CLARE LOCKE
LLP

THOMAS A. CLARE
[redacted]

10 Prince Street
Alexandria, Virginia 22314
[redacted]

www.clarelocke.com

July 10, 2020

***By Email*** **Not for Publication or Attribution**

James McLaughlin, Deputy General Counsel
The Washington Post
One Franklin Square
1301 K Street, NW
Washington, DC 20071
[redacted]

**Re: OxyContin Statement in May 4, 2020 Article**

Dear Jim:

I write in response to your thoughtful June 15, 2020 letter that raises important questions that we are pleased to address. We very much appreciate The Washington Post's willingness to engage in a meaningful, data-driven discussion about the actual role that OxyContin played in the opioid crisis. The Post's conclusion that Purdue has become a "too-easy scapegoat" for the crisis begs the equally important question of how that false narrative came to dominate media coverage and public perception.

The improper statement that OxyContin specifically (as opposed to other medications containing oxycodone more generally) "addicted millions" remains an important part of the false narrative that should be corrected. But our larger hope (and our primary purpose in writing) is that our ongoing fact-based dialogue will cause The Post to undertake a closer look at the false conclusions that have dominated the media coverage more broadly – and explore the flawed data and analyses that lie at the root of those false conclusions. In so doing, it will become apparent that the Sackler family has been badly maligned as this false narrative has built steam.

We hope that The Post will continue to examine these issues in detail and answer for your readers the fundamental question at the center of this dialogue: How exactly did OxyContin, Purdue Pharma, and the Sackler family combined become the "too-easy scapegoat" in this public health crisis?

Indeed, while we trust the arguments and sourced materials referenced in your letter were presented in good faith, much of the underlying "data" that you provided us is actually untrue. Upon detailed examination, they create a series of strawmen that collapse under scrutiny – even while successfully overcoming the inherent challenge of proving a negative. We believe our efforts to set the record straight will continue to reveal the many falsehoods not only in the arguments presented to us, but – more significantly – in the conventional narrative about OxyContin.

Our prior letters have provided critical facts demonstrating that OxyContin is not the root cause of the opioid crisis (and did not "addict millions" as The Post has stated without reliable evidence in support). Before turning to the problems with the arguments advanced in your most recent letter, a brief review of those facts is in order:

- "OxyContin" and "oxycodone" are often conflated, which in turn leads to confusion and misinformation. Over time, "OxyContin" emerged as the shorthand to reference any prescription opioid, with countless examples of media organizations (including The Post) using this brand-name medication to reference the whole universe of prescription opioids. Perhaps this is because the brand name OxyContin is an unusual example of a niche product having a brand name so similar to the underlying generic (in this case oxycodone). Notably, we have shown you examples where what was supposedly "OxyContin" may very well have been another medicine altogether.[1] The unfortunate reality is that all opioid medications are subject to abuse, and study after study show that abusers are much less selective than the false narrative around OxyContin purports – with a non-medical user of OxyContin just as apt to be a non-medical user of another prescription opioid.
- Prescriptions for opioid medications were rapidly and steadily increasing prior to the introduction of OxyContin.
- Since it was introduced in 1996, OxyContin has never been more than 4% of the market for prescription opioids based on the standard measurement of prescriptions. (Even using inapplicable formulas, such as MME or pills, OxyContin never broke out of the low-teens.)
- When OxyContin sales were dropping in the mid-2000s, prescriptions for other opioids were increasing. (OxyContin prescriptions peaked in 2003 while the rest of the opioid market continued growing for years.)
- Federal officials have testified that abuse of prescription opioids dates back to at least the 1980s, and the broader drug abuse crisis in America dates back to at least the 1970s.

[1] Here again, The Post is especially qualified to conduct this analysis based on the ARCOS data it obtained.

- Just last month and since our most recent correspondence: the CATO Institute reported that "non-medical use of licit or illicit drugs have been on a steady exponential increase since at least the 1970s – with different drugs predominating at different periods."[2]

- When Purdue became aware of the unanticipated widespread abuse of OxyContin in 2000-2001, the company jumped into action – seeking to become the industry leader in efforts to combat misuse of prescription opioids, with more than 65 programs costing well over $1 billion. Many of these programs have been hailed by those they were designed to help and continue to this day.

- Art Van Zee's study, which is widely cited in the media's reporting on these issues and also relied upon by The Post in response to many of the issues we have raised, is riddled with errors. Given The Post's groundbreaking work on obtaining previously secret ARCOS data, your newspaper is singularly equipped to identify and expose the many errors throughout his misleading study.

  How can The Post rely on Van Zee at all given the significance and volume of his errors? His wildly implausible claim, which is contradicted by your ARCOS data, that OxyContin was somehow 68% of oxycodone sales is just one example of his irresponsible conclusions that sadly influence so much news coverage. His false assertion that there was a "tenfold" increase in the use of OxyContin for non-cancer pain between 2007 and 2012 is likewise unsupported by the facts and stands out as another highlight of the report's falsehoods. It appears that many of The Post's inaccurate conclusions now turn out to be based on this highly unreliable source,

  The Post does not appear to quarrel with our assessment of Van Zee's inaccurate conclusions, but instead continues to give weight to his report for the simple reason that it "remains widely cited." The Post knows, of course, that repeating falsehoods merely because they have been widely adopted in the mainstream is no substitute for good science and the actual facts.

With this important background regarding the overall false narrative that we hope The Post will continue to examine closely, we will now explain how the newest arguments from your most recent letter also rely on fundamental factual and logical errors.

## I. The Underlying Data Does Not Support the Contention that OxyContin "Addicted Millions."

***First***, The Post argues that the number of non-medical users as of 2004 strongly suggests that the total number of people who developed an addiction to OxyContin was in the "millions." This

[2] *See* https://www.cato.org/blog/drug-czar-says-overdose-deaths-were-already-rising-pandemic-now-are-spiking-ultimate-blame.

argument falls short. Multiple studies show that non-medical abuse of opioids is not restricted to any particular drug, let alone OxyContin.

As just one example, a 2007 analysis of 28,000 people admitted to addiction treatment centers showed that just 5% had used OxyContin in the prior year (only 1% of the total receiving a prescription directly from a doctor).[3] This would indicate that non-medical users of opioids were significantly ***less likely*** to use OxyContin over other opioids.

The notion that OxyContin "addicted millions" is further undermined by prescription data following the 2010 introduction of the abuse-deterrent formulation of OxyContin, which targeted abusers' preferred route of administration by making it difficult to snort or inject the medication. If OxyContin had in fact been the "most prevalent" or "preferred" drug for non-medical users (who obtain through improper prescriptions), there almost certainly would have been a much bigger drop in OxyContin prescriptions after the reformulation. After all, Purdue's invention and introduction of the new pill was intended to significantly limit the likelihood of abuse. But rather than some sort of precipitous drop, the continuing decline in OxyContin prescriptions was consistent with the trend from prior to the new formulation. This further demonstrates that OxyContin was not the most "prevalent" opioid of choice for non-medical users.

***Second***, The Post attempts to justify the "addicted millions" statement by arguing that prescriptions for OxyContin increased from 670,000 in 1997 to 6.2 million in 2002. But this does not account for the fact that this increase was consistent with the overall growth in prescription opioids that was taking place long prior to the introduction of OxyContin. Importantly, sales of OxyContin peaked in 2003 (and it declined thereafter) even as the overall prescription opioid market continued to grow. Last month's CATO report also observed that "the evidence shows that there is no correlation between prescription volume and the non-medical opioid use or opioid use disorder."[4]

***Third***, and relatedly, The Post seeks to prop up its "millions" assertion by arguing that 8-12% of people who are prescribed opioids each year develop an opioid use disorder, which it then extrapolates to mean that "millions" over a longer period of time became addicted ***specifically*** to OxyContin.

This fallacy demonstrates the absurdity of the media's overall approach to this issue. There is simply no way that the 8-12% figures comport with reality, and yet these numbers and studies are never questioned by journalists – even as they are recycled again and again in support of the false

---

[3] *See* Carise, Deni, et al., *Prescription OxyContin Abuse Among Patients Entering Addiction Treatment*, Am. J. Psychiatry 2007.

[4] *See* https://www.cato.org/blog/drug-czar-says-overdose-deaths-were-already-rising-pandemic-now-are-spiking-ultimate-blame (emphasis added). This report likewise acknowledges that when chronic pain patients are "unable to follow up with their physicians" to help treat that pain, they are "seeking relief in the dangerous black market fueled by drug prohibition."

narrative. Given that NIDA is using these supposed facts to inform public policy, we would expect the media to vigorously scrutinize the data.

As a first step, The Post should closely review the 2015 study by Kevin E. Vowles and others, which is cited by NIDA as the source for the flawed 8-12% statistic. This report is yet another example of supposed science where the far-fetched conclusions are not actually supported by the underlying data.[5] It cites numerous studies with iatrogenic addiction rates supposedly ranging from .7% to 34.1%, and applies a confidence rating to each study. In convenient support for the report's conclusion, it generally assigned higher confidence rates to studies with the highest addiction rates.[6] And more concerning, many of the studies do not actually examine addiction (now referred to as opioid use disorder ("OUD") rates as claimed:

- The report assigns a confidence of 8 out of 8 to a study that reported a 23% addiction rate, despite the fact that the report's subjects had **received opioid *or* benzodiazepine prescriptions, and the rate of addiction was not broken down by medication.** This study does not appear to delineate incidence of abuse as between those participants taking opioids and those taking benzodiazepines. So while the entirety of the addiction observed in the studies might have been attributable to benzodiazepines, the Vowles report assigns this scientifically irrelevant study the highest confidence rating in making an argument about opioids.

  Furthermore, the study improperly used aberrant drug-related behaviors as a "proxy" for addiction, despite the fact that so-called ADRBs do not necessarily equate to addiction;[7]

- The report assigns a confidence of 7 out of 8 to a study that reported a 14.4% to 19.3% addiction rate – but likewise **relied upon behavior that could be present in non-addictive use**, such as increased tolerance to the drug, in the subject study's unique and incorrect definition of addiction. Remarkably, **the study acknowledged that its unique and unscientific diagnostic criteria "would tend to overestimate the prevalence of addiction in this population"**;

- The report assigns a confidence of 8 out of 8 to a study that reported a 13% addiction rate, even though **the study appears not to have actually assessed iatrogenic**

---

[5] *See* https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-crisis; 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(4):569-576. doi:10.1097/01.j.pain.0000460357.01998.f1.

[6] We have included an Appendix detailing the flaws, errors, and mischaracterizations by the Vowles report of the studies it claims support an 8-12% iatrogenic addiction rate for The Post's reference.

[7] Meltzer EC, Rybin D, Meshesha LZ, Saitz R, Samet JH, Rubens SL, Liebschutz JM. Aberrant drug-related behaviors: Unsystematic documentation does not identify prescription drug use disorder. Pain Med 2012;13:1436–43.

**addiction**. Instead, the study examined whether there are patient subtypes that could help identify potential problematic opioid users, while incidentally noting that some patients displayed aberrant drug-related behavior but not necessarily addiction;[8] and

- Perhaps most egregiously, the report assigns a confidence of 7 out of 8 in terms of assessing iatrogenic addiction to a **study that didn't actually examine addiction**, but rather investigated whether tolerance and hyperalgesia were common occurrences in patients taking prescription opioids.[9] And this particular report noted a 15.7% rate of patients who showed only aberrant drug-related behavior (not addiction), yet nonetheless, the authors of the Vowles report wrongly derived a 15.7% addiction rate from that report.

