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Review Article

Are Prescription Opioids Driving the Opioid Crisis? Assumptions vs Facts

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Abstract

Objective. Sharp increases in opioid prescriptions, and associated increases in overdose deaths in the 2000s, evoked widespread calls to change perceptions of opioid analgesics. Medical literature discussions of opioid analgesics began emphasizing patient and public health hazards. Repetitive exposure to this information may influence physician assumptions. While highly consequential to patients with pain whose function and quality of life may benefit from opioid analgesics, current assumptions about prescription opioid analgesics, including their role in the ongoing opioid overdose epidemic, have not been scrutinized.

Methods. Information was obtained by searching PubMed, governmental agency websites, and conference proceedings.

Results. Opioid analgesic prescribing and associated overdose deaths both peaked around 2011 and are in long-term decline; the sharp overdose increase recorded in 2014 was driven by illicit fentanyl and heroin. Nonmethadone prescription opioid analgesic deaths, in the absence of co-ingested benzodiazepines, alcohol, or other central nervous system/respiratory depressants, are infrequent. Within five years of initial prescription opioid misuse, 3.6% initiate heroin use. The United States consumes 80% of the world opioid supply, but opioid access is nonexistent for 80% and severely restricted for 4.1% of the global population.

Conclusions. Many current assumptions about opioid analgesics are ill-founded. Illicit fentanyl and heroin, not opioid prescribing, now fuel the current opioid overdose epidemic. National discussion has often neglected the potentially devastating effects of uncontrolled chronic pain. Opioid analgesic prescribing and related overdoses are in decline, at great cost to patients with pain who have benefited or may benefit from, but cannot access, opioid analgesic therapy.

Key Words. Analgesic; Chronic Pain; Opioids; Overdose; Prescribing; Safety

Introduction

Opioid analgesics remain the most effective drug class for controlling severe pain, but carry potential for adverse effects, misuse, and overdose [1,2]. Sharp increases in opioid prescriptions, and corresponding increases in overdose deaths in the 2000s, evoked widespread reactions to change perceptions of opioid analgesics. This reaction eventually led to a climate of polarization [3]. The nature of informational content may influence physician perceptions; repetitive exposure may strengthen perceptions into assumptions and conventional wisdom that guide clinical decision-making [4]. While highly consequential to patients whose quality of life and function benefit from opioid analgesia [3], current assumptions about opioid analgesic prescribing have not been scrutinized. Therefore, these assumptions were examined for validity. Data were obtained from multiple public, including governmental, sources, as described below. Although an effort was made to identify all relevant information, inadvertent omission is possible.

Background

The important role of opioid analgesics is broadly accepted in acute pain, cancer pain, and palliative/end-

of-life care, but opioid use in chronic noncancer pain is controversial, and this debate is polarized [1]. The 2000s witnessed a dramatic increase in prescribing of opioid analgesics, as well as increases in addiction, diversion, and fatal overdose [5].

The Centers for Disease Control and Prevention (CDC) identified this pattern; their prompt attention and broadcasting alerted physicians and the public to this crisis. The Drug Enforcement Agency (DEA) and CDC closed "pill mill" conduits for millions of opioid dose units into illicit markets. Talking points disseminated through the media began shifting public perception of opioid analgesics away from permissive entitlement and disregard of risk, such as expecting an opioid prescription for minor pain or sharing prescribed opioids [6].

The 2011 peaks of opioid analgesic prescribing [7–11] and overdose [12–14] were followed by multiyear sustained declines, which were not broadcast by the CDC [5,15,16]. Instead, CDC and media reporting focused on overuse of opioids for pain and related overdoses, and reported (not without justification) on opioid analgesics as an out-of-control hazard. The plight of patients with chronic pain who sought relief, or sociomedical barriers to accessing pain control, were less well publicized. Increased hardships for patients with chronic pain came while total numbers of deaths attributable to opioids rose [3]. Propagation by the CDC of one-sided information on opioid analgesic prescribing fueled sensationalized portrayals of opioid analgesics, prescribers, and patients [3,17–20]. These portrayals promoted stigma and misperceptions of opioid analgesics in health care and lay populations, with far-reaching consequences [17–21]. Public statements, such as those by the CDC leadership that "prescription opioids. . .are no less addictive than heroin" have not been helpful [22].

