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OTHER PAIN (A. KAYE AND N. VADIVELU, SECTION EDITORS)

# Oxycodone's Unparalleled Addictive Potential: Is it Time for a Moratorium?

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## Abstract

**Purpose of Review** This study and literature review were carried out to investigate whether oxycodone is the most addictive prescription opioid.

**Recent Findings** This was a cross-sectional survey from a pain management practice in south-central Alaska and review of the literature involving 86 patients diagnosed with opioid dependence/opioid use disorder from 2013 to 2018. Patients were given a list of prescription opioids and asked to identify the one (1) most desirable to themselves, (2) most desirable among drug-using associates or community, and (3) they deemed most addictive. Patients with a history of heroin use were asked which, if any, served as their gateway drug to heroin. The literature was reviewed using a PubMed search for articles containing the words "oxycodone" and "abuse," "addiction," "dependence," "disorder," and "euphoria." Oxycodone was ranked most highly in all four questions ($n = 50$, 60.2%; $n = 46$, 75.4%; $n = 38$, 60.2%; $n = 14$, 77.8%, respectively) by a wide margin.

**Summary** Numerous observational studies performed over the past few decades have demonstrated the supreme "likability" and abuse and dependence liability/addictiveness of oxycodone, with more recent mechanistic studies illuminating biological underpinnings including markedly increased active transport across the blood-brain barrier, increased phasic dopaminergism in the ventral tegmental area, nucleus accumbens and related striatal reward centers, and possibly increased kappa opioid receptor-mediated withdrawal dysphoria. Oxycodone possesses pharmacologic qualities that render it disproportionately liable to abuse and addiction and the risks of any long-term prescription outweigh the benefits.

**Keywords** Oxycodone · Heroin · Addiction · Dependence · Active transport · Phasic dopamine

## Introduction

> We find the risk of addiction [to oxycodone] greater than that attributed to morphine … We do not recommend the use of oxycodone continued past the initial phases of treatment for pain. – LM Halpern and JJ Bonica, 1976 [1]

Oxycodone is believed to be the most addictive prescription opioid and the primary gateway to heroin. In this manuscript, we present self-reported patient data from our practice as well as nationwide data and basic science published previously to support those claims.

Oxycodone was first synthesized in 1916, ironically in an attempt to provide a potent opioid analgesic devoid of the dependence and abuse liability issues plaguing heroin, previously marketed as an analgesic [2]. The compound itself was introduced into America in 1939 followed by combination products with salicylate and acetaminophen over the next three decades, and ultimately, an extended-release product (OxyContin®) was released in 1996 by Purdue Pharma.

Over the past two decades, oxycodone has become the opioid with the largest increase in distribution by volume

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and number of prescriptions [3]. At the risk of oversimplification, it is widely accepted that from a pharmacologic standpoint, OxyContin® was the agent responsible for the genesis of the American opioid epidemic which began in Appalachia [4–6]. This phenomenon has been attributed in part to aggressive marketing by the manufacturer in a ripe pyscho-socio-economic climate, which undoubtedly played a role, but it is also generally acknowledged that the relatively easily circumvented time-release mechanism of the formulation lent itself to instant delivery of huge quantities of opioid via crushing and snorting or injecting. And yet, extended-release morphine tablets and capsules, some with dose equivalence greater than OxyContin® 30 or 40 mg have been around longer, and at a significantly reduced price point; why then, has not MS Contin® or Kadian® enjoyed the same notoriety and popular demand?

Any methodology besides natural experiment to investigate these questions would be unconscionable in the face of our current knowledge of the consequences of such manipulation, and as such, we are relying upon observational data from our own practice and the literature over the past two decades. Relevant bench research and/or animal data are utilized in the present investigation. This brief pharmacologic excursion is followed by a strategic-level appeal to rethink whether or not oxycodone should occupy a place in our current formulary of analgesics. Tactical-level suggestions for replacing it in clinical practice with less problematic alternatives (e.g., when opioid analgesia is warranted) are also discussed.