Any close examination of the Vowles report leads inescapably to the conclusion that it is scientifically baseless for estimating iatrogenic addiction rates. It is stunning that this deeply flawed study is being used by NIDA to inform public policy.

A deep dive into the underlying data aside, The Post and other outlets should be asking a very basic, straightforward question: if a medication that was never more than 4% of the total prescription opioid market (and actually peaked at just a 3.7% share of prescriptions) "addicted millions," what would The Post and other outlets say about the medications that comprise the other 96.3% of prescriptions – and the total number of addictions resulting from those medications? It is inescapable that the numbers immediately become too large to fathom and to square with the best government estimates of OUD sufferers in the US.

It is frankly stunning that no news organization has yet analyzed this (and other) core assumptions about the rate of iatrogenic addiction – given that what the widely presumed 8-12% rate of iatrogenic addiction would mean for the US population. We trust that the Post will not make that same mistake.

***Fourth***, the fallacy of conflating measures of opioid dependence with addiction goes well beyond the Vowles report. Indeed, this medical and scientific rubbish has long been promoted by opponents of medical opioids, including some of the so-called "experts" who now admit they intentionally concealed their conflicts of interest by hiding payments from plaintiff law firms in opioid cases. (We appreciate the corrections The Washington Post has made in order to fully inform its readers of these facts.)

Take the paper in the Journal of the American Medical Association, which was written in part by the controversial Drs. Andrew Kolodny and Jane Ballantyne, entitled, "Opioid Dependence

---

[8] Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain—development of a typology of chronic pain patients. Drug Alcohol Depend 2009;104:34–42.

[9] Schneider JP, Kirsh KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. J Opioid Manag 2010;6:385–95.

vs. Addiction: A Distinction Without a Difference." This shocking claim is at the heart of the false assertion that well-monitored chronic pain patients on opioids exhibiting dependence are "addicts." Kolodny has routinely equated tolerance and dependence with addiction in calling for the drastic reduction of prescription opioids and has even testified that the actual rate of addiction is ***25%***.[10] (Kolodny has shamelessly referred to prescription opioids as "heroin pills."[11])

Stigmatization is the centerpiece of the strategy promulgated by Kolodny's organization, Physicians for Responsible Opioid Prescribing (PROP), in advocating for an unfettered reduction in opioid prescriptions, even for patients whose doctors say they are needed for effective pain relief.[12]

---

[10] *See* https://journalrecord.com/2019/07/01/risk-of-opioids-addiction-questioned-by-jj-witness/ ("people who take opioid pain medications over extended periods have about a 25% chance of becoming addicted."); *see also* https://www.kolmac.com/qa-dr-andrew-kolodny-chief-medical-officer-phoenix-house/ (doctors have "made the individual physiologically dependent on the drug. As a result, the patient develops a tolerance to the pain-relieving effect of the prescribed opioid and requires higher and higher dosages" and contributed to the "opioid addiction epidemic."); https://theconversation.com/the-opioid-epidemic-in-6-charts-81601; https://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2019/05/21/rapid-opioid-cutoff-is-risky-too-feds-warn; https://www.cleveland.com/metro/2020/04/ohio-doctors-pharmacies-slash-number-of-opioid-pills-distributed-last-year.html.

[11] *See* https://www.c-span.org/video/?328904-4/washington-journal-dr-andrew-kolodny-drug-abuse-us.

[12] *See, e.g.*, June 16, 2020 Letter from PROP to R. Redfield, Director, CDC (available at http://www.supportprop.org/wp-content/uploads/2020/06/PROP-Comment-CDC-Docket-2020.pdf) ("We know from clinical experience and from controlled studies that opioids are rarely beneficial for chronic pain . . . The focus now should be twofold: to find better ways to help people already on opioids and improve access to better means than opioids to treat chronic pain."); http://www.supportprop.org/resources/understanding-physical-dependence/ ("the bright line drawn by the pain community and opioid manufacturers between physical dependence on one hand as inevitable and ultimately benign, as contrasted with addiction or psychological dependence on the other hand, which is said to be not inevitable, is a lot blurrier than people would think."); Ballantyne JC, Sullivan MD, Kolodny A. Opioid Dependence vs Addiction: A Distinction Without a Difference? Arch Intern Med. 2012;172(17):1342–1343. doi:10.1001/archinternmed.2012.3212 ("Dependence on opioid pain treatment is not, as we once believed, easily reversible; it is a complex physical and psychological state that may require therapy similar to addiction treatment, consisting of structure, monitoring, and counseling, and possibly continued prescription of opioid agonists. Whether or not it is called addiction, complex persistent opioid dependence is a serious consequence of long-term pain treatment that requires consideration when deciding whether to embark on long-term opioid pain therapy as well as during the course of such therapy.").

This misguided effort to conflate chronic pain patients (who may develop dependence on their medication) with "addiction" has been firmly debunked.[13]

Here is the FDA Policy that distinguishes between tolerance/withdrawal and addiction:

> Because of the biology of the human body, ***everyone*** who uses a meaningful dose of opioids for a modest length of time develops a physical dependence. This means that there are withdrawal symptoms after the use stops. ***A physical dependence to an opioid drug is very different than being addicted to such a medication. Addiction requires the continued use of opioids despite harmful consequences on someone's life***. Addiction involves a psychological preoccupation to obtain and use opioids above and beyond a physical dependence. ***But someone who is physically dependent on opioids as a result of the treatment of pain but who is not craving the drugs is not addicted.***[14] ***(emphasis added)***

As recently as this year, publications on this topic have recognized that there is an important distinction between physical dependence and addiction, and that the former "occurs in most people who are given repeated doses of opioid medications and manifests as the emergence of acute withdrawal symptoms following discontinuance of opioid drugs."[15] Any failure to recognize that physical dependence is not the same as addiction feeds the incorrect "prevailing narrative." Those who seek to blur the lines between two distinct medical conditions should be viewed skeptically and their motives questioned.

## II. The Post Should Not Rely on Dr. Humphreys.

The Post's reliance upon Dr. Keith Humphreys follows an unfortunate pattern by the media to quote and give a microphone to so-called "experts" without closing examining their motives,

---

[13] The error of equating of dependence with addiction is obvious when you compare it to many patients who need chronic glucocorticoids (prednisone, prednisolong, dexamethasone) for myriad auto immune disorders, or seizure patients who require medication to protect them from seizures, or heart arrythmia patients who take chronic anti-arrythmia medicines. Yet, these and millions of other chronic medication-dependent patients are not typically deemed "addicts."

[14] FDA in Brief: FDA finalizes new policy to encourage widespread innovation and development of new buprenorphine treatments for opioid use disorder, Feb. 6 2018.

[15] Volkow, Nora D., Blanco, Charles, *Medications for opioid use disorders: clinical and pharmacological considerations*, J. Clin. Invest. 2020 (noting that there is a distinction between physical dependence and addiction, and which also recognize that the former "occurs in most people who are given repeated doses of opioid medications and manifests as the emergence of acute withdrawal symptoms following discontinuance of opioid drugs.").

conflicts, or actual expertise. The Post does not acknowledge Dr. Humphreys' extensive record of false statements about members of the Sackler family and Purdue:

- Dr. Humphreys has falsely stated that the Sackler family and Purdue "drove the early stages of the U.S. opioid crisis by promoting OxyContin in misleading and unethical ways."[16]
- Dr. Humphreys has publicly alleged (without any actual evidence or support) that the Sackler family ***intentionally*** hid their connection to Purdue and OxyContin.
- Dr. Humphreys falsely claimed "[t]he Sacklers have hidden their connection to their product. They don't call it 'Sackler Pharma.' They don't call their pills 'Sackler pills.' And when they're questioned, they say, 'Well, it's a privately held firm, we're a family, we like to keep our privacy, you understand.'"[17] The absurdity of this statement, suggesting that pharmaceuticals are generally named after the owners of the manufacturer, should raise serious questions about Dr. Humphreys' ability to provide The Post with objective input.
- Dr. Humphreys: "It's getting increasingly obvious that Purdue and the family particularly, knew exactly what was going on so each one of these cases strengthens the potential cases of others."[18]
- Dr. Humphreys: "The ***well of greed and sociopathy*** within Purdue Pharma is truly bottomless."[19]
- Dr. Humphreys: "If no Sacklers end up behind bars, an entire class of people will continue to feel that writing a check is the worst thing that will happen to them ever no [matter] what they do."[20]

---

[16] Keith Humphreys, Jonathan P. Caulkins, and Vanda Felbab-Brown, *What the US and Canada Can Learn from Other Countries to Combat the Opioid Crisis*, Brookings Institute (January 13, 2020), https://www.brookings.edu/blog/order-from-chaos/2020/01/13/what-the-us-and-canada-can-learn-from-other-countries-to-combat-the-opioid-crisis/.

[17] Christopher Glazek, *The Secretive Family Making Billions from the Opioid Crisis*, Esquire (October 16, 2017), https://www.esquire.com/news-politics/a12775932/sackler-family-oxycontin/ (quoting Dr. Humphreys).

[18] Erin Beck, *In New Lawsuit, Morrisey Alleges Purdue Caused Switch to Heroin*, The Register Herald (May 16, 2019), https://www.register-herald.com/news/state_region/in-new-lawsuit-morrisey-alleges-purdue-caused-switch-to-heroin/article_fb11abaf-2b44-52f0-b5e6-a4438eff5261.html (quoting Dr. Humphreys).

[19] Keith Humphreys (@KeithNHumphreys) Twitter (April 13, 2020), https://twitter.com/donaldhtaylorjr/status/1249732380614688768.

[20] Keith Humphreys (@KeithNHumphreys) Twitter (August 27, 2019), https://twitter.com/KeithNHumphreys/status/1166504370311032832.

These inflammatory and hyperbolic statements are as preposterous and extreme as they are false and misguided — and they fully expose Dr. Humphreys' unreliability as a serious source of information for fact-based reporting.[21]

Consistent with these overreaching and exaggerated statements, Dr. Humphreys now tells The Post that it is "quite likely" (an unscientific term if there ever was one) that "millions" of Americans became addicted to OxyContin. But he provides *no evidence* that this is actually the case, nor can he. Dr. Humphreys' opinion rests entirely on his *speculation* that a high percentage of those who admitted to "misusing" OxyContin later became addicted to OxyContin.[22] The Post's determination that "misusing" a medication leads to any indication of "addiction" rates has a lot in common with the flaws that underlie the Vowles report and PROP's deception discussed above – as a person who reports "misusing" a medication (or any drug) should not be automatically labeled an addict.

Dr. Humphreys' damning and scientifically unsound statements demonstrate why The Post should not blindly rely on his say-so to support the very "prevailing narrative" that The Post concedes has been "too-easy" for the media to adopt.

