrant."[45] By using such pejorative terminology, researchers insinuate that patients are "drug abusers" if they do not follow the prescribers' instructions exactly. It also denies that individuals have agency and can have good reasons for deviating from the instructions for use.

Rational policies require accurate analysis

None of this discussion is meant to suggest that prescribers should not always prescribe the appropriate amount of medicines. Prescribers should put the care of their patients first while endeavoring to not fuel

Table 1. Recommendations for responsible prescribing of opioids.

- Follow the dosage guidelines as recommended in guidelines
- Assess the patient's pain and functioning regularly and adjust the dosage accordingly to achieve optimal pain relief
- Avoid prescription of more than is necessary to treat the pain in order to avoid diversion of medicines or accumulation of stock at the patient's home
- Avoid under treatment of pain in order to prevent "doctor shopping"
- Inform the patient and his/her caregivers about the correct use of the prescribed medicines and instruct them to return for further consultation if the medicines do not have the expected effect
- Instruct the patient and his/her caregivers to store the opioid medicines safely and out of sight and reach of others
- Instruct the patient and his/her caregivers how to safely dispose of unused medicines, so as to prevent medicines being diverted into illicit markets.
- Be aware that caregivers may potentially divert and/or misuse prescribed opioids.
- Consider prescribing naloxone kits along with education of the patient's care givers and family members

harmful use by others. This includes providing the most appropriate medications to treat their pain along with information and guidance to minimize the risks of harmful use, diversion, and overdose. This may even include providing the most appropriate among the increasingly diverse and user-friendly forms of naloxone administration kits that are increasingly available and recommended.[46] Regardless of whether treatment involves opioids or other medicines, such practice can also limit the potential for misuse of leftover medication. Recent research has shown that the most important predictor of the amount of opioids retrieved using a take-back event was the amount of prescribed opioids.[47] These practices help ensure that prescribers are contributing to comprehensive approaches to addressing opioid-related problems while providing the best possible care for their patients. For opioid analgesics, we listed a number of possible policies to be applied in clinical practice in Table 1.

Concerning comprehensive opioid approaches, the U.S. Department of Health and Human Services has provided recommendations that could be helpful, including expanded surveillance and prevention efforts, encouragement of the use of state-wide prescription monitoring programs, expanded education of prescribers, increasing access to drug dependence treatment programs for those who do abuse opioids and other drugs, and increased access to naloxone medications to prevent overdose deaths.[48] The U.S. FDA also deserves credit for its efforts to ensure that the needs of patients are addressed with the safest possible medicines through promotion of increasingly safe and abuse-deterring opioids.[3] Governments and policy makers (including the hospital, clinic, hospice or palliative care service) should also ensure that staff are provided with up-to-date pain management education regularly. Health care professionals should also have access to a method for return of unused medicines and to clearly communicate to patients about methods to securely store their current medications and to dispose of unused medications to avoid accumulation and potential diversion.

Implementing the WHO policy guidelines, and similar recommendations made by UNODC, will contribute measurably to the prevention of diversion without impeding access for legitimate patients.[23,49] Rational policies require accurate evaluation of the nature of the problem. This includes a root-cause analysis showing which aspects influence the phenomenon that then need to be influenced. Based on such a model, measures can be developed that affect one or more of the cause-effect relations. Therefore, any measures taken to reduce the risks of nonmedical use of opioid medicines should be based on sound analyses of the mechanisms leading to such use, including diversion. Responses should be comprehensive approaches to discourage harmful use of opioids and reduce overdose without increasing the suffering of people with pain.

Too often, new policies seem not to be based on such analyses and therefore cannot be assumed to be rational policies. Policies should take into account the overall public health outcomes, not simply one parameter. Use of prescription opioids is often safer than use of street opioids such as heroin, which is often adulterated, and sometimes adulterated with very potent and dangerous fentanyl derivatives. A policy that has the effect of shifting from harmful use of prescription opioids to street heroin is not a public health asset. Similarly, public health policy should take pain management into account. Blocking access to prescription opioids should not have a negative impact on the treatment of pain, like it should not have a negative impact on the epidemiology of overall harmful substance use.