In aggregate, actions by the DEA [23,24] and CDC [5,15,16], together with media sensationalism [6,17], have intensified barriers to appropriate access to opioid analgesics for patients with chronic pain. From 2012 to 2015, reports from Florida, Georgia, Indiana, Massachusetts, Montana, Nevada, and Texas described increasing numbers of physicians refusing to issue opioid prescriptions [25–27] or withdrawing patients from their stable opioid regimens regardless of pain control and functional improvement [28]. Pharmacies increasingly refused to fill prescription opioid orders [24,25,29,30], even for patients with terminal illness and cancer pain [31] or acute postsurgical pain [32]. Patients felt criminalized by hostile interactions, such as being called "drug-seeking addicts" in front of other pharmacy customers [23,25,29].

Unable to access opioid analgesics, patients previously stable on opioid regimens were forced into opioid withdrawal [27,33], the "pharmacy crawl" [23] of trying to locate a pharmacy willing to fill their prescription during opioid withdrawal or intense pain [23], repeated emergency department (ED) visits and hospitalizations [24,33], or, for some, suicide [24,33]. The DEA rescheduling of hydrocodone from CS III to CS II in 2014 adversely impacted patients with chronic pain who had benefited from this agent. Increasingly, many experienced their prescribed hydrocodone replaced by less effective analgesics and/or stigma and negative pharmacy interactions when filling a hydrocodone order. Some turned to marijuana or borrowed pain medications for pain control after lost hydrocodone access, missed work from the ban on refills, or experienced suicidal ideation from blocked efforts to access hydrocodone or other medication for pain control [34]. It should be noted that the evidence above, while compelling, is anecdotal.

When exposed to misinformation and/or covert threats by drug enforcement or regulatory bodies, physicians change their opioid prescribing patterns through increased subanalgesic dosing, tapering patients off opioids, refusing to prescribe opioids or even to see patients with pain complaints. The improvement of prescribing patterns is best achieved through presentation of comprehensive and balanced information [6,18,35]. Some experts in pain medicine [19,36–38] have opined that the 2016 CDC opioid prescribing guideline [16] falls short of this mark. Longer-term decreases in physicians' prescribing of opioids, combined with a lack of third-party coverage, availability, or efficacy of nondrug and nonopioid pain therapies, have made access to pain control, including opioid analgesics, increasingly difficult if not impossible for patients with pain [38,39].

Why This Matters: Consequences of Uncontrolled Chronic Pain

The negative impact of severe chronic pain is hard to overstate. A pioneer in pain research observed that prolonged uncontrolled pain can destroy the quality of life, the will to live, and drive some patients to suicide [40].

Psychosocial consequences of unmanaged pain can be severe, with adverse psychological (impaired cognitive function, pathologic anxiety/depression, suicidal ideation, despair, hopelessness) and social/interpersonal (relationship disruption, loss of employment/financial ruin) outcomes [1,39,41–44]. The following sequelae underscore the gravity of poorly controlled chronic pain.

Suicide

Chronic pain is second only to bipolar disorder as a medical cause of suicide [45–47]. The distress, exhaustion, and hopelessness of chronic unrelieved pain can invite intended overdose. Death is no longer feared, but instead, becomes a welcome prospect of permanent relief from suffering and anguish [18,48].

Premature Death

Of 6,940 primary care patients followed over 10 years, the mortality risk from poorly controlled moderate to severe chronic pain was 68% greater than from cardiovascular disease and 49% greater than all other causes combined [49].

Neurotoxicity

Chronic undercontrolled pain is associated with peripheral and central nervous system (CNS) neuroplastic alteration [50]. Chronic pain-induced neuroplasticity can activate CNS glial cells and other neurotoxic pathways, leading to neuroinflammation, tissue destruction, and loss of CNS tissue mass and receptors, with resultant loss of opioid and other analgesic response [51,52]. Patients may require high doses of opioids to attain a modest analgesic response sufficient to reduce suffering and suicide risk [52].

Degraded Quality of Life

The negative impact of chronic pain on quality of life (QOL) is more severe than heart failure, renal failure, or major depression [53] and is comparable with the QOL of patients dying of cancer [54].

Self-Medication

Negative attitudes of primary care (PC) and other clinicians toward patients with chronic pain who use illicit substances or misuse prescribed drugs are widespread due to presumption of hedonistic pursuit. Reality may be more complex, and patients with chronic pain may use substances to alleviate poorly controlled pain. This possibly was explored in a study of nearly 600 adult PC clinic patients who tested positive for illicit or nonprescribed prescription drugs. Of these patients, 87% reported chronic pain (13% mild, 24% moderate, 50% severe); 74% reported impairment from pain (15% mild, 23% moderate, 36% severe); 51% of 576 patients who used illicit drugs (marijuana, heroin) did so to treat pain; 81% of 121 patients who misused prescription drugs did so to self-medicate pain; and 38% of 265 patients who reported past-three-month heavy drinking did so to control pain, as did 79% of 57 high-risk alcohol users [55].