## Methods

A survey of various prescription opioid abuse and addiction liability indices was conducted among 113 patients in our practice treated between 2013 and 2018 with a diagnosis of opioid use disorder/dependence (ICD 10 code F11.20 series and ICD 9 code 304.0 series.) There were 86 respondents, but not all patients answered all of the questions, or in some cases, provided meaningless data (e.g., multiple answers to a single question) in which case no data were recorded.

Participants were stratified into two groups: those who exclusively abused non-heroin opioids enterally, and those who injected opioids including (and primarily) heroin. Demographic data on the two groups are presented in Table 1. The vast majority of participants ($n = 66$; 76.7% of sample) were participating in a buprenorphine medication-assisted treatment (MAT) program or were being treated for chronic pain using buprenorphine.

Participants were presented with a list of commonly prescribed oral prescription opioids (e.g., hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol), excluding rarely prescribed, and weaker agents (e.g., butorphanol, codeine, meperidine, nalbuphine, pentazocine, tramadol), or those with a non-enteral vehicle (e.g., buprenorphine, fentanyl.) Three simple questions designed to communicate the universally understood/accepted concepts of likeability and addiction while attempting to avoid incrimination or "turn-off" were asked. The first question was "Which of these is the most desirable to you?" They were also asked "Which of these is the most desirable in the drug-using community you know?" The authors deliberately chose the term "desirable" rather than "likeable" or "enjoyable" to try to capture the essence of both perceived therapeutic (analgesic) benefit as well as hedonic reward. Patients were also asked "Which of these is the most addictive?" Finally, patients with a history of heroin use were asked "Which was your gateway drug to heroin?"

In addition, the MEDLINE database was searched for articles containing the words "oxycodone" and "abuse," "addiction," "dependence," "disorder," and "euphoria." Select relevant articles from this search and other basic science articles pertinent to the unique pharmacology of oxycodone are presented within the "Results and Literature Review" section.

**Table 1** Demographic and clinical information for participants

| Mean age | | 43 years |
|---|---|---|
| Gender | Female | 54 (62.8%) |
| | Male | 32 (36.2%) |
| Chief complaint: | Pain | 33 (38.4%) |
| | OUD | 53 (61.6%) |
| Heroin use | Yes | 34 (39.5%) |
| | No | 52 (60.5%) |
| Buprenorphine MAT or pain treatment | Yes | 66 (76.7%) |
| | No | 20 (23.3%) |
| Tobacco use | Yes | 68 (79.1%) |
| | No | 18 (20.9%) |
| Other drug use | Yes | 51 (59.3%) |
| | No | 35 (40.7%) |
| Payer | Government (non-DoD) | 52 (59.3%) |
| | Private Insurance (including DoD) | 29 (33.7%) |
| | Self | 5 (5.8%) |

*OUD* opioid use disorder, *MAT* medication-assisted treatment

## Results and Literature Review

Of 113 patients with a diagnosis of opioid dependence or opioid use disorder, 86 provided data for this study. The mean age of participants was 43 years. There were 54 (62.8%) females and 32 (36.2%) males. The chief complaint for 53 (61.6%) of the patients was opioid use disorder, with 33 (38.4%) presenting with a pain complaint. Sixty-six (76.7%)

were receiving buprenorphine for either medication-assisted treatment of opioid use disorder or for chronic pain. Sixty-eight (79.1%) of patients used tobacco products, and 20 (20.9%) used other drugs by report or by urine drug screening. Fifty-two (59.3%) of patients presented with government-provided health insurance (Medicare, Medicaid, or Veterans Administration); 29 (33.7%) had private insurance including TRICARE; and 5 (5.8%) had no health insurance. Results from the survey are shown in graphic form in Fig. 1, and are discussed below, question by question.

## Question #1a and 1b: Which Is the Most Desirable Prescription Opioid?

There were 83 valid, i.e., singular/discrete responses to the first question, i.e., "which is the most desirable prescription opioid to you?" The prescription opioid rated most desirable by the largest number of study participants was oxycodone (60.2%, $n = 50$) followed by hydrocodone (16.9%, $n = 14$) with hydromorphone and methadone tied for third place (9.6%, $n = 8$.)