## III. The Post is Uniquely Positioned to Report the Truth of This Important Public Policy Discussion.

We hope this review of facts will convince The Post that its published statement about "addicted millions" needs to be changed. But more broadly, we hope that the errors in the studies cited by The Post's June 15 letter will prompt the newsroom to examine why these falsehoods have

---

[21] Significantly, Dr. Humphreys has also displayed a tendency to exaggerate and mischaracterize data to support his conclusions. For example, Dr. Humphreys co-authored a paper that made the preposterous and unsubstantiated claim that American doctors were prescribing opioids "not just for terminal pain but for ordinary injuries" such as "wobbly knees." *See* Vanda Felbab-Brown, Jonathan P. Caulkins, Keith Humphreys, Rosalie Liccardo Pacula, Bryce Pardo, Peter Reuter, Bradley Stein, Paul H. Wise, *The Opioid Crisis in American*, Brookings Institute, 4 (June 2020), https://www.brookings.edu/wp-content/uploads/2020/06/0_Overview.pdf. Dr. Humphreys' flippant and unsupported statement that there was widespread prescribing of OxyContin by doctors for "wobbly knees" or similarly minor injuries is certainly inappropriate.

[22] Nor does the study that Dr. Humphreys cites substantiate his earlier speculation: at most, that study suggests that OxyContin was more likely to be misused than other opioids (and this is itself a highly contested opinion). *See* T.J. Cicero, J.A. Inciardi, A. Muñoz, *Trends in Abuse of OxyContin® and Other Opioid Analgesics in the United States: 2002-2004*, 6 Journal of Pain 662, 662-672 (2005) (noting in the abstract that the results of the study indicate that "OxyContin® abuse is a pervasive problem in this country, but that it needs to be considered in the context of a general pattern of increasing prescription drug abuse.").

been allowed to permeate reporting for so long – with so little scrutiny, pushback, or – most importantly – scientific review.

We urge The Post to continue its leadership in reporting on this important topic by pressure testing the outlandish claims that have misled public understanding, and to independently scrutinize the underlying data – rather than simply cite studies that are demonstrably flawed. As an example of a question that could be examined: How many OUD patients does the government report each year? The historically prevailing answer to this question leads to mathematically implausible numbers. Yet, no media organization has challenged the experts behind these studies on why the government has failed to find the millions, or in many cases tens of millions, of Americans who are supposedly suffering from OUD.

This goes far beyond seeking a correction from The Washington Post about the false claim that OxyContin "addicted millions" – or even the overarching goal to correct the "too-easy" false narrative about my clients and their company. These flawed studies have played a big role in industry-wide litigation that has led to enormous legal settlements. And more importantly, they cut to the core of public policy for – and of the public's understanding of – a medically essential class of medications and the patients that rely upon them.

These studies, and the experts who cite them, have been granted an enormous amount of power (and latitude) to shape the future of American medicine, yet they have never been asked the tough questions about the flawed data that forms the basis of their advocacy.

We believe The Post is sincerely committed to accurate reporting and that the newspaper's reliance on all of this erroneous data to support false assertions about addiction are good-faith errors. We appreciate the time and effort you and The Post's newsroom have taken to research and respond to the points we have raised, and we trust the information we have provided will now be deemed sufficient to support the need for changing the article that falsely states OxyContin "addicted millions." Either way, we are eager to stay focused on the bigger picture of continuing to assist The Post reporters, editors, and fact-checkers (and lawyers) with analyzing and scrutinizing the voluminous and complex data surrounding opioid use and addiction. The rabbit hole of flawed data and analysis surrounding the opioid crisis goes much deeper than the issues discussed here, and we intend this letter to be another step in our shared goal of determining how so much reporting about the opioid crisis has been incorrect.

We look forward to a continued and open dialogue with The Post to get this right.

Very truly yours,

Thomas A. Clare, P.C.

Thomas A. Clare, P.C.

Enclosure

# Analysis of 2015 Vowles Report - Addiction Rates

| FN | Study | Year | Addiction Rate | Vowles Confidence (on a Scale of 8) | Description of Flaws with Study and Vowles Report's Reliance |
|---|---|---|---|---|---|
| 1 | Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll SH, Senay EC, Woody GE. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage 2006;31:465–76. | 2005 | 4.9 | 7 | This study was not intended to measure the rate of iatrogenic addiction. The study was designed to measure the rates of abuse and dependence for Tramadol, NSAIDs and hydrocodone. The study was not aimed at finding the true rate of addiction for any of these substances; rather it was to compare whether Tramadol was more or less prone to abuse then NSAIDs or hydrocodone. The study participants must have had chronic (more than 4 months) nonmalignant pain, were between 18 and 74, and were starting a new therapy that included one of the three study medications. Ultimately, there were 11,352 patients in the study, 3,145 of them were prescribed hydrocodone.<br><br>The study did not measure addiction, let alone iatrogenic addiction. Rather, through a manufactured Abuse Index Algorithm, it measured "abuse and dependence." Patients were interviewed to determine if there was (1) inappropriate use; (2) use for purposes other than intended; (3) inability to stop use; or (4) evidence of opioid withdraw. Patients who met 3 out of 4 of the criteria were considered to be abusing and dependent. Alternatively, if for any reason evidence of opioid withdrawal was excluded, then the study found that just 2 out of the first 3 criteria yielded a positive result.<br><br>Additionally, the study included anyone who took a medicine and reported feeling in a "good mood and feeling intoxicated" - without any other criteria - as abusing and being dependent on the medication. These individuals are included in the 4.9% statistic that the Vowles study touts. Adams acknowledges that these individuals may state that the medication made them feel in a "good mood and feeling intoxicated" because the medication relieved their pain. Importantly, e**liminating these individuals reduces the abuse and dependence rate for hydrocodone from 4.9% to 2.2%.**<br><br>Lastly, the "inability to stop use" criteria used by this study only requires that a patients agrees with the statement that they "did not try to stop [taking the drug] but said it would be hard." A patient that is legitimately in pain, and not addicted or abusing the drug, would agree with this statement since the fear of being in pain again would make it difficult to stop taking the drug. Notably, DSM-5 guidelines explicitly exclude this diagnostic criteria -- withdrawal -- for assessing OUD in |
| 5 | Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain—development of a typology of chronic pain patients. Drug Alcohol Depend 2009;104:34–42. | 2009 | 13 | 8 | This study examined the overlapping issues of pain, addiction, and mental health to determine if patients could be categorized into groups to help identify and predict potential problematic use of opioids. The study was a retrospective cohort study among pain patients between 21 and 79 with opioid prescriptions for chronic pain. Patients were included in the study if they had "chronic opioid use in the 12 month period 1 year prior to the time of the interview." Chronic opioid use is defined as either (1) filling 10 or more opioid prescriptions during the 12 month period; or (2) filling a prescription for at least a 120-day supply of opioids and six or more opioid prescriptions during the 12 month period. Notably, cancer patients were excluded from the study in order to focus on chronic noncancer pain patients. Patients reporting no opioid use in the 90 days preceding the interview were excluded from the analysis. Ultimately, 704 patients were included in the analysis.<br><br>Importantly, the study examined patient behavior a minimum of one year **after** the 12 months of chronic opioid use, which strongly suggests that this study is not examining iatrogenic addiction.<br><br>The study found that "[o]pioid dependence was present among 13% of subjects with another 8% diagnosed without concomitant dependence per DSM-IV criteria." The DSM-IV criteria for opioid dependence includes normal physiological behaviors for those on long-term opioid therapy, which has been removed under the most recent DSM-5 guidelines. *See* Fleming, et al. 2007, below. This study does not acknowledge this issue or how it would certainly undermine the 13% rate. |
| 16 | Cowan DT, Wilson-Barnett J. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med 2003;4:340–51. | 2003 | 2.8 | 7 | This study reviewed 3,500 patient records "from a pain clinic at a London district general hospital." It was designed to "generate more evidence of the long-term safety and efficacy of opioids" in chronic noncancer pain patients. The survey looked at 1,393 patients who were seen in 1998. Of those, 125 had been prescribed controlled-release oral morphine sulphate, transdermal fentanyl, or both. Of those, 104 patients agreed to participate in the study. Data was either collected in face-to-face interviews (49%) or via questionnaires and phone calls if they were no longer attending the pain clinic (51%).<br><br>Of the 104 patients, three patients "were judged to be addicted." This equates to 2.8%, the statistics listed in the Vowles study. One patient "exhibited behavior suggestive of uncontrolled and compulsive use of up to 120-130mg/day destromoramide, despite adequate pain relief experienced at lower doses, and a preoccupation with ensuring an adequate supply. The two other patients "reported previous experience of opioid drug craving as well as some physical withdrawal symptoms. Those patients were initially given opioids postoperatively, necessating high doses of continuous intravenous infusions, which were then suddenly stopped. At the time of the survey, both patients were maintained on 25% and 10% of their respective peak doses and reported no problems. It is, therefore, likely that their previous symptoms could have been avoided by careful downtitration of dosage." Accordingly, 2 of the 3 patients were addicted solely due to poor physician decisions, rather than the nature of drug. Removing these patients reduces the addiction rate to just 0.96%. |