With nearly one-third of study patients reporting both severe pain and disabling impairment, this study suggests that significant pain is quite prevalent in PC patients with positive drug screens. Poor pain control was common; self-medication to alleviate pain may have driven apparent substance use disorder (SUD) in this study population [55].

Assumptions Informing the Current Opioid Debate: Fallacies or Facts?

Safety is the foundation of opioid analgesic prescribing and a basic principle of good medical practice [56], but misinformation has influenced current assumptions of opioid analgesic prescribing safety, risk, and efficacy. These assumptions are dispelled by data; some are unreported or obscured. In the discussion below, "prescriptions" refers to total outpatient retail pharmacy–dispensed prescriptions.

Opioid Analgesic Prescribing Rates

Misperception: Continued increases in opioid analgesic prescribing fuel the opioid epidemic.

Fact: Hydrocodone, oxycodone, and overall opioid prescribing have been in multiyear decline beginning in 2012 through early 2017.

Hydrocodone Short Acting (SA) was rescheduled to CS II from CS III in October 2014. One year later, prescriptions decreased 22%, and dispensed tablets 16% [7]. Hydrocodone SA prescriptions decreased 33% from 2011 (144.5 million) to 2015 (97 million) [8,9]. Hydrocodone extended-release (ER) accounted for <1% of ER opioid prescriptions in 2015 [57], suggesting minimal contribution to trends in hydrocodone prescribing.

Oxycodone ER also showed steady decreases in prescribing, including a 39% decrease in a health plan with 31.3 million adult members from late 2009 to late 2012 [58]. Nationwide data on oxycodone ER comparing 2009 with 2013 [10] found decreases in: national poison center surveillance system mentions (48%), mentions in a national drug treatment system (32%), prescribing using a claims database (27%), doctor shopping (50%), and fatal overdose reported to the manufacturer (65%) [10]. Total oxycodone ER prescriptions decreased >29.7% from 2007 (>8 million) to 2011 (5.7 million) [59] and decreased 39% from 2010 to 2015 [11].

In a parallel trend, methadone prescriptions decreased 28% from 2010 to 2015 [11]. Prescriptions for transmucosal immediate-release fentanyl decreased 39% from 2011 (147,322) to 2015 (90,556) [60]. Total opioid analgesic prescriptions decreased 4.5% from 2011 to 2014, despite increases in tramadol (+25.5%) and buprenorphine (+49.4%) prescriptions [9]. Total dispensed morphine dose equivalents decreased 18.7% from 2010/fourth quarter (Q4; 68.5 million) to 2015/Q4 (55.7 million) [12]. The US proportion of world consumption decreased for oxycodone from 2000 (92.8%) to 2011 (81.0%) and 2014 (73.1%), and decreased for fentanyl from 2003 (56.9%) to 2009 (42.8%) and 2014 (30.1%) [12,61,62].

During a May 2016 FDA Advisory Committee workshop, the question was raised of how to interpret multiyear

declines in opioid analgesic prescribing in light of CDC data that show continued increases in prescription opioid analgesic overdoses [11]. The data below resolve this apparent contradiction.

Opioid Analgesic Overdose Fatalities: Incidence and Trends

Misperception: Prescription opioid analgesic overdose (OD) deaths soared in 2014 and continue to increase.

Fact: Fatal prescription opioid analgesic ODs have steadily declined since 2011; in contrast to earlier reports [63–66], the 2014 increase was not due to prescription opioid analgesics [67,68].

The CDC classifies opioids as: 1) natural (morphine, codeine) and semisynthetic (oxycodone, hydrocodone) opioid analgesics; 2) methadone; 3) nonmethadone synthetic opioid analgesics (fentanyl, tramadol); and 4) illicit opioids (heroin). Groups 1–3 can be combined as opioid analgesics or prescription opioids, distinct from illicit opioids [5,13].

In late 2013, illicit Chinese fentanyl surged into US drug markets through Mexico, and fentanyl ODs soared in 2014. Subsequently, direct import from China expanded to include Internet crypto-markets and the ultrapotent fentanyl analog carfentanil [69]. The CDC decided in early 2014 to continue recording fentanyl overdoses as prescription opioid analgesic overdoses, stating that toxicology cannot distinguish illicit from diverted pharmaceutical fentanyl [12]. In March 2016, a CDC Injury Center webpage stated that the 2014 spike in opioid analgesic overdoses were primarily driven by fentanyl, almost entirely illicit in origin. The 2014 figures were corrected retroactively by removing overdoses involving synthetic opioid analgesics other than methadone (fentanyl, tramadol) [13]. The revised figures indicated approximately 14,000 ODs involving prescription opioid analgesics. This policy was changed in 2016 to deaggregate fentanyl from other prescription opioid analgesics [68].