There were 61 valid, i.e., singular/discrete responses to the second question, i.e., "which do you think is the most desirable prescription opioid among people you know who use opioids or among the general drug-using populace?" The prescription opioid rated most desirable among drug-using peers/associates or the general drug-using populace by the largest number of study participants was oxycodone (75.4%, $n = 46$) followed by hydromorphone (11.5%, $n = 7$) with methadone in third place (6.6%, $n = 4$.)

The pharmacokinetics and biology of oxycodone's active CNS transport (and phasic striatal activity discussed below) may undergird and predict reward and desirability. Increased presentation of a highly euphorigenic substance to hedonic reward processing centers within the brain is related to increased abuse potential [7] and oxycodone possesses disproportionate access to the CNS, both in terms of rate and residence. Animal studies show increased cerebral/plasma concentration ratios [8, 9•, 10, 11•, 12] and increased blood-brain barrier permeability with various active transport mechanisms demonstrated both in vitro and in vivo have been invoked to explain these findings.

There has been some speculation as to the contribution of oxycodone's more potent active metabolite oxymorphone to its analgesia and abuse/dependence liability. The hepatic CYP2D6 enzyme is responsible for this conversion, and it has been proposed that phenotypic variability in this enzyme's efficiency/activity may confer increased (or decreased) analgesic efficacy of oxycodone [13, 14]. It appears, however, that the parent compound is responsible for the vast majority of analgesic effect [8, 15], and head-to-head comparison studies between the two agents show considerably less CNS effect and abuse liability for oxymorphone as discussed below [16, 17]. Larger investigations [18, 19] have also revealed that there is no clinically significant effect of these polymorphisms.

The literature corroborates oxycodone's place as the drug of choice for the majority of prescription opioid abusers. Among their many other publications examining abuse liability and abuse-related factors of various drugs, Zacny et al. published a series of National Institute of Drug Abuse-funded studies in the previous decade comparing likeability/abuse liability of oxycodone to other opioids, all of which showed increased problematic potential for oxycodone. The four published studies all utilized non-opioid abusing persons, with sample sizes ranging from 16 to 20 individuals [20–23]. All were double-blinded, placebo-controlled crossover trials comparing subjective/experiential and objective/physiologic effects of oxycodone to what were judged to be equipotent doses of morphine or hydrocodone based upon current literature consensus and also degree of miosis observed in the subjects. Both local institution-developed assessment tools as