# Analysis of 2015 Vowles Report - Addiction Rates

| | | | | | |
|---|---|---|---|---|---|
| 18 | Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? Pain Med 2007;8:647–56. | 2007 | 0.7 | 5 | The goal of this study was to determine whether those prescribed opioids for chronic noncancer pain had higher rates of opioid misuse, any problem opioid misuse, nonopioid illicit drug use, nonopioid problem drug use, or any problem alcohol use, compared with those who have not been prescribed opioids. The survey contained 9,279 respondents.<br><br>The only 0.7% statistic in the entire study is from the problem opioid misuse rate of the entire sample population - including nonopioid users. It appears that that is the basis for the Vowles report including the 0.7% rate. This undermines the process and legitimacy of the entire Vowles report - the authors inclued this rate even though it lumps opioid and nonopioid users together.<br><br>Notably, the study defined "problem opioid misuse" as opioid misuse with the added criteria of either tolerance and/or psychological problems due to drug use. "Opioid misuse" is defined as using prescription medication either without a doctor's prescription, or in larger amounts than prescribed, or for a longer period than prescribed. This is more expansive definition of "opioid misuse" than the definition of addiction given in the Vowles study. |
| 20 | Fleming MF, Balousek SL, Klessig CL,Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain 2007;8:573–82. | 2007 | 3.8 | 8 | The goal of this study was to find the rate of substance use disorders in patients receiving opioid therapy from their primary care physician. A secondary goal was to determine the relation of positive urine screens and aberrant drug behaviors to opioid use disorders. Study participants were between 18 and 81, had a diagnosis of chronic noncancer pain, and were currently in long-term opioid therapy treatment by a PCP. 1,009 patients met the initial criteria and were interviewed, of these 801 patients were taking opioids daily for the last 3 months. These 801 patients were the study population.<br><br>The Vowles report takes its 3.8% addiction rate for this study from the percentage of subjects that met DSM-IV criteria for opioid abuse or dependence. 25 patients met the DSM-IV criteria for opioid dependence, while only 5 patients (0.6%) met the DSM-IV criteria for opioid abuse. The study acknowledges that "the 7 primary DSM-IV criteria [for opioid dependence] include tolerance and physical withdrawal, which are normal physiologic effects of chronic opioid therapy." In light of this, the opioid dependent patients likely do not meet the Vowles definition of addiction. |
| 21 | Fleming MF, Davis J, Passik SD. Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. Pain Med 2008;9:1098–106. | 2008 | 3.4 | 6 | This study examined the frequency of aberrant drug behaviors and their relationship to substance abuse disorders among patients receiving opioids for chronic pain. The average duration of chronic pain was 16 years, and the average duration of opioid therapy was 6.4 years. The study subjects were 904 patients who were taking daily or intermittent opioids in the previous 6 months.<br><br>The study found that 31 of the 904 patients met the DSM-IV criteria for either opioid abuse or dependence, which the study defines as "substance use disorder." Therefore, 3.4% of the study participants had substance abuse disorder. The Vowles report uses this statistic for an addiction rate of 3.4% even though the DSM-IV criteria for opioid dependence is likely over inclusive for people on long-term opioid therapy. |
| 23 | Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. Eur J Pain 2010;14:1014–20. | 2007 | 14.4-19.3 | 7 | This study aimed to estimate the prevalence of addiction among chronic pain patients at a "tertiary pain centre," measured both by ICD-10 criteria and criteria established by Russell Portenoy. The study population included 236 noncancer pain patients and 17 cancer pain patients, for a total of 253 patients. An addiction diagnosis under ICD-10 requires three or more of the following six criteria: (1) a strong desire to take the drug; (2) difficulties in controlling its use; (3) persisting in its use despite harmful consequences; (4) higher priority given to the drug use than to other activities and obligations; (5) increased tolerance; and (6) sometimes a physical withdrawal state. Importantly, criterion 3, 5, and 6 could be present in normal long-term opioid therapy patients, such as a patient persisting on opioids despite the common side effects of nausea or constipation.<br><br>The study also estimated the prevalance of addition using the Portenoy criteria for addiction, which are: "An intense desire for the drug and overwhelming concern about its continued availability (psychological dependence), evidence of compulsive drug use (characterised for example by unsanctioned dose escalation, continued dosing despite significant side effects, use of drugs to treat symptoms not targeted by therapy, or unapproved use during periods of no symptoms) and/or evidence of one or more of a group of associated behaviours (including manipulation of the treating physician or medical system for the purpose of obtaining additional drug, acquisition of drugs from other medical sources or from non-medical sources, drug hoarding or sales, unapproved use of other drugs).”<br><br>Under the ICD-10 criteria, 14.4% of the patients were determined to be addicted to opioids, while under the Portenoy criteria, 19.3% of patients were determined to be addicted to opioids. The study acknowledges that DSM-IV criteria has been criticized as overestimating addiction rates, and that "[a]ccording to this criticism, the ICD-10 criteria would tend to overestimate the prevalence of addiction in this population."<br><br>The data for this study is not entirely clear. The 14.4% addiction rate comes from finding that 27 patients were classified as addicted to opioids and that 187 patients were prescribed opioids. There is no indication that these 27 patients were in fact prescribed opioids as 66 patients in the study were on nonopioid painkillers.<br><br>The study did not estimate the number of patients determined to be addicted to opioids among those patients that were prescribed long-acting opioids - which although still flawed given the nature of the study and the criteria used, would have been more appropriate. Of these patients, 8.7% were found to be addicted according to ICD-10 criteria, and 13.5% were found to be addicted according to the Portenoy criteria. Another issue is that each patient was screened for addiction by both a doctor and a nurse, separately, with the screeners blind from the other's results. The study counted the patient as addicted even if the doctor and nurse came to different conclusions on addiction. In other words, if the nurse determined a patient to be addicted, but the doctor did not, the patient was still counted as |

# Analysis of 2015 Vowles Report - Addiction Rates

| | | | | | |
|---|---|---|---|---|---|
| 26 | Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender differences in risk factors for aberrant prescription opioid use. J Pain 2010;11:312–20. | 2010 | 34.1 | 4 | The sample set consisted of 622 chronic noncancer pain patients who had been prescribed a wide variety of IR and ER pain medication. The study does not state what percentage of participants were prescribed IR vs. ER, but among the ER medications oxycodone accounted for only 22.7 percent, while methadone and fentanyl patches made up the balance. The study does not state whether these patients were abusing prescription medication prior to being prescribed opioids for chronic pain.<br><br>The 34.1 addiction rate reported by Vowles was, in fact, a positive result on Jameson's Aberrant Drug Behavior Index, which triangulated patient self reporting, physician screening and urinalysis to derive an ADBI score. Further to the comment above that the study did not state whether these patients abused drugs previously, it should be noted that a positive result on the urinalysis was given to anyone with evidence of having taken an illicit substance (e.g. cocaine) or an additional opioid medication that was not prescribed.<br><br>The study does not define the 34.1 percent of patients as having been "addicted," but rather "as to whether they engaged in aberrant medication-related behavior, which relates positively to opioid medication abuse." **Indeed, the author writes that "a smaller number of pain patients may have an addiction disorder and may** |
| 35 | Damron KS, Beyer CD, Barnhill RC, Fellows B. Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. J Ky Med Assoc 2003;101:511–17. | 2003 | 8.4 | 4 | This study is now 17 years old and focused exclusively on patients in an extremely confined geographic location where abuse of prescription opioids was especially prevelant. Regardless, Vowles gives it a very low confidence rate. |
| 39 | Meltzer EC, Rybin D, Meshesha LZ, Saitz R, Samet JH, Rubens SL, Liebschutz JM. Aberrant drug-related behaviors: Unsystematic documentation does not identify prescription drug | 2012 | 23 | 8 | This study included patients who were prescribed benzodiazepines and looked at addiction to those medications too. Nor does the study break down its 23% addition rate by medication. Further, the study proposes using aberrant drug-related behaviors as a "proxy" for prescription drug use disorder, but as noted above, ADRBs do not equal addiction.<br><br>Lastly, the study appears to have relied upon DSM-IV criteria for opioid dependence, which includes normal physiological behaviors for those on long-term opioid therapy. See Fleming, et al. 2007. This study does not acknowledge this issue. Despite these obvious issues, the Vowles report rubber-stamped this study with a confidence rating of 8 out of 8. |
| 45 | Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. J Pain Symptom Manage 2011;41:116–25. | 2011 | 6-11 | 7 | This study is a retrospective analysis designed to identify the types and frequency of aberrant drug-related behaviors and associated patient characteristics in opioid-tolerant patients with chronic pain. The study examined clinical study data for fentaynl buccal tablets (FBT) for breakthrough pain.<br><br>The Vowles report appears to get its 6-11% addiction rate for this study from the aberrant drug behavior rates found in the FBT study. The possible abberant behaviors involving FBT listed in the study are: overadministration of study medication; medication theft; overdose; motor vehicle accident; abuse/dependence; fear of addiction; loss of study medication; unapproved administration of drug to treat another symptom. Abberant behaviors not involving the study medication include: lost to follow-up; positive UDS test; taking nonprescribed medications; overdose; abuse/dependence; sought prescriptions from other sources; discharged from pain management practice. 11% of the patients had an aberrant behavior involving the study drug, while 6% had an aberrant behavior not related to the study drug. Accordingly, by using this statistic, Vowles is claiming that each patient that had one aberrant behavior was "addicted" to opioids, despite the fact that many of the aberrant behaviors could easily be unrelated to addiction and do not on their own indicate an addiction.<br><br>In contrast, the study found that only 10 patients (<1%) had an abuse-related event, 18 (<2%) had a positive urine drug screening, and 12 (1%) experienced an event consistent with opioid overdose (all patients recovered). Assuming, at bottom, that there is no overlap amongst these patients and that these events are consistent with addiction (which is not even certain), the addiction rate would be 3.8% (40/1160). |
| 49 | Schneider JP, Kirsh KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. J Opioid Manag 2010;6:385–95. | 2010 | 15.7 | 7 | This study reviewed the charts of 197 patients treated by a pain specialist for at least 1 year to determine whether tolerance and hyperalgesia were common occurrences and whether they occur within any type of specified timeframe.<br><br>The Vowles report claims that this study supports an addiction rate of 15.7% for opioid users. But once again, the Vowles report is wrong. The reference to a 15.7% rate is the rate for patients exhibiting some aberrant drug-related behaviors in their medical charts (ie, obtaining opioid prescriptions from more than one prescriber without a credible explanation, increasing medication dose without authorization, repeatedly running out early, inconsistent UDT results, and frequent medication “loss”). The study acknowledges that this only suggests (but does not demonstrate for certain) abuse or addiction, but Vowles takes the 15.7% to represent actual, diagnosed addiction - and yet another example of the Vowles report taking a massive leap unsupported by the underlying study. |

Comprehensive Review

PAIN®

# Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis

Kevin E. Vowles[a,*], Mindy L. McEntee[a], Peter Siyahhan Julnes[a], Tessa Frohe[a], John P. Ney[b], David N. van der Goes[c]



**Abstract**

Opioid use in chronic pain treatment is complex, as patients may derive both benefit *and* harm. Identification of individuals currently using opioids in a problematic way is important given the substantial recent increases in prescription rates and consequent increases in morbidity and mortality. The present review provides updated and expanded information regarding rates of problematic opioid use in chronic pain. Because previous reviews have indicated substantial variability in this literature, several steps were taken to enhance precision and utility. First, problematic use was coded using explicitly defined terms, referring to different patterns of use (ie, misuse, abuse, and addiction). Second, average prevalence rates were calculated and weighted by sample size and study quality. Third, the influence of differences in study methodology was examined. In total, data from 38 studies were included. Rates of problematic use were quite broad, ranging from <1% to 81% across studies. Across most calculations, rates of misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%-38%). Rates of addiction averaged between 8% and 12% (range, 95% CI: 3%-17%). Abuse was reported in only a single study. Only 1 difference emerged when study methods were examined, where rates of addiction were lower in studies that identified prevalence assessment as a primary, rather than secondary, objective. Although significant variability remains in this literature, this review provides guidance regarding possible average rates of opioid misuse and addiction and also highlights areas in need of further clarification.

**Keywords:** Opioids, Chronic pain, Problematic use, Abuse, Addiction, Misuse

## 1. Introduction

In the treatment of chronic pain, there may be no area of greater controversy than the use of opioids. Changes in attitudes with respect to opioid use toward the end of the 20th century, and subsequent exponential increases in use, have been well documented.[2,31,56,58] More recently, the burgeoning public health issue regarding opioid-related adverse events has perhaps been equally well documented, as the use of opioids in chronic pain brings with it marked potential for adverse events for the patient, including overdose, experience of physiological dependence and subsequent withdrawal, addiction, and negative impacts on functioning.[2,6,38,56] Attention paid to the so-called "opioid epidemic" (eg, Refs. 19,32) has highlighted the need to clearly differentiate and identify the types of problematic prescription opioid use (eg, misuse, abuse, addiction) and discern their frequency in treated patients with chronic pain.

Attempts to calculate rates of problematic opioid use behavior have suffered from imprecise and poorly defined terminology. Two recent sets of expert consensus statements, one suggesting a framework for measuring abuse liability for use in trials of analgesics for those with chronic pain[53] and the other a set of definitions for opioid-related adverse events,[44] identified 8 loose and overlapping categories of problematic use, including misuse, abuse, addiction, aberrant use, dependence, nonmedical or nontherapeutic use, physical dependence, and psychological dependence (also see the review of Webster and Fine,[60] who further define "pseudoaddiction"). The vagueness inherent in these definitions, areas of overlap among them, and their sometimes interchangeable use have made it difficult to determine exact rates and types of problematic opioid use. For example, the narrative review of Højsted and Sjøgren[24] detailed the findings of 25 studies involving patients with chronic pain prescribed with opioids, concluding that the prevalence of problematic opioid use behavior ranged from 0% to 50%. Although this span was representative of the literature at the time, it was of questionable value for delineating the scope, impact, and prevalence of the problem or in facilitating informed clinical and policy decisions regarding the allocation of screening and treatment resources. Martell et al.,[38] in their review of opioid use for low back pain, reported a similar range of current problematic opioid use (3% to 43%).