The nonmedical use of prescription of opioid analgesics is documented for the United States and some other countries, including Canada.[50,51] In Europe, it is much less of an issue, for example, the European Union's (E.U.) European Monitoring Centre on Drugs and Drug Addiction does not mention this in its annual report for 2015.[52] Moreover, two thirds of the world

lacks access to opioid analgesics for medical use. There, the real concern is how to improve access for the adequate treatment of pain.[4,5] However, in the absence of a good situational analysis, some North American authors and presenters at national and international conferences have tended to impose the problem on countries where it does not exist, encouraging these countries to remedy imaginary complaints.[53] The real problems associated with harmful use of prescription drugs will not be resolved by overly restricting their use by or access to patients and their health care professionals. Rather, drug control policies that provide a better balance of demand reduction efforts, including treatment and prevention programs, are vital.

Doctors are supposed to act in the interest of their patients. Researchers are supposed—at least—to not act against their subjects' interests. Politicians act in the interest of being reelected, but should know the limits of what is ethical. However, we see a disturbing tendency of doctors, researchers, politicians, and the media to be preoccupied by the wrong aspects of opioid use, losing sight of the picture as a whole. The result is often that patients are bearing the burden of efforts to minimize nonmedical use.

Balanced and comprehensive drug control policies that ensure patient access to the most appropriate medicines to help manage pain and other disorders, including substance use disorders, should be foremost in efforts to address the problems of harmful use of opioids and overdose. All such policies should be based to the greatest extent possible on accurate evaluation of the science and epidemiology.

Acknowledgments

The authors acknowledge Aaron Gilson PhD, MSSW, Pain & Policy Studies Group/WHO Collaborating Center, Carbone Comprehensive Cancer Center, University of Wisconsin–Madison, Madison, Wisconsin, USA, for his review of this paper. Parts of this work are based on older unpublished work that the first author developed together with the Guidelines Development Group for the WHO guidelines on the pharmacological treatment for persisting pain in children with medical illnesses.[1]

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. WS provides consulting services on issues related to controlled substances, including access to opioid analgesics. He received funding from Mundipharma and Grünenthal for speaking on accessibility of analgesia at conferences and meetings.

JEH provides consulting services through PinneyAssociates on drug dependence potential assessment and regulation and this has included speaking on accessibility of opioid analgesics at conferences and meetings funded by Mundipharma and Janssen Scientific Affairs.

References

1. World Health Organization. *WHO Guidelines for the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses*. Geneva, Switzerland: World Health Organization; 2012. Available at: http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines.pdf. Accessed November 14, 2015.
2. Meier B. *Pain Killer: A "Wonder" Drug's Trail of Addiction and Death*. New York: Rodale Books; 2003.
3. Food and Drug Administration. Timeline of selected FDA activities & significant events addressing opioid misuse & abuse. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM332288.pdf). Accessed November 10, 2015.
4. Seya MJ, Gelders SFAM, Achara UA, Milani B, Scholten WK. A first comparison between the consumption of and the need for opioid analgesics at country, regional and global level. *J Pain Palliat Care Pharmacother*. 2011;*25*:6–18.
5. Duthey B, Scholten W. Adequacy of opioid analgesic consumption at country, global, and regional levels in 2010, its relationship with development level, and changes compared with 2006. *J Pain Symptom Manage*. 2014;*47*:283–297.
6. Scholten W. Extended fact sheet on ketamine scheduling. Available at: https://www.dropbox.com/s/hwofjb66xxfdx96/Extended%20Fact%20Sheet%20on%20ketamine%20scheduling.pdf?dl=0. Accessed November 13, 2015.
7. Centers for Disease Control and Prevention. Vital Signs: Overdoses of prescription opioid pain relievers—United States, 1999—2008. *MMWR Morb Mortal Wkly Rep*. 2011;*60*:1487–1492. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w. Accessed July 2, 2012.
8. Centers for Disease Control and Prevention. CDC Grand Rounds: Prescription drug overdoses Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm. Accessed July 2, 2012.
9. Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Med*. 2011;*12*(Suppl 2):S26–S35.
10. Gwira Baumblatt JA, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, Jones TF. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. *JAMA Intern Med*. 2014;*174*:796–801.