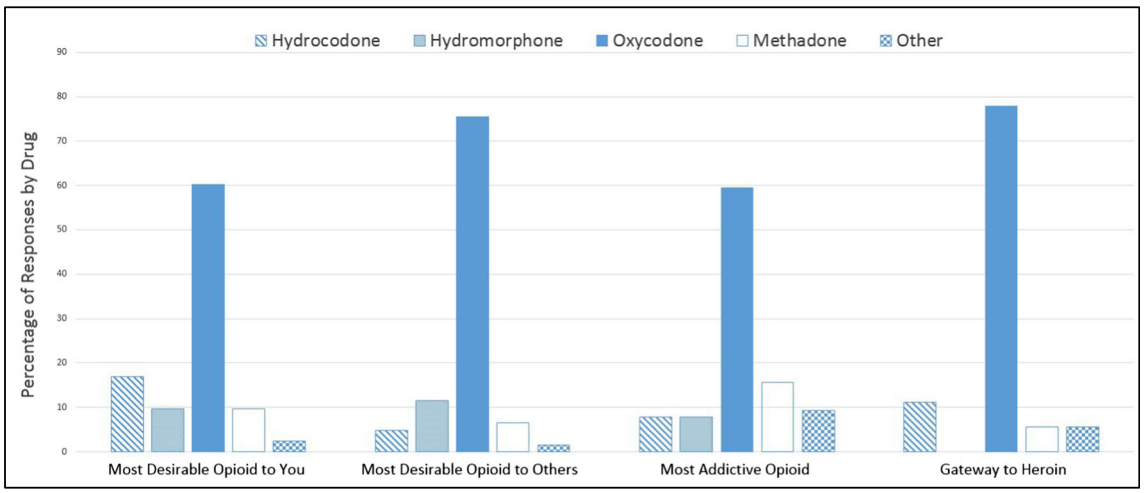


**Fig. 1** Prescription opioid desirability and addictive potential ratings by participants

well as a short-form version of the Addiction Research Center Inventory (ARCI) were used to collect outcome data. In all four trials, participants reported notably greater scores of subjective psychological reward (e.g., "dreamy," "elated," "high," "sedated [calm, tranquil]", liking the drug and desiring it again) during estimated peak plasma oxycodone levels compared to alternate opioid or to placebo. Interestingly, during trough levels, drug-liking and desiring it again were notably lower for oxycodone compared to morphine or hydrocodone.

Comer et al. in 2008 [24] studied eight heroin-dependent individuals who were maintained on oral morphine at 120 mg/day for the duration of their study, and who also received intravenous buprenorphine, fentanyl, heroin, morphine, and oxycodone. While no significant differences in positive/reward indices among these opioids were shown in this small sample, the authors noted that oxycodone provided some of the most robust likability ratings and no negative ratings, which prompted the warning that this imbalanced reward to adverse effect ratio may confer disproportionate abuse liability for oxycodone. They relayed also that "our research finding is consistent with verbal reports from heroin-dependent individuals, who have stated that oxycodone is the 'Rolls Royce' of opioids and that it produces a 'smooth' high."

Using a then-novel approach, Katz et al. in 2008 reported results of an Internet-based survey assaying non-medical use of prescription opioids via a 111-question survey posted on the Erowid.org website [25]. They reported significantly higher relative nonmedical use rate with oxycodone products vs. hydrocodone or morphine products in the 896 participants, and furthermore reported that the agents most frequently reported as enjoyed the most or designated "favorite" were: OxyContin (41.7%), Dilaudid (13.9%), fentanyl (8.3%), generic oxycodone (5.6%), Vicodin (5.6%), methadone (5.6%), and Actiq (5.6%).

Cicero et al. [26••] surveyed 1818 prescription opioid-dependent patients entering drug treatment programs in various parts of the country to determine the desirability of opioid drugs with the hypothesis that discrepancy may exist between drug desired and drug used, based upon practical considerations such as accessibility and safety. While oxycodone was the most commonly listed "primary drug" abused most frequently by roughly 40% of this sample (compared to hydrocodone at around 30%), its place as most desirable drug was even more pronounced, with over 50% of the sample listing it as their preferred drug. Hydrocodone and heroin followed in this category at less than 25% each. The authors provided corroboration of these findings in a second survey published in 2013 [27•]; among 3520 opioid-dependent patients entering treatment around the country, oxycodone was the leading drug in terms of primary use and also preference (45% and 56%, respectively) with hydrocodone following at 29% and 19%, respectively. The authors also reported that among primary hydrocodone abusers, 70% would prefer to use oxycodone were it accessible. Osgood et al. in 2012 published the disturbing results of a youth survey focusing on immediate-release oxycodone products [28]. Participants were enrolled in (or recent graduates of) "recovery high schools"; 24 youth completed the survey, and 96% had abused oxycodone. 56% of respondents designated oxycodone as their preferred drug, and of those, 39% chose immediate-release oxycodone products. When stratified by amount typically consumed (with intranasal and oral routes being the most common), at doses less than 100 mg, there was no material difference in terms of extended-release vs. immediate release abuse patterns; only at or above 100-mg doses did extended-release abuse significantly exceed immediate-release product abuse. In a follow-up study published in 2016 [29], 31 youth participated in a survey investigating relationships between prescription opioid abuse, addiction, and transition to heroin use. The authors report that oxycodone products (IR or ER) were the most common initiating opioids of abuse, but these data are not presented clearly. Among opioids abused by the cohort, oxycodone products were consumed by the majority (97% of students abused oxycodone IR, followed by codeine in second place at 71%, hydrocodone at 68%, and oxycodone ER at 55%.) The group was then stratified into categories of prescription opioid abuse, addiction, and heroin use; in all three categories, oxycodone products were the favored/preferred drug (by 55% of abusers, 61% of those categorized as addicted, and 80% of those who used heroin.)