The purpose of this study was to perform an updated review of problematic opioid use in chronic pain using explicitly defined terms[44,53] for rates of problematic use in the literature. We synthesized the data to clarify and calculate prevalence estimates to increase precision and utility. As a secondary set of analyses, we investigated whether variation in the rates of problematic opioid use were related to differences in study characteristics (ie, primary study purpose, study design, method of assessment, clinical setting).

*Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.*

[a] *Department of Psychology, University of New Mexico, Albuquerque, NM, USA,*
[b] *Department of Neurology, University of Washington, Seattle, WA, USA,*
[c] *Department of Economics, University of New Mexico, Albuquerque, NM, USA*

**Corresponding author. Address: Department of Psychology, University of New Mexico, MSC03 2220, Logan Hall, 1 University of New Mexico, Albuquerque, NM 87131, USA. Tel: +1 505-277-4121; fax: +1 505-277-1394. E-mail address: k.e.vowles@gmail.com (K. E. Vowles).*

*PAIN 156 (2015) 569–576*



*http://dx.doi.org/10.1097/01.j.pain.0000460357.01998.f1*

## 2. Methods

### 2.1. Literature search strategy

We searched the clinical and scientific literature using Science Direct, Google Scholar, PubMed, and PsychINFO/PsycArticles databases for articles published between January 2000 and January 2013. We repeated the search in November 2013 to include articles published or accepted since January 2013. We used broad search terms to increase the probability of accurate identification of target articles (**Table 1**). We also reviewed reference lists to identify any articles that the initial search had missed.

### 2.2. Abstract screening

The abstracts of all studies identified in the literature search were read by 2 reviewers to assess eligibility for full-text data extraction. To be eligible for data extraction, studies met the following criteria: (1) only adult participants (ie, 18+ years of age), (2) sample composed of individuals with chronic noncancer pain (persistent pain lasting longer than 3 months), (3) participants were using opioids orally (to exclude studies of opioids delivered transdermally or through injection/intrathecal pump), (4) the abstract listed 1 or more of the following terms in reference to opioid use: abuse, misuse, dependence, addiction, or aberrant/problematic behavior, and (5) quantitative information was provided (as opposed to a commentary or qualitative review) regarding rates of problematic opioid use.

### 2.3. Full-text data extraction

Each study fitting the inclusion criteria was read in full by 2 members of the study team to extract and record data on a standardized data extraction form. The extracted information included participant demographics and pain details (ie, sample size, gender, age, pain duration, ethnicity, pain location), primary objective (eg, assessment of prevalence, medication safety/efficacy), study design (ie, cross-sectional/prospective/retrospective), study setting details, country of data collection), and method used to identify problematic opioid use (ie, structured/unstructured clinical interview, urine drug screen [UDS], chart review, clinical judgment, questionnaire).

#### 2.3.1. Coding of current opioid misuse, abuse, and addiction

Problematic use of opioids was categorized according to recent consensus statements published by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[44] and Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION)[53] panels, an overlapping group of experts with representation from private, public, and governmental domains. Based on these consensus statements, and the associated commentaries of Butler[9] and Sullivan,[54] the following definitions were used to categorize problematic use as misuse, abuse, or addiction.

(1) Misuse: Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects.
(2) Abuse: Intentional use of the opioid for a nonmedical purpose, such as euphoria or altering one's state of consciousness.
(3) Addiction: Pattern of continued use with experience of, or demonstrated potential for, harm (eg, "impaired control over drug use, compulsive use, continued use despite harm, and craving").[9(p2243)]

Only these 3 terms were coded. Additional categorization of terms was not deemed appropriate because the terms defined in the consensus statements were either not relevant to the purposes of the present review (eg, diversion, intoxication, suicide-related use) or were not specific enough in their delineation of problematic use patterns (eg, aberrant opioid-related behaviors, nonmedical opioid use).

The following guidelines were used to code the type of problematic use. First, the percentage of study participants meeting criteria for each type of problematic use was extracted and recorded, where possible, to the tenths decimal place. A single percentage was recorded from studies that met the criteria for only a single type of problematic use, whereas studies that reported separately on more than 1 type of problematic use provided more than 1 estimate (eg, 1 for participants meeting criteria for misuse and 1 for participants meeting criteria for addiction). Second, when studies reported a range of values regarding the percentage of patients meeting criteria for 1 type of problematic use, a minimum and maximum value was recorded. Third, only current problematic opioid use was recorded; data were not used if a study reported only on historical or lifetime problematic opioid use. When insufficient or ambiguous information was provided in the published articles or available supplemental data, we contacted study authors for additional details.

When possible, rates of opioid misuse, abuse, and addiction were recorded directly from study text (eg, Refs. 5,36). When no specific rate was reported, a calculation was performed based on the number of patients meeting criteria for misuse, abuse, or addiction divided by the sample size (eg, Refs. 57,65). When multiple forms of behavior indicating the same type of problematic use were collapsed and reported in the study as a single value, the single value was recorded (eg, Ref. 17, where a percentage of 3.2% was presented as a combined value for various forms of opioid misuse). Finally, when the original study included a psychometric evaluation of a questionnaire and used nonquestionnaire data to evaluate issues of sensitivity and specificity (eg, in the identification of questionnaire cut-scores), then rates of problematic use from the nonquestionnaire data were recorded (eg, Ref. 21).

Each included study had at least 1 codeable percentage (with an upper limit of 6 if minimum and maximum values for misuse, abuse, and addiction were all reported). Categorization of problematic opioid use was performed independently by 2 reviewers (K.E.V and M.L.M) and, in the case of disagreement regarding categorization, a consensus was reached after discussion.

#### 2.3.2. Rating of study quality

The quality of each study was rated using 8 of the 9 criteria used by Chou et al.[13(p.146.e3)] in their review of measures to predict and identify problematic drug-related behaviors. The first criterion of Chou et al., which determines whether the study evaluated test performance in a population other than the one used to derive the instrument (ie, derivation vs validation study), was coded but eventually discarded as it was deemed less useful in discriminating between high and low quality.

The remaining 8 criteria evaluate study sampling issues (eg, consecutive sample or random subset, proportion of missing

**Table 1**

**Search terms**

<*chronic pain*> AND
(<*opioid*> OR <*opiate*>) AND
(<*addiction*> OR <*dependence*> OR <*abuse*> OR <*misuse*> or <*aberrant behavior*>)

data), adequate description of study methods (eg, sample and patterns of opioid prescription, criteria to identify problematic behavior), and potential influence of raters on identification of problematic behavior (eg, rater blinding regarding the identification of problematic use). Consistent with Chou et al., studies that met the majority of the criteria (5 or more) were regarded as higher quality.

### 2.4. Analytic plan

Extracted data were entered into SPSS (version 21; IBM Corporation). The primary variables of interest were average rates of misuse, abuse, and addiction across studies. Because a small number of studies reported these rates as a range of values, 2 sets of calculations were performed for each type of problematic use, a minimum and a maximum. When only a single value was recorded, that value was entered as both the minimum and maximum value as that ensured that both the minimum and maximum calculations included the complete set data. Although we expected minimum and maximum values to be close to one another, this method of calculation was deemed to make best use of all available data and allow equal weightings for each study's data.

The first analytic step involved the calculation of unweighted raw means and SDs for rates of misuse, abuse, and addiction across all included studies. In addition, we calculated a number of weighted means, including weighting for raw sample size and log-transformed sample size. The log transformation was performed to address the large variability in sample size and apparent exponentiation of the sample size distribution within the largest studies. In addition, a Winsorizing procedure was performed for studies with sample sizes of greater than 1334 participants, which was the point at which outliers were identified within stem-and-leaf plots; there was also evidence of a bimodal distribution at this cut-point. For the analyses using the Winsorized sample size data, samples size for all studies with greater than 1334 participants were set to 1334, the value of the next largest sample size.

In addition to the analyses involving weightings by sample size, weighted means were calculated for study quality. Furthermore, means for studies of high and low quality were evaluated separately. Finally, a weighted interaction term of log-transformed sample size and quality rating was calculated using standardized scores (z-scores).

As a secondary set of analyses, differences in rates of problematic use were assessed in relation to primary study purpose (ie, Was the assessment of prevalence of misuse, abuse, and addiction the primary aim?), study design (ie, retrospective, cross-sectional, prospective), method of identification (eg, questionnaire, structured/semistructured interview, chart review, UDS), and clinical setting (eg, primary care, pain clinic). A series of analyses of variance (ANOVAs) was used to analyze for differences in rates of problematic use based on these study characteristics.

## 3. Results

### 3.1. Search results

**Figure 1** displays the flow of information throughout the different phases of the search in a manner consistent with the PRISMA statement.[41] The search yielded a total of 311 records for screening after the exclusion of 46 nonempirical papers, such as reviews, letters, and commentaries. An additional 9 records were identified in the updated, November 2013, search, yielding a total of 320 records for screening.

Kappa values indicated an acceptable level of agreement among raters, range $\kappa = 0.79$ to 0.91. All articles that had a discrepant rating after this stage of evaluation were retained for full-text data review.

A total of 78 articles were retained for full-text review. Of these, 40 were excluded for the reasons outlined in **Figure 1**. Therefore, 38 articles were used in data synthesis.

### 3.2. Characteristics of selected studies

Individual study characteristics are located in **Table 2**. The majority of studies, 35 (92%), reported on either misuse or addiction, whereas the remaining 3 studies reported on both. In total, 29 studies (76%) reported on rates of misuse and 12 (32%) on rates of addiction. Abuse was reported in only a single study, that of Banta-Green et al.,[5] as this was the only study that reported specifically on participant intention. Therefore, no further calculations of abuse prevalence were performed.

Generally, considerable variability regarding study characteristics was apparent. Sample size, for example, ranged from 63 to 938,586 participants. Quality ratings ranged from 0 to 8. Sample size and quality ratings were significantly and negatively correlated with one another, $r = -0.36$, $P < 0.05$. There was also variability in reporting basic demographic and pain-related information. Specifically, 77.5% of studies reported on participant sex, 70.0% provided some information on age (with 15.0% providing nonnumeric information that could not be extracted—eg, "most patients fell into the 35- to 50-year-old range"), 47.5% provided information of any kind on participant ethnicity, and only 22.5% provided information on education. Regarding pain-related information, a minority of studies provided information on pain location (42.5%), or information on pain duration (37.5%).