Prescribing patterns of dispensed fentanyl dose units (in millions) in 2014 (6.7) and 2013 (6.8) were unchanged [9], and nearly all fentanyl involved in fatal opioid ODs is illicit and not diverted [70]. The same CDC Injury Center webpage stated that the corrected 2014 figure of ~14,000 was "an increase…of 693 since 2013," or roughly 13,650 nonfentanyl opioid analgesic overdoses. The purpose or method of this 2013 revision was absent. The cited reference, the Wide-Ranging Online Data for Epidemiologic Research (WONDER) database, is a public-access CDC database [13]. Other CDC releases show differing figures. Recent opioid analgesic overdose figures by the CDC are inconsistent; these are presented in Table 1.

In 2013, heroin was detected in 1,342 (10%) of opioid analgesic fatalities, increasing to 26% in 2014 [5,66]. However, heroin ODs may be misclassified as morphine ODs. The metabolite 6-monoaceytlmorphine (6-MAM) is unique to heroin, but rapidly metabolizes into morphine. Some medical examiners may be reluctant to label a death heroin-related without 6-MAM present; because morphine is present, the cause of death is listed as morphine, not heroin [71].

The CDC bases their opioid overdose statistics on all-cause overdose. The US Government Accountability Office (GAO) reported prescription opioid analgesic fatalities from 2003–2008 by searching the National Vital Statistics System (NVSS) database used by the CDC for overdose and other statistics. In published overdose data, the CDC includes all causes (unintentional, suicide, homicide, undetermined) leading to death. In this report, GAO limited their results to unintentional (accidental) overdose leading to death. Compared with published CDC data [72], GAO data for accidental fatal overdose in 2003–2008 were 20–24% lower—not an insignificant difference (Table 2) [73]. Opioid analgesic overdoses of undetermined cause include accidental overdoses of unknown proportion. The nature of accidental (vs intentional) overdose death may evoke a stronger visceral response to a greater danger and has driven the backlash against opioid prescribing. Overdose calculation methods are stated in the technical sections or footnoted fine print of CDC publications, and so may not be noticed by readers. The GAO report is not current, but Table 2 suggests a stable ratio between all-cause vs accidental opioid analgesic deaths.

Importantly, within-state trends can diverge from nationwide trends discussed in this paper. Utah is an example, where fatal opioid analgesic overdoses began increasing in 2011, persisting into 2016 [74].

Opioid Analgesics as Causative Agent in Overdose Fatalities

Misperception: Fatal ODs reflect the inherent lethality of opioid analgesics.

Fact: Opioid analgesics are infrequently the sole cause of fatal overdose.

Recent data demonstrate that fatal opioid analgesic ODs primarily result from either methadone or the combination of opioids and benzodiazepines of other CNS depressants [21,75]. The extent that co-ingested agents have driven overdose rates is little reported in the media. Data from 2011, when prescription opioid analgesic deaths peaked, is used as a reference point when relevant. Primary contributors to fatal opioid analgesic overdose are the following.

Methadone prescribing for pain began in the late 1990s, and overdose fatalities increased from 784 in 1999 to

Table 1 Disparate opioid overdose fatality data published by the CDC

Evaluated Opioids	2015	2014	2013
Opioid analgesics	n/a	18,893 [63–65]	16,235 [64,65]
Opioid analgesics minus fentanyl*,† [13]	n/a	~14,000	693 fewer than 2014
Prescription opioids [66]	~22,000	~19,000	n/a
Prescription opioids minus fentanyl*,† [66]	More than 15,000	443 fewer than 2015	n/a
Natural and semisynthetics‡ [67,68]	12,727	12,159	n/a
Natural, semisynthetics,‡ methadone [67,68]	16,028	15,559	n/a
Fentanyl* [67,68]	9,580	5,544	n/a
Heroin [67,68]	12,989	10,574	n/a
Fentanyl* plus heroin [67,68]	22,569	16,118	n/a

CDC = Centers for Disease Control and Prevention.
*Illicit fentanyl, phrased in the cited reference as "non-methadone synthetic opioids."
†Removed to eliminate deaths involving illicit opioids.
‡Semisynthetic opioid analgesics.