In 2015, Setnik et al. published data from 174 Canadian and 80 American recreational opioid users completing a survey on prescription opioid abuse potential [30]. Among Americans, the most frequently abused prescription opioid (used with recreational intent) was hydrocodone at 91% followed by oxycodone at 85%; in Canada, oxycodone abuse was far more prevalent at 94% of the sample followed by codeine at 59%. When asked, however, which opioid participants enjoyed the most, oxycodone was the leader in both countries: 75% of American opioid abusers preferred oxycodone (compared to 60% reporting hydrocodone; the results evidently did not require exclusivity as they total greater than 100%) whereas 88% of Canadian abusers preferred oxycodone (with codeine a distant second at 21%.)

Numerous patients dependent upon oxycodone readily admit that the drug confers unique energy and even a sense of "invincibility" which is corroborated in the literature [31, 32]. Many reports exist both within the literature [33–35] and by anecdotal report from tens of thousands (based on extrapolation from our clinic sample) bearing witness to the relatively side effect-free experience abusers enjoy until withdrawal dysphoria and other central nervous withdrawal symptoms are elicited. In this regard, many in the pain management field have noted a disproportionate degree of induced hyperalgesia with oxycodone, exceeding that of any other opioid with the exception of remifentanil.

This may correlate with increased kappa opioid receptor (KOR) agonism as discussed further below.

## Question #2: Which Is the Most Addictive Prescription Opioid?

There were 64 valid, i.e., singular/discrete responses to this question. The prescription opioid rated most addictive by the largest number of study participants was oxycodone (59.4%, $n = 38$) followed by methadone (15.6%, $n = 10$) with hydromorphone and hydrocodone tied for third place (7.8%, $n = 5$.) When stratifying by history of heroin use, an interesting but non-significant trend was seen with 21 of 30 heroin users (70.0%) vs. only 17 of 33 non-heroin users (51.5%) reporting oxycodone as the most addictive prescription opioid; chi-square statistic was 2.24 with a $p$ value of 0.13.

Addictive potential is not easily quantifiable; biology once again lends plausibility here. An intriguing recent investigation by Vander Weele et al revealed that in rats, oxycodone in comparison to morphine, resulted in significantly elevated dopaminergic activity within the ventral tegmental area and the nucleus accumbens and related striatal reward centers [36•]. Besides overall increases in dopaminergism, specific and significant increases in both phasic dopamine transmission, and nucleus accumbens shell activity (relative to core activity) were seen with oxycodone. Both of these phenomena have been shown to correlate with increased abuse and dependence [37–40].

Oxycodone's unparalleled addictiveness, however, may stem from more than simply increased hedonic reward. It has been long recognized that while the development of addiction is certainly mediated by the pursuit of pleasure, its establishment may be more related to the avoidance of withdrawal in later phases—at which point the drug of choice provides not positive reward so much as relief from negative drivers. The widely endorsed current phenomenologic model of addiction (supported by neurobiologic evidence) postulates a three-phase cycle involving craving/anticipation followed by indulgence followed by withdrawal [41]. This negative/withdrawal avoidance phase is mediated in part by the dynorphin-KOR system [42, 43] and oxycodone exhibits strong KOR agonism, in some murine models apparently more potent than its mu opioid receptor effects [44, 45]. The effects of the KOR system upon opioid tolerance, hyperalgesia, withdrawal, etc. are complex [46] and remain an area of active research.

While it must be remembered that likely interspecies variation in mechanisms as well as the increased complexity of our biology's intersection with the psychosocial-spiritual renders animal data suggestive rather than conclusive, the plausibility of extrapolation of these pharmacologic data to humans is supported by decades of congruent clinical evidence.