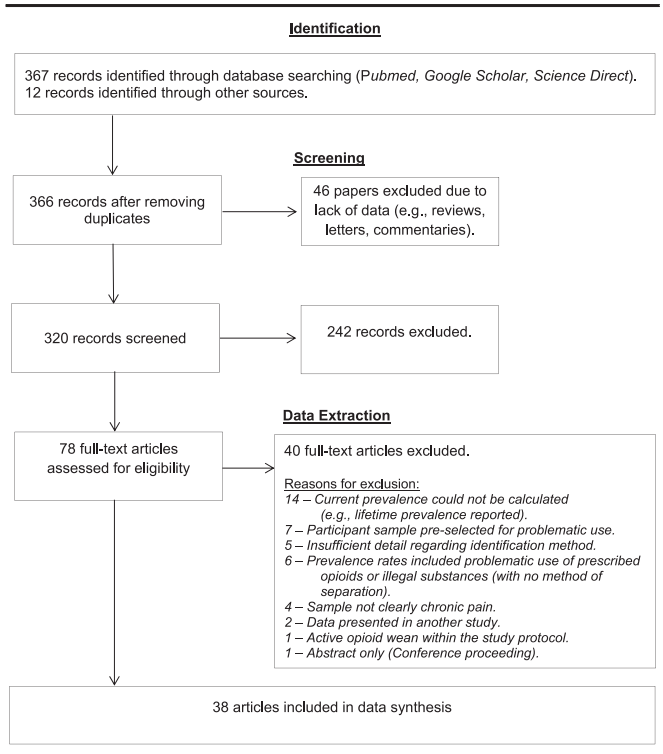


**Figure 1.** Flow of information thought the different phases of the review, as specified by the PRISMA statement.

**Table 2**

**Characteristics of included studies.**

| First author (year) | Sample size (country) | Design | Setting | Method of assessment | Rate (%) of problematic use, % | | | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | | | Misuse | Abuse | Addiction | |
| Adams et al.[1,*] | 4278 (USA)† | Prospective | Not specified | Q | — | — | 4.9 | 7 |
| Banta-Greenet al.[5] | 704 (USA) | Retrospective | Primary care | SI | — | 8 | 13 | 8 |
| Brown et al.[8,*] | 561 (USA/Puerto Rico) | Prospective | Primary care | CJ, Q, UDS | 2-6 | — | — | 6 |
| Butler et al.[11] | 95 (USA) | Prospective | Pain clinic | CJ, Q, UDS | 46.3 | — | — | 5 |
| Butler et al.[10] | 226 (USA) | Prospective | Pain clinic | CJ, Q, UDS | 34.2 | — | — | 3 |
| Chelminski et al.[12] | 63 (USA) | Prospective | Primary care | CJ, UDS | 32 | — | — | 2 |
| Compton et al.[14] | 135 (USA) | Prospective | Pain clinic | CJ, UDS | 28 | — | — | 5 |
| Couto et al.[15,*] | 938,586 (USA) | Cross-sectional | Toxicology laboratory database | UDS | 75 | — | — | 0 |
| Cowan and Wilson-Barnett [16,*] | 104 (UK) | Retrospective | Pain clinic | SI | — | — | 2.8 | 7 |
| Edlund et al.[18,*] | 9279 (USA) | Cross-sectional | Community database | Q | 3.3 | — | 0.7 | 5 |
| Edlund et al.[17,*] | 46,256 (USA) | Cross-sectional | Not specified | INSUR CL | 3.2 | — | — | 5 |
| Fleming et al.[20,*] | 801 (USA) | Cross-sectional | Primary care | SI | — | — | 3.8 | 8 |
| Fleming et al.[21,*] | 904 (USA) | Cross-sectional | Primary care | SI | — | — | 3.4 | 6 |
| Højsted et al.[23,*] | 207 (Denmark) | Cross-sectional | Pain clinic | CJ | — | — | 14.4-19.3 | 7 |
| Ives et al.[25,*] | 196 (USA) | Prospective | Pain clinic | CJ, UDS | 32 | — | — | 4 |
| Jamison et al.[26] | 455 (USA) | Prospective | Pain clinic | CJ, SI, UDS | 24.0-37.1 | — | 34.1 | 4 |
| Jamison et al.[27,‡] | 110 (USA) | Cross-sectional | Pain clinic | Q | 46.4 | — | — | 1 |
| Katz et al.[29,*] | 122 (USA) | Retrospective | Pain clinic | CJ, UDS | 43 | — | — | 4 |
| Manchikanti et al.[36] | 100 (USA) | Retrospective | Pain clinic | CJ | 24 | — | — | 6 |
| Manchikanti et al.[35,*] | 500 (USA) | Retrospective | Pain clinic | CJ | 9.4 | — | 8.4 | 4 |
| Manchikanti et al.[34,*] | 200 (USA) | Cross-sectional | Pain clinic | UDS | 3-12 | — | — | 1 |
| Manchikanti et al.[33,*] | 500 (USA) | Prospective | Pain clinic | CJ | 9 | — | — | 5 |
| Manchikanti et al.[30,*] | 500 (USA) | Prospective | Pain clinic | UDS | 9 | — | — | 3 |
| Meltzer et al.[40] | 238 (USA) | Cross-sectional | Primary care | SI | 11 | — | — | 4 |
| Meltzer et al.[39] | 264 (USA) | Cross-sectional | Primary care | CR | — | — | 23 | 8 |
| Morasco et al.[42] | 127 (USA) | Cross-sectional | Primary care | Q | 78 | — | — | 1 |
| Naliboff et al.[43] | 135 (USA) | Prospective | Pain clinic | CJ, UDS | 27 | — | — | 5 |
| Passik et al.[45] | 1160 (USA) | Retrospective | Clinical database | CJ | — | — | 6-11 | 7 |
| Portenoy et al.[46] | 219 (USA) | Prospective | Clinical trial registry | Q | 2.6 | — | — | 3 |
| Reid et al.[47] | 98 (USA) | Retrospective | Primary care | CJ | 24-31 | — | — | 7 |
| Schneider et al.[49] | 184 (USA) | Retrospective | Pain clinic | CJ, UDS | — | — | 15.7 | 7 |
| Sekhon et al.[50] | 797 (USA) | Retrospective | Primary care | CJ | 22.9 | — | — | 5 |
| Skurtveit et al.[52,*] | 17,252 (Norway) | Prospective | Prescription database | CJ | 0.08-0.3 | — | — | 3 |
| Vaglienti et al.[57,*] | 184 (USA) | Retrospective | Pain clinic | CJ, UDS | 25.5 | — | — | 5 |
| Wasan et al.[59] | 455 (USA) | Cross-sectional | Pain clinic | CJ, Q, UDS | 34.1 | — | — | 7 |
| Webster and Webster[61] | 183 (USA) | Prospective | Pain clinic | Q | 56.3 | — | — | 6 |
| Wilsey et al.[62] | 113 (USA) | Cross-sectional | Emergency department | Q | 81 | — | — | 2 |
| Wu et al.[65] | 136 (USA) | Prospective | Pain clinic | CJ, UDS | 27.9 | — | — | 3 |

* The primary study aim was assessment of prevalence of opioid misuse, abuse, or addiction.
† Adams et al.[1]—only data from the group taking hydrocodone used.
‡ Jamison et al.[27]—only baseline data used (ie, patients who screened as "high risk" on questionnaire).
Method of assessment: CJ, clinical judgment (including chart review); INSUR CL, Insurance Claims Database; Q, questionnaire.
SI, structured interview; UDS, urine drug screen; USI, unstructured interview.
Quality: possible range 0 to 8; higher scores indicate higher quality (quality criteria adopted from Chou et al.[13]).

### *3.3. Rates of opioid misuse and addiction*

Overall, sizeable variability in rates of both misuse and addiction was indicated across reviewed studies. Rates of abuse ranged from 0.08% to 81.0% and addiction rates ranged from 0.7% to 34.1% across all studies. For high-quality studies ($n$ = 13 for misuse and 10 for addiction), misuse rates ranged from 2.0% to 56.3% and addiction rates from 0.7% to 23.0%. For low-quality studies ($n$ = 16 for misuse and 2 for addiction), misuse rates

**Table 3**

**Opioid misuse—unweighted and weighted means, SDs, and 95% confidence interval (CI).**

| | Minimum, % | | Maximum, % | |
|---|---|---|---|---|
| | Mean (SD) | 95% CI | Mean (SD) | 95% CI |
| Unweighted | 28.1 (22.9) | 19.8-36.4 | 29.3 (22.5) | 21.1-37.5 |
| Weighted means | | | | |
| Sample size | 69.4 (19.1) | 62.4-76.4 | 69.5 (19.1) | 62.5-76.5 |
| Log sample size | 27.4 (24.5) | 18.5-36.3 | 28.4 (24.1) | 19.6-37.2 |
| Winsorized | 21.7 (24.2) | 12.9-30.5 | 22.6 (24.1) | 13.8-31.4 |
| Quality rating | 25.2 (18.9) | 18.3-32.1 | 26.4 (18.7) | 19.6-33.2 |
| Sample size × quality* | 23.8 (20.6) | 16.3-31.3 | 24.9 (20.4) | 17.5-32.3 |
| Quality | | | | |
| High-quality studies | 23.6 (16.4) | 14.7-32.5 | 24.5 (16.2) | 15.7-33.3 |
| Low-quality studies | 31.8 (31.2) | 16.5-47.1 | 33.2 (30.3) | 18.4-48.0 |

* Interaction term the product of standardized scores for the log-transformed sample size and quality rating.

ranged from 0.08% to 81.0% and for addiction from 8.4% to 34.1%.

**Table 3** and **Table 4** display means, SDs, and 95% CI calculations for misuse and addiction, respectively. Regarding the calculation methods used to evaluate average rates of misuse and addiction, most means (excluding means calculated by raw sample size weighting and low-quality studies) were within 8% of one another for misuse and within 3% of one another for addiction. Specifically, rates of misuse ranged from a minimum of 21.7% for the mean weighted by the Winsorized sample size to a maximum of 29.3% for the unweighted mean. Rates of addiction ranged from a minimum of 7.8% for the mean weighted by Winsorized sample size to a maximum of 11.7% for the unweighted mean. Calculation of 95% CI indicated an overall range across all methods of mean calculation of 12.9% to 37.5% for misuse and 3.2% to 17.3% for addiction.

Two mean calculation methods yielded means that were markedly different from the rest including means weighted by raw sample size and means of low-quality studies. Means weighted by raw sample size were approximately 69% for misuse and approximately 4% for addiction. For low-quality studies, means were approximately 32% for misuse and 23% for addiction. The 95% CI calculated for these 2 methods were also noticeably broader than those calculated using the other methods, overall range of 16.5% to 76.5% for misuse and 0.8% to 39.2% for addiction.

**Table 4**

**Opioid addiction—unweighted and weighted means, SD, and 95% confidence interval (CI).**

| | Minimum, % | | Maximum, % | |
|---|---|---|---|---|
| | Mean (SD) | 95% CI | Mean (SD) | 95% CI |
| Unweighted | 10.9 (9.8) | 5.3-16.5 | 11.7 (9.9) | 6.1-17.3 |
| Weighted means | | | | |
| Sample size | 4.3 (6.2) | 0.8-7.8 | 4.7 (6.5) | 1.0-8.4 |
| Log sample size | 10.1 (9.5) | 4.7-15.5 | 10.8 (9.6) | 5.4-16.2 |
| Winsorized | 7.8 (8.2) | 3.2-12.4 | 8.6 (8.3) | 3.9-13.3 |
| Quality rating | 10.5 (8.8) | 5.5-15.5 | 10.4 (8.9) | 5.4-15.4 |
| Sample size × quality* | 9.9 (8.7) | 5.0-14.8 | 10.7 (8.9) | 5.7-15.7 |
| Quality | | | | |
| High-quality studies | 8.8 (7.3) | 4.3-13.3 | 9.8 (7.8) | 5.0-14.6 |
| Low-quality studies | 23.1 (12.9) | 3.4-39.2 | 23.1 (12.9) | 3.4-39.2 |

*Interaction term the product of standardized scores for the log transformed sample size and quality rating.