Table 2 Opioid analgesic overdose fatalities: Nonintentional (GAO: 2003–2008) [73] vs all-cause (CDC: 2003–2014) [13,72]

	Overdoses	
Year	GAO	CDC
2003	6,493	8,535
2004	7,541	9,876
2005	8,534	10,947
2006	10,986	13,755
2007	11,509	14,408
2008	11,877	14,800
	Overdoses: CDC	
2009	15,597	
2010	16,651	
2011	16,917	
2012	16,007	
2013	13,600*	
2014	~14,000*	

CDC = Centers for Disease Control and Prevention; GAO = Government Accountability Office.
*Retroactively calculated for prescription opioid analgesics by removing fentanyl (illicit) overdose deaths [13].

5,518 in 2007, decreasing to 4,418 in 2011 and 3400 in 2014 [76,77]. Methadone accounted for a disproportionately large share of fatal prescription opioid analgesic toxicities in 2007 (38%), decreasing in 2011 (26%) and 2014 (24%) [76,77]. Fatal methadone overdoses were fueled by prescriber inexperience with the complex pharmacology, and its designation as the firstline chronic pain opioid by insurer/third-party payers on the sole basis of cost savings [78]. For example, methadone 5-mg tablets, taken three times daily, cost an average of $17 per month in 2012, compared with $306 per month for branded oxycodone (ER 40 mg taken twice daily) [79].

Benzodiazepines (BZDs) contributed to 31% of opioid analgesic fatalities in 2011 (vs 18.4% in 2004), according to the CDC [80], but this may understate their true contribution. A Canadian study evaluated 607,156 people aged 15–64 years. Of those prescribed opioids for pain who died of opioid analgesic toxicity, coprescribed BZDs were detected at death in 84.5% [81]. In a statewide study of 2,182,374 North Carolina residents who received one or more opioid analgesic prescriptions in 2010, BZDs were present in 61.4% who fatally overdosed on their prescribed opioid. Compared with opioid OD alone, opioid + BZD OD rates were 2.8 times greater in persons taking <75.0 mg/d in morphine-equivalent dose (MED) and 45.8 times greater in those taking >300 mg/d MED [75]. In contrast to opioid analgesics, dispensed BZD prescriptions increased 226% from 2009 (40.9 million) to 2014 (133.4 million). Increases were comparable for the top three prescribed BZDs (alprazolam, clonazepam, lorazepam) [82].

In 2014, alcohol contributed to OD deaths where the following opioids were present: fentanyl (12.2%), heroin (20.7%), hydrocodone (17.2%), morphine (13.0%), and oxycodone (16.7%). Alcohol contribution to opioid OD deaths is likely underestimated [83]. Concurrent heroin and prescription opioid detection by toxicology testing in fatal overdose creates uncertainty over the relative contribution of each agent to death. In such cases, the OD is recorded as both a prescription opioid OD and a heroin OD [67].

Between 2000 and 2010, when fatal respiratory depression occurred, it typically developed during the first five days of opioid therapy initiation, with the highest rates in the initial 24 hours [84]. Opioid initiation at too high a starting dose, or failure to consider other risk factors for respiratory depression such as coprescribed CNS

sedatives, indicate prescriber knowledge deficits [84]. Also during 2000–2010, equianalgesic dose tables (EDT) were commonly used in opioid switching to determine dose equivalence between original and replacement opioids. EDT use increased as more patients with chronic pain were prescribed opioids. With EDT calculations generally based upon observations in opioid-naïve postsurgical patients administered single-dose opioids and other flaws and limitations, EDT use was associated with increased fatal opioid toxicity [85].

Prescription Opioid Analgesic Abuse and Heroin Initiation

Misperception: Prescription opioid analgesics are the gateway to heroin.

Fact: Progression from prescription opioid abuse to heroin initiation is infrequent.

Data from 609,000 persons at risk for nonmedical pain reliever use (NMPR; use of any nonprescribed opioid analgesic, prescribed opioid analgesic use departing from intended purpose) or heroin initiation during 2002–2011 indicated that 3.6% of NMPR users initiated heroin within five years of prescribed opioid abuse onset [86]. Most current heroin users initially abuse prescription opioids [69], but the unreported flipside is the infrequent progression of NMPR to heroin [86].

A Cochrane Review evaluated 26 prospective opioid trials in subjects with chronic pain (N = 4893; opioid therapy for six or more months) with prior nonopioid analgesic failure [87]. In studies specifically reporting abuse or addiction rates (N = 2613), seven patients (0.27%) developed opioid use disorder (OUD) of their prescribed opioid. Most studies screened subjects for SUD history, and all subjects were prescribed opioids under long-term medical supervision. The low OUD rates may not generalize to unselected populations or to opioid prescribing without adequate medical supervision [87]. Another systematic review using less restrictive study inclusion evaluated opioid therapy outcomes in subjects with chronic pain, with or without SUD history (17 studies; N = 88,235). Opioid treatment was long-term (three months to several years) in 10 studies, short-term (one study), or unreported (six studies). The incidence rates of OUD ranged from 0–24% (median = 0.5%), and the prevalence rates ranged from 0–31% (median = 4.5%). Studies with a greater proportion of subjects with SUD history reported higher OUD rates [88].