As early as 1954, the French [47] noted that oxycodone "has proved to be particularly dangerous with regard to drug addiction. It seems to act more like heroin than like morphine."

The first report warning of the addictive potential of oxycodone in the USA was published in 1963 [48] in a case series detailing the then unprecedented phenomena of physicians, pharmacists, a clergy member, and other upstanding citizens becoming addicted to Percodan (oxycodone-salicylate) and forging prescriptions. The report details the practice of rendering an intravenous solution from Percodan by heroin addicts who had discovered the greater availability and lower cost of that agent; it labels Percodan "the principal choice as a substitute for heroin." It also notes the well-validated observation that most adverse effects are fewer/less severe compared to morphine.

By the 1970s, oxycodone products were beginning to forge a reputation as having a greater addictive potential than that of morphine [1], which had for decades been regarded as the most addictive prescription opioid. Maruta et al. in 1979 [49] reported that among a sample of 144 chronic pain patients treated at the Mayo Clinic, those dependent upon oxycodone experienced far lower treatment success in both pain management and also opioid weaning compared to other opioids represented within that sample. In 1981, they reported expanded data from over 600 patients again showing markedly worsened pain management and functional outcomes as well as weaning success in the oxycodone-dependent group [50••]. They noted frequent patient reports of euphoria with oxycodone and postulated that disproportionate dysphoria was associated with oxycodone weaning.

Rosenblum et al. in 2007 [51] reported that among 5663 methadone treatment clients in 2005 (spanning 33 states), individuals who abused prescription opioids primarily (38% of this population) reported an overwhelming proclivity toward oxycodone as their drug of choice (54.6%; compared to 24% hydrocodone, 8% methadone, 6% morphine, and 5% hydromorphone.) Among heroin users (53% of this population), the abuse of any-formulation (extended or immediate-release) oxycodone occurred within 30 days of survey at an incidence of 19% compared to hydrocodone and methadone (each at 16%).

Atluri et al. in 2014 [52] published data gleaned from both the Drug Abuse Warning Network (DAWN) system of emergency department records and from distribution data obtained from the federal Automation of Reports and Consolidated Orders System (ARCOS) between the years 2004 and 2011. For each year from 2005 to 2011, in terms of grams sold, oxycodone was the most prescribed opioid, increasing steadily and disproportionately to 40.6% of all prescription opioids in 2011, with hydrocodone in distant second place at 27.1%. For every year from 2004 to 2011, oxycodone was also associated with the largest proportion of opioid-related emergency

visits, comprising 37.3% in 2011 (nearly twice that of the second-place agent, hydrocodone with 20.2% of visits.) While few inferences may be drawn from these data, it is clear that population-level demand, as well as population-level harms are disproportionate for oxycodone.

## Question #3: Which Drug Was your Gateway to Heroin?

There were 18 valid, i.e., singular/discrete responses to this question, which was asked only of patients with a reported history of heroin use ($n = 34$). It should be noted that the largest group of non-respondents came from this subsample due to inability to contact them. Among heroin users, the prescription opioid alleged as their gateway drug to heroin use by the largest number of study participants was oxycodone (77.8%, $n = 14$) followed by hydrocodone (11.1%, $n = 2$.)

Siegal et al. in 2003 [53] first suggested a relationship between prescription opioid (most notably OxyContin®) and heroin abuse, and presented a small series of 10 patients from Ohio who had recently begun using heroin. Five (50%) of this sample reported that "they would never have tried heroin had they not become addicted to OxyContin®."

Grau et al. in 2007 provided a subanalysis of cross-sectional data attempting to investigate the question of whether OxyContin® served as a gateway drug to heroin injection [54]. They stratified 112 opioid abusers in Maine into three groups based upon first opioid abused: OxyContin® (23%), OxyContin® and another opioid used within that initial year of drug abuse (27%), and other opioid/s (50%.) Whether immediate-release oxycodone was represented within the polyopioid groups is unknown. Using a regression model analyzing Kaplan-Meier survival curves of time from initial opioid use to heroin use, the authors reported that the OxyContin® plus other opioid group was significantly more likely than the other two groups to progress to heroin use within 2 years. They interpreted this as indication that OxyContin® is not a gateway drug to heroin; rather, polyopioid use is the salient risk factor. It should be noted that this study was funded by Purdue Pharma, L.P., the manufacturer of OxyContin®.