11. Leiderman DA. Risk management of drug products and the U.S. Food and Drug Administration: evolution and context. *Drug Alcohol Depend*. 2009;*105*(Suppl 1):S9–S13.
12. Brooks MJ. Mitigating the safety risks of drugs with a focus on opioids: are risk evaluation and mitigation strategies the answer? *Mayo Clin Proc*. 2014;*89*:1673–1684.
13. 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*:241–248.
14. Simon K, Worthy SL, Barnes MC, Tarbell B. Abuse-deterrent formulations: transitioning the pharmaceutical market to improve public health and safety. *Ther Adv Drug Saf*. 2015;*6*:67–79.
15. United Nations Office on Drugs and Crime. *World Drug Report 2013*. New York: United Nations; 2013.
16. Becker WC, Tobin DG, Fiellin DA. Non-medical use of opioid analgesics obtained directly from physicians: prevalence and correlates. *Arch Intern Med*. 2011;*171*:1034–1036.
17. Joranson DE, Gilson AM. Drug crime is a source of abused pain medications in the United States [letter]. *J Pain Symptom Manage*. 2005;*30*:299–301.
18. Lewis ET, Cucciare MA, Trafton JA. What do patients do with unused opioid medications? *Clin J Pain*. 2014;*30*:654–656.
19. Inciardi JA, Surratt HL, Kurtz SP, Cicero TJ. Mechanisms of prescription drug diversion among drug-involved club and street based populations. *Pain Med*. 2007;*8*:171–183.
20. Inciardi JA, Surrat HL, Kurtz SP and Burke JJ. The diversion of prescription drugs by health workers in Cincinnati, Ohio. *Subst Use Misuse*. 2006;*41*:255–264.
21. Substance Abuse and Mental Health Services Administration. *Results From the 2010 National Survey on Drug Use and Health: Summary of National Findings*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011. NSDUH Series H-41, HHS Publication No. (SMA) 11–4658. Available at: http://www.samhsa.gov/data/sites/default/files/NSDUHNationalFindingsResults2010-web/2k10ResultsRev/NSDUHresultsRev2010.pdf. Accessed November 14, 2015.
22. Rutkow L, Chang H, Daubresse M, Webster DW, Stuart EA, Alexander GC. Effect of Florida's prescription drug monitoring program and pill mill laws on opioid prescribing and use. *JAMA Intern Med*. 2015;*175*:1642–1649.
23. Rigg KK, March SJ, Inciardi JA. Prescription drug abuse & diversion: role of the pain clinic. *J Drug Issues*. 2010;*40*:681–702.
24. Nelson LS, Juurlink DN, Perrone J. Addressing the opioid epidemic. *JAMA* 2015;*314*:1453–1454.
25. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* 2008;*300*:2613–2620.
26. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose a cohort study. *Ann Intern Med*. 2010;*152*:85–92.
27. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain*. 2015;*16*:769–780.
28. US Department of Health and Human Services. Results from the 2012 national survey on drug use and health (NSDUH): detailed tables. Available at: http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.htm#tab7-1b. Published 2013. Accessed November 10, 2015.
29. Institute for Health Metrics and Evaluation. Results by risk factor: Table 4. In: *Global Burden of Disease Study 2013 (GBD 2013) Risk Factor Results 1990–2013*. Seattle, WA: Institute for Health Metrics and Evaluation; 2015. Available at: http://ghdx.healthdata.org/sites/default/files/record-attached-files/IHME_GBD_2013_RISK_FACTORS_1990_2013.zip. Accessed November 14, 2015.
30. Institute for Health Metrics and Evaluation. Comments of life lost from opioid use disorders. In: *Global Burden of Disease Study 2013 (GBD 2013) Risk Factor Results 1990–2013*. Seattle, WA: Institute for Health Metrics and Evaluation; 2015. Available at: http//cloud.ihme.washington.edu/index.php/s/b89390325f728bbd99de0356d3be6900:(tableIHME_GBD_2013_YLL_1990_2013_OPIOID_USE_DISORDERS_Y2014M12D17.CSV). Accessed November 14, 2015.
31. World Health Organization. Ensuring balance in national policies on controlled substances, guidance for availability and accessibility of controlled medicines. Available at: http://www.who.int/medicines/areas/quality_safety/guide_nocp_sanend/en/. Accessed November 13, 2015.
32. Lipman AG. Opioid abuse, politicians and blame. *J Pain Paliat Care Pharmacother*. 2015;*29*:2–3.
33. Pain and Policy Studies Group. United States of America: opioid consumption in morphine equivalence (ME), mg per person. Available at: http://www.painpolicy.wisc.edu/sites/www.painpolicy.wisc.edu/files/country_files/morphine_equivalence/unitedstatesofamerica_me_methadone.pdf. Accessed November 13, 2015.
34. Physicians for Responsible Prescribing. Available at: http://www.supportprop.org/about-prop/. Accessed November 14, 2015.
35. Hedegaard H, Chen L-H, Warner M. *Drug-Poisoning Deaths Involving Heroin: United States, 2000–2013. NCHS Data Brief, no. 190*. Hyattsville, MD: National Center for Health Statistics; 2015. Available at: http://www.cdc.gov/nchs/data/databriefs/db190.pdf. Data table for Figure I available at: http://www.cdc.gov/nchs/data/databriefs/db190_table.pdf#1. Accessed December 2, 2015.
36. National Institute on Drug Abuse. Drug Facts: Heroin. Available at: http://www.drugabuse.gov/publications/drugfacts/heroin. Revised October 2014. Accessed December 2, 2015.
37. Jones CM, Logan J, Gladden M, Bohm MK. Vital Signs: Demographic and substance use trends among heroin users—United States 2002–2013. *MMWR Morb Mort Wkly Rep*. 2015;*64*:719–725. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6426a3.htm?s_cid=mm6426a3_w. Accessed November 13, 2015.
38. United Nations Office on Drugs and Crime. World Drug Report 2014. New York, United Nations, 2014, p 30.