Proportion of US to World Consumption of Opioid Analgesics

Misperception: The United States consumes 80% of the world opioid supply and 99% of the hydrocodone supply, proving that opioid overprescribing is rampant.

Fact: These often-cited figures mislead by omission.

The World Health Organization (WHO) has calculated that of the world's population (7 billion in 2010), 7.6% live in countries with adequate access to opioid analgesics (US, Canada, Australia, some Western European countries), 4.1% live in countries with moderately inadequate access, and 80% (5.8 billion) have nearly or entirely nonexistent access [89]. The WHO calls this unavailability of opioids for severe pain an epidemic and declares global access to opioid analgesics a moral imperative [90]. The United States uses 99% of hydrocodone because other countries with adequate opioid access prefer dihydrocodeine or low-dose morphine to hydrocodone for moderate to moderately severe pain [91]. Compared with opioid analgesic access in the United States, access is greater in Canada and comparable in Austria [89].

From 2010/Q3 to 2014/Q4, decreased rates were found of opioid analgesic misuse reported to poison centers when adjusted by 1) population: –44% ER/LA opioids, –31% SA opioids; 2) prescription: –44% ER/LA opioids, –25% SA opioids; and 3) dosing unit: –37% ER/LA opioids, –25% SA opioids [92].

Evidence of Long-term Opioid Benefit in Chronic Pain

Misperception: There is no evidence that long-term opioids are safe or effective.

Fact: Few if any analgesic drugs used in chronic pain have evidence of long-term safety and efficacy from randomized controlled trials (RCTs) of one or more years' duration.

This talking point to discredit opioid prescribing in chronic pain comes from recent AHRQ [14] and CDC [16] reviews of long-term opioid analgesic therapy that found few RCTs of one or more years' duration comparing opioid pain or function outcomes with another analgesic or placebo. This phrase misleads with strongly biased wording and omitted information; no recommended nonopioid therapy for chronic pain has longer aggregate clinical trial duration than opioids, and all modalities show aggregate study durations $\leq$12 weeks [93]. Absence of evidence is not evidence of absence [94]. Bias-neutral wording may resemble "few controlled long-term opioid safety and efficacy studies in chronic pain have been published." Opioid and other analgesic drug RCTs are seldom evaluated for $>$12 weeks. Obstacles that interfere with conduct of long-term RCTs for drug and nondrug treatments include ethical prohibition of assigning subjects in substantial pain to placebo, the complexity, expense, and unattractiveness to industry funding of long-term trials using active-drug controls, and high dropout rates of subjects in chronic pain randomized to receive placebo or sham interventions [95–97].

Opioid analgesic efficacy is especially difficult to demonstrate in controlled RCTs. Studies report average opioid responses of large numbers of patients receiving rigid, predetermined starting doses and titration [48]. Opioid response in chronic pain is bimodal and not normally distributed [94]; patients primarily show substantial or negligible analgesic response. With individual patient responses pooled and averaged, modest benefit is typically reported [94]. Strict, inflexible dosing parameters or titration algorithms lead to high dropout rates from analgesic failure or intolerability, resulting in underestimates of efficacy and overestimates of toxicity. Many such patients would likely gain analgesia and tolerability using an individualized approach tailored to patient factors that influence the analgesic response to opioids [48,96]. Moreover, non-RCT opioid analgesic trials of one or more years demonstrate substantive clinical value [95].

Other Factors Related to Opioid Analgesic Prescribing Safety

Medical cannabis laws were examined for potential impact on fatal opioid analgesic OD during 1999 to 2010 [98]. Compared with states without medical cannabis laws, states that enacted medical cannabis laws before 2011 (N = 13) showed a mean 24.8% reduction in annual opioid analgesic OD fatalities. The relationship between access to medical cannabis (vs states without access) and reductions in opioid analgesic OD deaths was evident one year after the passage of medical cannabis laws, and it strengthened over time: year 1 (–19.9%), year 2 (–25.2%), year 3 (–23.6%), year 4 (–20.2%), year 5 (–33.7%), and year 6 (–33.3%). Reductions in opioid analgesic deaths in states with (vs without) medical cannabis access were statistically significant for each year (range = $P < 0.001$ to $P = 0.02$). The association between medical cannabis laws and opioid analgesic deaths remained after including all heroin OD deaths, even when opioid analgesics were not present. In states with medical cannabis laws, there was no relationship between opioid analgesic OD deaths two years before passage and one year before passage [98].