Young and Havens in 2011 [55] reported that of 394 injection drug users in Kentucky, OxyContin® exposure/use was by far the most common risk factor (odds ratio 6.7 [95% confidence interval 2.6–17.1]) for initiation of injection drug use (IDU) in general; 48% of injection users initiated this practice as a result of OxyContin® use compared to 49% for other prescription opioids, heroin and stimulants combined. Also of concern was the fact that while the median timeframe for transition from overall illicit use to IDU was 10 years; the median timeframe for transition from illicit OxyContin® use to OxyContin® injection was only 3 years. While this study did not specifically address the question of whether oxycodone leads to heroin, subsequent studies as detailed below are directly applicable.

Pollini et al. in 2011 [56] reported that in the San Diego area, almost 40% of a sample of 123 heroin injectors abused prescription opioids prior to transitioning to heroin; monoproduct oxycodone (both IR and ER) were the most frequent opioids consumed with 75.5% of the sample reporting prior abuse, and 20.4% reporting abuse of combination oxycodone-acetaminophen; there exists overlap between drugs used. Unfortunately, few inferences can be made as the data were not gathered in a way that allowed analysis of most commonly abused/preferred opioid in the polysubstance mix; however, the overall picture is consonant with oxycodone's favored status prior to transitioning to heroin.

In a Morbidity and Mortality Weekly Update, the Centers for Disease Control in 2011 [57] reported that of 26 newly diagnosed Hepatitis C patients (average age of 22 years) with illicit drug use history, 89% had used heroin with a median age of initiation of 17 years, and 92% had used oxycodone products (IR and ER) with a median age of initiation of 17 years [51]. Ninety-five percent of these used oxycodone prior to transitioning to heroin.

Lankenau et al. in 2012 [58] reported that among 40 heroin-injecting individuals surveyed in both New York and Los Angeles, among the group that progressed from abuse of prescription opioids prior to proceeding to heroin ($n = 15$) oxycodone ER was by far the most common initiating opioid injected (60% of that sample.) Interestingly, in the larger group ($n = 25$) that initiated heroin use prior to injecting other opioids, oxycodone ER was also the most commonly abused prescription drug (36%.)

Mars et al. in 2014 [59] provided an analysis of heroin users from both Philadelphia ($n = 22$) and San Francisco ($n = 19$) stratified by age. Older users (mean ages 44 and 50, respectively) had been injecting heroin for two decades or more on average, and among this geographically blended cohort, only one had abused prescription opioids prior to heroin; the authors note that their heroin habit began "before the proliferation of opioid pills in medicine cabinets and on the streets." In contrast, the younger heroin users (mean age 25 between both cities) essentially all (18 of 19) transitioned from prescription opioid abuse, with oxycodone products (combination, immediate-release monoproduct, or OxyContin®) reported as the "usual" gateway.

Carlson et al. in 2016 provided one of the earliest, if not the first prospective study following a cohort of 383 illicit prescription opioid users forward over a 3-year period [60]. Twenty-seven of these initiated heroin use during the study period, and all of these (compared to 43% of non-heroin users) had abused OxyContin® prior to initiation of heroin use.

While not directly answering the question of whether oxycodone use leads to heroin use, much note has been made in the literature as well as in the popular press about the temporal correlation between recent oxycodone ER formulation changes (increasing the difficulties in rendering it injectable/snortable) and the devastating increase in heroin use. While numerous other factors (including overall reduction in opioid prescription, increasing cost of prescription drugs, and decreasing price of heroin) are undoubtedly contributory, most of the heroin-using patients within our practice and the literature cite difficulties in procuring/abusing oxycodone ER as the chief reason they switched to heroin [61–63]. At best then, oxycodone indirectly bears uniquely culpability for the heroin epidemic that is upon us.