Available at: https://www.unodc.org/documents/wdr2014/World_Drug_Report_2014_web.pdf. Accessed November 13, 2015.
39. 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 comments. *JAMA Psychiatry*. 2014;*71*:821–826.
40. Centers for Disease Control. Data overview. Available at: http://www.cdc.gov/drugoverdose/data/index.html. Accessed November 13, 2015.
41. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015;*156*:569–576.
42. 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 [letter]. *Pain*. 2015;*156*:1576–1577.
43. Minozzi S, Amato L, Davoli M. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. *Addiction*. 2013;*108*:688–698.
44. Gigerenzer G, Marewski JN. Surrogate science: the idol of a universal method for scientific inference. *J Manage*. 2015;*41*:421–440. Available at: http://www.dcscience.net/Gigerenzer-Journal-of-Management-2015.pdf. Accessed November 11, 2015.
45. Webster RL, Webster RM. predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *Pain Med*. 2005;*6*:432–442.
46. Wermeling DP. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. *Ther Adv Drug Saf*. 2015;*6*:20–31.
47. Welham GC, Mount JK, Gilson AM. Type and frequency of opioid pain medications returned for disposal. *Drugs Real World Outcomes*. 2015;*2*:129–135.
48. The Behavioral Health Coordinating Committee Prescription Drug Abuse Subcommittee of the US Department of Health and Human Services. Addressing prescription drug abuse in the United States, Current activities and future opportunities. Available at: http://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf. Accessed November 14, 2015.
49. United Nations Office on Drugs and Crime. Ensuring availability of controlled medications for the relief of pain and preventing diversion and abuse: striking the right balance to achieve the optimal public health outcome. *Discussion paper based on a scientific workshop*. Available at: http://www.unodc.org/docs/treatment/Pain/Ensuring_availability_of_controlled_medications_FINAL_15_March_CND_version.pdf. Accessed November 13, 2015.
50. Fischer B, Nakamura N, Urbanoski K, Rush B, Rehm J. Correlations between population levels of prescription opioid use and prescription-opioid-related substance use treatment admissions in the USA and Canada since 2001. *Public Health*. 2012;*126*:749–751.
51. Fischer B, Jones W, Rehm J. High correlations between levels of consumption and mortality related to strong prescription opioid analgesics in British Columbia and Ontario, 2005–2009. *Pharmacoepidemiol Drug Saf*. 2013;*22*:438–442.
52. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2015, *Trends and Developments*. Luxemburg: Publications Office of the European Union; 2015. Available at: http://www.emcdda.europa.eu/publications/searchresults?action=list&type=PUBLICATIONS&SERIES_PUB=a237. Accessed December 2, 2015.
53. Rehm J. Prescription opioids and public health in the European Union. ALICE RAP Policy Paper Series, Policy Brief 4. Available at: http://www.alicerap.eu/resources/documents/doc_download/139-policypaper-4-prescription-opioids-and-public-health.html. Accessed December 2, 2015.