Liberalized opioid analgesic prescribing in some European countries has not led to the addiction and overdose rates seen in the United States [61,99]. This disparity was thought to reflect the contribution of uniquely American factors beyond opioid analgesic exposure that include preferential insurance coverage for drug over nondrug chronic pain therapies and aggressive pharmaceutical industry marketing of ER opioids [100]. For example, of 870,000 German health insurance enrollees in 2012, the one-year prevalence of prescribed opioid analgesic problems (fatal overdose, ED visits, OUD diagnosis) was 0.008% [101].

The CDC Opioid Prescribing Guideline for Chronic Pain

In March 2016, the CDC published an opioid prescribing guideline for chronic pain in primary care [16]. Of its 12 recommendations, most represent standard practice, including risk mitigation strategies. A minority of these recommendations, however, provoked intense criticism and alarm by pain professionals and patient advocacy groups, and concerns by the American Medical Association [102], American Cancer Society [103], American Academy of Pain Management [37], American Academy of Pain Medicine [36], and other organizations [104]. The CDC guidelines have already begun to have a major impact on opioid prescribing. Nonetheless, they perpetuate the misperceptions of opioid analgesics discussed above. Discussion of specific recommendations is beyond the scope of this paper, but aspects of the development process merit closer attention, as this shaped the contents of the end product [37,105].

Guideline recommendations can be influenced by the opinions, experience, and makeup of the Guideline Development Group (GDG). Instead of placing patient needs as the priority, practices can be regulated to control costs, serve societal needs, or protect special interests [106]. Much of the opposition to the CDC guideline reflected the perception that it was not patient-centered.

As both a public health and clinical issue, the prescribing of opioid analgesics must balance access for patients who benefit with control to prevent inappropriate use. Emphasis on access over control was associated with increased prescribing, addiction, and overdose. The current focus on control has added or reinforced barriers to patient access. Well-intentioned but narrowly targeted, unbalanced interventions to such complex issues generate consequences [104].

Of the 17 members of the CDC GDG, 15 were emergency medicine, addiction, public health, or state regulatory professionals [16]. The remaining two members with pain profession backgrounds are discussed below. On November 17, 2015, the directors of a public interest law firm sent a letter of concern to the two top officials of the CDC regarding what was then the draft of the CDC opioid guideline [105]. The law firm requested that the CDC withdraw this draft guideline and start over after protections for the treatment of patients with pain were in place and a new GDG was created. The law firm expressed greatest concern over the following [105]:

1. the CDC did not initially disclose author and advisor backgrounds and credentials;

2. the GDG comprised members whose public records indicated strong support for restrictive prescribing guidelines that would significantly reduce opioid prescriptions for patients suffering from chronic pain;

3. stakeholders whose views diverged from the GDG's were apparently excluded;

4. conflicts of interest were present among GDG members. Both pain medicine professionals were

members of Physicians for Responsible Opioid Prescribing (PROP), an activist group dedicated to limiting the use of opioid analgesics. PROP lobbied Congress and federal regulators for years to reduce opioid prescribing. One GDG member was elected president of PROP in 2015 and served as a paid consultant to a law firm that litigates against opioid analgesic manufacturers.

Also instrumental in developing the guidelines were the PROP founder and Executive Director, and PROP Board members who were Stakeholder Review Group members who reviewed the CDC guidelines. Another PROP board member was on the CDC peer review panel [107]. The law firm observed that this represented serious ideological and financial conflicts of interest [105]. The CDC's understandable framing of all opioids as vectors of an epidemic influenced its selection of GDG members [37].

Review committee bias and stakeholder representation can influence the conclusions of systematic reviews [108], including those that inform guidelines. This is evident when separate reviews draw different conclusions from analyzing the same pool of clinical trial data [109]. As described above, the CDC guidelines were based on a 2014 AHRQ systematic review [14] that excluded opioid RCTs of less than one year's duration and all opioid studies other than RCT design. These new criteria eliminated the pool of evaluable studies analyzed in a 2009 systematic review of opioid analgesics [110] co-authored by some of the PROP members who authored the CDC guidelines. The conclusions of the 2014 AHRQ review and the 2016 CDC guidelines differed markedly from the 2009 review, despite little or no change in the body of best available evidence [37].