### *3.4. Comparisons of study design, diagnostic method, and clinical setting*

As noted, because the studies identified for data extraction were quite varied regarding their characteristics, we examined rates of misuse and addiction across studies regarding primary study purpose, study design, assessment method used to identify problematic behavior, and clinical setting. For each of these 4 variables, 4 ANOVAs were conducted (minimum/maximum; misuse/addiction). A Bonferroni correction was used for all pairwise comparisons to help control against the commission of a type I error.

Across all analyses, results indicated only 1 significant difference in relation to study characteristics. Specifically, mean unweighted rates of opioid addiction were lower in the 7 studies that identified the assessment of prevalence as the primary study objective, minimum/maximum mean = 5.5%/6.2% (SD = 4.6%/6.2%; 95% CI = 2.1%-10.8%), in comparison with 5 studies for which prevalence assessment was a secondary objective, minimum/maximum mean = 18.4%/19.4% (SD = 10.7%/9.4%; 95% CI = 9.0%-27.6%), all $F > 8.3$, all $P < 0.02$.

For opioid misuse, 11 studies (37.9%) identified the assessment of prevalence as the primary study aim and 18 studies (62.1%) as a secondary aim. No significant differences were indicated in average rate of misuse across studies, all $F \leq 2.7$, all $P \geq 0.11$.

All other comparisons did not indicate any significant differences in relation to the additional study characteristics evaluated. Specific findings are detailed in the following paragraphs and descriptive information is provided in **Table 5**.

Regarding study design, of the 38 studies reviewed, 39.5% were prospective, 34.2% were cross-sectional, and 26.3% were retrospective. No significant differences were indicated by any of the analyses comparing rates of misuse and addiction with design, all $F \leq 1.0$, all $P \geq 0.37$.

The assessment method used also varied substantially across studies with the majority, 64.9%, using only a single assessment method (questionnaire: 21.6%, clinical judgment/chart review: 21.6%; structured/semistructured interview: 13.5%; UDS: 8.1%). The remaining 35.1% of studies used a UDS plus at least 1 other method, which were coded as a single assessment category

**Table 5**

**Descriptive information regarding comparisons of study design, diagnostic method, and clinical setting.**

| | Misuse, % | | Addiction, % | |
|---|---|---|---|---|
| | Minimum (SD) | Maximum (SD) | Minimum (SD) | Maximum (SD) |
| Study design | | | | |
| Prospective | 23.6 (17.0) | 24.8 (17.0) | 19.5 (20.6) | 19.5 (20.6) |
| Cross-sectional | 37.2 (34.0) | 38.2 (33.0) | 9.1 (9.4) | 10.0 (10.3) |
| Retrospective | 25.0 (10.7) | 26.2 (11.0) | 9.1 (5.2) | 10.2 (4.9) |
| Method of assessment | | | | |
| Questionnaire | 38.2 (35.9) | 38.3 (35.9) | 2.8 (3.0) | 2.8 (3.0) |
| Clinical judgment | 17.9 (7.9) | 19.3 (9.7) | 13.0 (7.6) | 15.4 (6.9) |
| (Semi-) Structured interview | 11.0 (—) | 11.0 (—) | 5.8 (4.9) | 5.8 (4.9) |
| Urine drug screen (UDS) | 29.0 (39.9) | 32.0 (37.3) | — | — |
| Multiple methods (including UDS) | 29.0 (22.8) | 30.2 (22.3) | 10.9 (9.8) | 11.7 (10.0) |
| Setting | | | | |
| Primary care | 28.3 (26.5) | 30.2 (25.7) | 10.8 (9.3) | 10.8 (9.3) |
| Pain clinic | 28.3 (14.8) | 29.6 (14.1) | 15.1 (11.8) | 16.1 (11.9) |

(ie, UDS plus at least one other method). The misuse comparisons were nonsignificant, all $F \leq 0.71$, all $P \geq 0.59$. For addiction, although comparisons of questionnaire and structured/semistructured interviews with multiple assessment methods reached a traditional level of significance, $P < 0.05$, the follow-up Bonferroni-controlled pairwise comparisons were not significant.

Finally, for evaluations involving clinical setting, 52.6% of studies involved data collected within a specialty chronic pain clinic with an additional 26.3% of data collected in primary care. Of the remaining studies, the clinical setting from which the data were collected was not clearly identified (eg, clinical trials registry; toxicology laboratory). Given the diversity in clinical setting, comparisons used only data from pain clinics and primary care. Consistent with the other analyses of study characteristics, no significant differences were indicated, all $F \leq 0.52$, $P \geq 0.49$.

## 4. Discussion

Accurate identification and enumeration of problematic opioid use in those with chronic pain is important. Our review evaluated the current state of the literature regarding rates of opioid misuse, abuse, and addiction in chronic pain. The results are concordant with previous work in many ways. Chiefly, the substantial variability in studies evaluating problematic opioid use remains apparent as there were many designs used, methods of identification used, and study settings examined. The range of rates of problematic use was even broader than that has been reported in previous work[24,38] with rates ranging from 0.08%[52] to 81%.[62]

We took several steps within the review to address this expected variability. First, we coded for specific types of problematic use by adopting the definitions offered by the IMMPACT and ACTTION groups.[44,53] In the order of severity, these types were: misuse (use not in accordance with prescribed directions, regardless of the presence or absence of harm resulting from use), abuse (intentional use for a nonmedical purpose), and addiction (use demonstrated harm or high potential for harm). In total, 38 articles were included in the full review, with 76% providing information on misuse and 32% providing information on addiction. Only a single study reported on abuse. Although the rates of misuse encompassed the entire range documented (ie, 0.08%-81%), the range for rates of addiction was somewhat more constrained, 0.7% to 34.1%.

Second, we calculated several weighted means and also separate means for high- and low-quality studies, with the overall goal of determining whether a subset of these scores would provide a degree of confidence with the rates identified. With the exception of means weighted by sample size and means for low-quality studies, which were particularly different than other means calculated, there appeared a level of concordance across the majority of mean calculations. On average, misuse was documented in approximately 1 of 4 or 5 patients (actual mean percentage range: 21.7%-29.3%) and addiction in approximately 1 of 10 or 11 patients (actual mean percentage range: 7.8%-11.7%). Perhaps the 2 most robust calculation methods were the sample size by study-quality interaction term and the mean of the high-quality studies only. For these 2 methods, rates of misuse ranged from 23.6% to 24.9% and rates of addiction from 8.8% to 10.7%. Furthermore, the observed SD for the high-quality studies was approximately half of that observed for the low-quality studies and two-thirds of that observed across all other calculations, suggesting a lesser degree of variability among these studies, and therefore perhaps bolstering confidence to some degree in the accuracy of these values.

Third and finally, we examined whether differences in study results could be at least partially explained by variability in the study methods that were used. Almost all comparisons based on study characteristics indicated a lack of significant differences regarding rates of abuse and addiction across different study designs, methods of assessment, and clinical settings (specialty pain clinic vs primary care). Only a single statistically significant difference was indicated between studies with a primary purpose of assessing addiction prevalence and those that assessed it as a secondary purpose such that lower rates of addiction were indicated in studies specifically designed to assess prevalence. As these analyses were likely underpowered because small cell sizes and the ranges analyzed were broad, these results ought to be interpreted cautiously, and we include them here to primarily provide information of potential use to future studies in this area.

We can make several recommendations for future studies of problematic opioid use in chronic pain. First, studies must specify the relevant demographic and pain-related details. At a minimum, we suggest that these include gender, age, and ethnicity, as well as pain location and duration. These details were included in a surprisingly small number of studies despite their demonstrated relevance in treatment response and role in the potential for problematic opioid use.[24] The inclusion of measures of pain intensity and interference would likely provide valuable additional information. Second, there is likely a benefit to be found in specifying type of problematic use that is being assessed and specifically designing studies to evaluate prevalence as a primary objective. Such specification may aid in decreasing variability across studies regarding rates of problematic use and perhaps also have the added benefit of allowing for greater precision in the language used in relation to patterns of opioid use in chronic pain. Third, at present, there is no clear gold standard for use in the identification of misuse, abuse, and addiction.[48] Perhaps the most thorough method is the Aberrant Drug Behavior Index (ADBI) used by Butler et al.[10] The ADBI involves a triangulation approach consisting of self-reported patterns of opioid use evaluated by a structured interview, physician-reported patterns of use, and a UDS. A positive ADBI, indicating the presence of problematic opioid use, consisted of either a positive rating on the structured clinical interview or positive ratings on both the physician report and UDS. In this review, this triangulation method was coded as indicating misuse, but it seems feasible to modify it so that it also provides information regarding abuse and addiction.

The results of this review have 2 key implications. First, misuse and addiction do seem to be distinct patterns of problematic opioid use, at least based on the definitions used here and the differences in observed mean rates between them. Second, misuse seems more common than addiction. Several types of misuse were identified within studies and included underuse, erratic or disorganized use, inappropriate use (eg, to manage symptoms of anxiety or other sorts of distress), use in conjunction with alcohol or illegal substances (eg, marijuana), and, of course, overuse. If it is accurate that approximately 1 in 4 patients on opioids display patterns of opioid misuse, but not addiction, then perhaps more efficient targeting of treatment resources would be of benefit. Some forms of misuse, for example, may be readily addressed through relatively low-intensity methods such as education or frequent follow-up visits. One prominent example of a fairly low-intensity intervention is that of Jamison et al.,[28] who held monthly meetings with patients deemed to be at "high risk" of opioid misuse. These meetings were a combination of motivational approaches, opioid education, and opioid use monitoring, including a UDS, held monthly over the course of 6 months. At the conclusion of the study period, the documented

rates of aberrant behavior was low and comparable to rates documented for another group of patients, who were deemed to be of "low risk" of opioid misuse at the onset of the study. These findings suggest that there are alternatives available to providers who treat high-risk patients beyond simply not prescribing the medications at all. A more recent study from the same group[37] further highlights a potential key role of cravings in opioid misuse, which presents another option for intervention given that the substance abuse literature already provides effective interventions directed at altering the impact of drug cravings more generally, and these could perhaps be readily adapted to problematic opioid use.[7,63,64]

The results of this review have several limitations. The most obvious is the degree of variability within this literature. In spite of our attempts to minimize the impact of this variability, the range of misuse and addiction was incredibly broad, as were measures of dispersion. Furthermore, there are other potential sources of variability in findings that were not possible to code and extract in a uniform manner. These include duration of opioid use, history of nonopioid substance misuse, abuse, or addiction, dosage levels and frequency of use, as well as health care system variables, such as frequency of prescription reviews, drug testing, or use of opioid "contracts." These sources of variability will likely continue to cloud our ability to make precise estimates. There is clearly room here for a series of carefully controlled studies where sources of variability are held constant, or as constant as possible, to more clearly illuminate prevalence rates of problematic opioid use in individuals with chronic pain.