Despite the above flaws, the authority and prestige of the CDC guideline have already led to its implementation as a mandate. This outcome is expected to further restrict opioid access for patients in need [21,37,38]. Unfortunately, although opioid analgesics certainly possess abuse liability, few other options are equally effective when pain is severe and requires powerful analgesic control [2].

Discussion

This paper examined the factual basis supporting or refuting common assumptions about opioid analgesic prescribing. Publically available data on opioid analgesic prescribing show long-term decline and corresponding decline in ODs. When taken as prescribed and not combined with sedatives and/or alcohol, fatal OD is infrequent. Population-wide, misusing prescription opioid analgesics infrequently leads to heroin use. Importantly, recent data show a fundamental shift in the "opioid overdose epidemic" away from prescription opioid analgesics and toward illicit opioids (heroin and fentanyl).

To illustrate this dramatic change, a February 2017 report on Massachusetts data indicated that opioid-related deaths/100,000 residents increased 250% from 9.3 in 2011 to 25.8 in 2015. Toxicology results in opioid OD decedents found important trends: 1) fentanyl, almost all illicit in origin, was present in 42% in 2014 vs 75% in 2016; 2) heroin, present in 77% in mid-2014 vs ~50% in 2016; 3) prescription opioid analgesics fell 34.68% from early 2014 to 2016; and 4) BZD presence rose from 55% in 2014 to 63% in 2016. Unlike the CDC methods, suicides were excluded in these analyses. Thus, in 2016, 3 in 4 fatal opioid toxicities involved illicit fentanyl, approximately three in five involved BZDs, and prescription opioid analgesic fatalities continued declining [111]. It is worth noting that, in light of an earlier scandal involving years of falsified drug testing results by one chemist in the Massachusetts state toxicology laboratory, this chemist's behavior was uncovered and dealt with well before the earliest of the above results was obtained [112].

Solutions to opioid analgesic overprescribing, increasing overdose, and overpermissive attitudes in the 2000s were driven by the DEA's and CDC's respective drug and disease control paradigms. For example, in late 2016, the DEA announced a mandated 25% production rollback of all Schedule II opioids (33% for hydrocodone) in 2017, relative to 2016 levels [113]. These rollbacks did not apparently reflect any considerations of clinical need. Yet, patients with chronic pain requiring opioid analgesia increasingly encounter blocked access to pain control, stigma, and hostility in the health care system. Patients with cancer pain or acute pain have not been spared [18,20,24,33,35,114]. The disconnect of authorities and regulators from physicians and their patients with chronic pain who benefit from opioids is obvious [62].

Lobbying by advocates of opioid prescribing restrictions may contribute to proposals advocating blanket restrictions on access to opioid analgesics regardless of individual patient need. Some advocates are motivated by the tragedy of losing a loved one to prescription opioid toxicity or OUD that began during opioid analgesic therapy. One can appreciate the pain they experienced and their desire to spare others the fate of their relative. However, unidimensional solutions to complex public health issues often yield undesired consequences. Suicide by patients with chronic pain unable to access, or cut off from, opioid pain relief may come to rival fatal prescription opioid analgesic overdoses [115–117].

Opioid analgesic prescribing has received greater media attention than other drug classes or prescribing patterns linked to highly concerning outcomes. This negative attention may reflect the corrosive effects of OUD upon families and society. In contrast, inappropriate antibiotic overprescribing is the single greatest contributor to antibiotic-resistant bacteria. Recent estimates indicate that more than 2 million Americans are afflicted annually, with 23,000 fatalities [118]. *Clostridium difficile*, an

infection resulting from antibiotic use, annually afflicts around 500,000 and kills 15,000 [119]. The CDC guideline endorses nonsteroidal anti-inflammatory drug (NSAID) use before considering opioids [16], but every year, NSAIDs cause 7,000 to 10,000 fatalities from gastrointestinal hemorrhage [120].

Many unsafe opioid prescribing practices and overdose risk factors have been identified over the past two decades, yet until new analgesics enter clinical use, and there are few alternatives to opioids for controlling severe pain, and none that are widely available. The National Pain Strategy recommends that pain management in our health care system be improved by pain education of patients and pain training of clinicians [121]. When prescribed judiciously with careful attention to possible comorbid psychiatric, substance use, or medical disorders and potential adverse drug interactions [4], morbidity and mortality associated with prescription opioid analgesics, including overdosage, can be reduced, and in fact have steadily declined since peaking in 2011. In contrast, the recent upsurge in opioid-related deaths is attributable to the illicit opioids fentanyl and heroin. This pattern of overdose fatality is unlikely to respond to regulation of access to medically prescribed opioid analgesics.

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