There was 1 curious finding that we have not yet emphasized. The overwhelming majority of studies within this review took place in the United States. Only 3 of the 38 studies took place in other countries, which suggests that this issue is of both high interest and is perhaps a problem that is somehow uniquely relevant to the US. The latter interpretation is supported by the finding of Manchikanti et al.[31] indicating that the US population, which represents approximately 5% of the Earth's population, consumed approximately 80% of the global supply of prescribed opioids in the first decade of this century. This is an intriguing issue and although there are likely many factors involved, neither the abundance of opioids prescribed for the treatment of chronic pain nor the large proportion of studies of problematic opioid use seem to have helpfully diminished the prevalence, impact, or cost of chronic pain in the US since the explosion in opioid use for chronic pain.[22]

One final, related, comment on the use of opioids in chronic pain seems appropriate. In short, it is not clear whether the risks of opioid use outweigh the potential for benefit. The efficacy of opioids and their suitability for the long-term management of chronic pain still remain very much in question[3,4,13,51,54,55] and while this uncertainty in effectiveness is well established, it stands in somewhat stark contrast to the clinical reality of chronic pain treatment, where rates of prescriptions have skyrocketed such that opioids are now among the most frequently prescribed medications. What does seem clear, however, is that the rapid increase in opioid use has had what Sullivan[54] referred to as "unintended" consequences that, for at least some patients, require an additional form of intervention to curtail patterns of problematic use and potential for harm. We are not certain whether the benefits derived from opioids, which are rather unclear based on the extant literature, compensate for this additional burden to patients and health care systems.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

This research was supported by a grant from the Center for Health Policy at the Robert Wood Johnson Foundation to the first and last authors.

## Acknowledgements

The authors thank Dr Robert Valdez for his insightful and helpful comments on a previous version of this report.

**Article history:**
Received 13 May 2014
Received in revised form 27 December 2014
Accepted 29 December 2014

## References

[1] Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll SH, Senay EC, Woody GE. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage 2006; 31:465–76.
[2] Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioids analgesics from 2004 to 2011. Pain Physician 2014;17:E119–28.
[3] Ballantyne JC. Is lack of evidence the problem? J Pain 2010;11:830–2.
[4] Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. Clin J Pain 2008;24:469–78.
[5] Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain—development of a typology of chronic pain patients. Drug Alcohol Depend 2009;104:34–42.
[6] Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med 2011;12:657–67.
[7] Bowen S, Chawla N, Marlatt GA. Mindfulness-based relapse prevention for addictive behaviors: a clinician's guide. New York, NY: Guilford Press, 2010. p. 179.
[8] Brown J, Setnik B, Lee K, Wase L, Roland CL, Cleveland JM, Siegel S, Katz N. Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. J Opioid Manag 2011;7:467–83.
[9] Butler S. The IMMPACT factor or IMMPACT strikes again! Pain 2013;154: 2243–4.
[10] Butler SF, Budman SH, Fanciullo GJ, Jamison RN. Cross validation of the Current Opioid Misuse Measure (COMM) to monitor chronic pain patients on opioid therapy. Clin J Pain 2010;26:770–6.
[11] Butler SF, Budman SH, Fernandez K, Jamison RN. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain 2004;112:65–75.
[12] Chelminski PR, Ives TJ, Felix KM, Prakken SD, Miller TM, Perhac JS, Malone RM, Bryant ME, DeWalt DA, Pignone MP. A primary care, multidisciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. BMC Health Serv Res 2005;5:3.
[13] Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. J Pain 2009;10:131–46.
[14] Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement non-compliance. J Pain Symptom Manage 2008;36:383–95.
[15] Couto JE, Romney MC, Leider HL, Sharma S, Goldfarb NI. High rates of inappropriate drug use in the chronic pain population. Popul Health Manag 2009;12:185–90.
[16] Cowan DT, Wilson-Barnett J. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med 2003;4:340–51.
[17] Edlund MJ, Martin BC, Fan M, Devries A, Braden JB, Sullivan MD. Risks of opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. Drug Alcohol Depend 2010;112:90–8.
[18] Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? Pain Med 2007;8:647–56.
[19] Federal Drug Administration. Attention prescribers: FDA seeks your help in curtailing the US opioid epidemic. 2013:1–5. Available: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm330614.htm. Accessed 13 May, 2014.

[20] Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain 2007;8:573–82.
[21] Fleming MF, Davis J, Passik SD. Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. Pain Med 2008;9:1098–106.
[22] Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain 2012;13:715–24.
[23] Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. Eur J Pain 2010;14:1014–20.
[24] Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. Eur J Pain 2007;11:490–518.
[25] Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, Shilliday BB, DeWalt DA, Pignone MP. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. BMC Health Serv Res 2006;6:46.
[26] Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender differences in risk factors for aberrant prescription opioid use. J Pain 2010;11:312–20.
[27] Jamison RN, Link CL, Marceau LD. Do pain patients at high risk for substance misuse experience more pain? A longitudinal outcomes study. Pain Med 2009;10:1084–94.
[28] Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: a randomized trial. Pain 2010;150:390–400.
[29] Katz NP, Sherburne S, Beach M, Rose RJ, Vielguth J, Bradley J, Fanciullo GJ. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg 2003;97:1097–102.
[30] Manchikanti L, Cash KA, Damron KS, Manchukonda R, Pampati V, McManus CD. Controlled substance abuse and illicit drug use in chronic pain patients: an evaluation of multiple variables. Pain Physician 2006;9: 215–26.
[31] Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. Pain Physician 2010;13:401–35.
[32] Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, Grider JS, Boswell M V. Opioid epidemic in the United States. Pain Physician 2012; 15:ES9–E38.
[33] Manchikanti L, Manchukonda R, Damron KS, Brandon D, McManus CD, Cash K. Does adherence monitoring reduce controlled substance abuse in chronic pain patients? Pain Physician 2006;9:57–60.
[34] Manchikanti L, Manchukonda R, Pampati V, Damron KS. Evaluation of abuse of prescription and illicit drugs in chronic pain patients receiving short-acting (hydrocodone) or long-acting (methadone) opioids. Pain Physician 2005;8:257–61.
[35] Manchikanti L, Pampati V, Damron KS, Beyer CD, Barnhill RC, Fellows B. Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. J Ky Med Assoc 2003;101:511–17.
[36] Manchikanti L, Pampati V, Damron KS, Fellows BM, Barnhill RC, Beyer C. Prevalence of opioid abuse in interventional pain medicine practice settings: a randomized clinical evaluation. Pain Physician 2001;4:358–65.
[37] Martel MO, Dolman AJ, Edwards RR, Jamison RN, Wasan AD. The association between negative affect and prescription opioid misuse in patients with chronic pain: the mediating role of opioid craving. J Pain 2014;15:90–100.
[38] Martell B, O'Connor P, Kerns R, Becker W, Morales K, Kosten T, Fiellin D. Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann Intern Med 2007;146:187–92.
[39] Meltzer EC, Rybin D, Meshesha LZ, Saitz R, Samet JH, Rubens SL, Liebschutz JM. Aberrant drug-related behaviors: Unsystematic documentation does not identify prescription drug use disorder. Pain Med 2012;13:1436–43.
[40] Meltzer EC, Rybin D, Saitz R, Jeffrey H, Schwartz SL, Butler SF, Jane M. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). Pain 2011;152:397–402.
[41] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Br Med J 2009;339:332–6.
[42] Morasco BJ, Dobscha SK. Prescription medication misuse and substance use disorder in VA primary care patients with chronic pain. Gen Hosp Psychiatry 2008;30:93–9.
[43] Naliboff BD, Wu SM, Schieffer B, Bolus R, Pham Q, Baria A, Aragaki D, Van Vort W, Davis F, Shekelle P. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain 2011;12:288–96.
[44] O'Connor AB, Turk DC, Dworkin RH, Katz NP, Colucci R, Haythornthwaite J A, Klein M, O'Brien C, Posner K, Rappaport BA, Reisfield G, Adams EH, Balster RL, Bigelow GE, Burke LB, Comer SD, Cone E, Cowan P, Denisco RA, Farrar JT, Foltin RW, Haddox JD, Hertz S, Jay GW, Junor R, Kopecky EA, Leiderman DB, McDermott MP, Palmer PP, Raja SN, Rauschkolb C, Rowbotham MC, Sampaio C, Setnik B, Smith SM, Sokolowska M, Stauffer JW, Walsh SL, Zacny JP. Abuse liability measures for use in analgesic clinical trials in patients with pain: IMMPACT recommendations. Pain 2013;154:2324–34.
[45] Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. J Pain Symptom Manage 2011;41:116–25.
[46] Portenoy RK, Farrar JT, Backonja MM, Cleeland CS, Yang K, Friedman M, Colucci S V, Richards P. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain 2007;23:287–99.
[47] Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 2002;17:173–9.
[48] Savage SR. Assessment for addiction in pain-treatment settings. Clin J Pain 2002;18:S28–38.
[49] Schneider JP, Kirsh KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. J Opioid Manag 2010;6:385–95.
[50] Sekhon R, Aminjavahery N, Davis CN, Roswarski MJ, Robinette C. Compliance with opioid treatment guidelines for chronic non-cancer pain (CNCP) in primary care at a Veterans Affairs Medical Center (VAMC). Pain Med 2013;14:1458–556.
[51] Sites BD, Beach ML, Davis MA. Increases in the use of prescription opioid analgesics and the lack of improvement in disability metrics among users. Reg Anesth Pain Med 2014;39:6–12.
[52] Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? Pain 2011;152:1555–61.
[53] Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, Degroot A, Edwards RR, Haddox JD, Jaffe JH, Jones CM, Kleber HD, Kopecky EA, Markman JD, Montoya ID, O'Brien C, Roland CL, Stanton M, Strain EC, Vorsanger G, Wasan AD, Weiss RD, Turk DC, Dworkin RH. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain 2013;154:2287–796.
[54] Sullivan M. Clarifying opioid misuse and abuse. Pain 2013;154:2239–40.
[55] Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, Patel S, Manchikanti L. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. Pain Physician 2008;11:S5–S62.
[56] 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 health outcome. 2011 Available at: www.unodc.org/docs/treatment/Pain/Ensuring_availability_of_controlled_medications_FINAL-15_March_CND_version.pdf. Accessed 1 March 2014
[57] Vaglienti RM, Huber SJ, Noel KR, Johnstone RE. Misuse of prescribed controlled substances defined by urinalysis. WV Med J 2003;99:67–70.
[58] Volkow ND, McLellan TA, Cotto JH, Marithanom M, Weiss RRB. Characteristics of opioid prescriptions in 2009. J Am Med Assoc 2011; 305:1299–300.
[59] Wasan AD, Butler SF, Budman SH, Fernandez K, Weiss RD, Greenfield SF, Jamison RN. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? Clin J Pain 2009;25:193–8.
[60] Webster LR, Fine PG. Approaches to improve pain relief while minimizing opioid abuse liability. J Pain 2010;11:602–11.
[61] Webster LR, Webster RM. Predicting aberrant behaviors opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med 2005;6: 432–43.
[62] Wilsey BL, Fishman SM, Tsodikov A, Ogden C, Symreng I, Ernst A. Psychological comorbidities predicting prescription opioid abuse among patients in chronic pain presenting to the emergency department. Pain Med 2008;9:1107–17.
[63] Witkiewitz K, Bowen S. Depression, craving, and substance use following a randomized trial of mindfulness-based relapse prevention. J Consult Clin Psychol 2010;78:362–74.
[64] Witkiewitz K, Bowen S, Donovan DM. Moderating effects of a craving intervention on the relation between negative mood and heavy drinking following treatment for alcohol dependence. J Consult Clin Psychol 2011; 79:54–63.
[65] Wu SM, Compton P, Bolus R, Schieffer B, Pham Q, Baria A, Van Vort W, Davis F, Shekelle P, Naliboff BD. The addiction behaviors checklist: validation of a new clinician-based measure of inappropriate opioid use in chronic pain. J Pain Symptom Manage 2006;32:342–51.