## Discussion

As discussed above, the present investigation as well as a review of the literature support that oxycodone is the most addictive and thus abuse-liable prescription opioid. Therefore, the authors do not prescribe it in any formulation with exceedingly rare exception.

Self-report is frequently criticized as yielding suboptimal or spurious data. Nonetheless, it has been shown in the context of abuse liability studies that beyond face validity, reports of drug liking are one of the most sensitive and reliable measures of likelihood of abuse [64].

The fact that the authors do not prescribe oxycodone, and universally educate and instruct against its use may be a source of bias in this survey albeit bidirectionally. First of all, there is some degree of selection for patients in our practice that do not continue to seek oxycodone, which might underestimate the proportion of patients who might otherwise report oxycodone as their drug of choice, most addictive opioid, etc. On the other hand, our frequent instruction and education may influence patient responses, thus potentially inflating responses incriminating oxycodone. Additional weaknesses of the study include its relatively small sample size, and the high likelihood that not all patients have been exposed to all agents. Nonetheless, we feel that the literature reviewed herein supports our concerns and call for a national discussion regarding the suitability of this supremely troublesome drug in America's formulary.

Addiction is a construct that needs no explanation to anyone in America. Not that unanimity of understanding exists—psychologists and psychiatrists, sociologists, philosophers, legal professionals, neurobiologists, healthcare providers, and addicted individuals all bring nuance and bias from their camp and experience into the discussion. The adjective "addictive" may be even more difficult to establish consensus on; individual user or "host" diatheses may be far more important in the development of addiction to a substance than any quality inherent to that substance. Nonetheless, we are defining "addictive" as "possessing potent qualities that cause an individual experiencing those qualities to compulsively desire and pursue repetitive experience of the agent with little or no practical regard for the consequences."

Likeability is well-studied in substance abuse literature, and instruments such as the Addiction Research Center Inventory [65] or Drug Effects Questionnaire [66] have been used for over half a century to investigate the desirability of drugs in terms of subjective reward. Likeability or desire, however, does not always correlate with addiction. Robinson and Berridge [67] showed us that liking does not necessarily equal wanting, a concept that should be familiar to all. We can like something we do not truly want, and want or need something we no longer like if we ever did in the first place. It has become well-accepted in the scientific community, and ratified by the addicted population that the initial stage of addiction is marked by the pursuit of hedonic reward, whereas the latter, more established stage is cemented by the avoidance of withdrawal. Cicero et al. also made the point [26••] that pragmatic considerations such as drug availability, cost, adverse effect profile, and perceived/actual risk all affect abuse and addiction.

Nonetheless, the indices of likeability and addiction often correlate. The likeability of oxycodone stands supreme among prescription opioids, possibly influenced/confounded by (perceived) low adverse effect rate. The addictiveness of oxycodone is also unparalleled, mediated in part by its rewarding properties but also by its extraordinary withdrawal scourge. When talking with current or former oxycodone addicts who desire freedom/sobriety from the drug, in our experience, they almost universally admit to a "love-hate" relationship with the drug, acknowledging its incomparable desirability in terms of euphoria along with the profound psychological and physiological misery experienced when the drug is gone.

How then do we intervene? While we advocate a primarily "Keynesian" (demand reduction) approach to treating opioid dependence [68], there is certainly a role for supply side intervention as well. The recent proliferation of both regulatory and advisory guidelines restricting illegitimate opioid prescription has been shown by some metrics to have been successful to a degree in reducing serious outcomes such as morbidity and mortality, and we can assume a corresponding decrease in misuse and abuse as well. Another operational-level supply-side intervention we propose is the specific elimination (or at the very least more aggressive restriction on prescription) of oxycodone. This approach has been adopted on a local/regional scale recently; in the Puget Sound area, at least one hospital system has decided to eliminate oxycodone from its formulary [69] and in 2012 Ontario became the first Canadian province to delist it from their public drug benefit program based on addictive properties [70].

Such elimination/restriction is not without precedent at a larger, national scale either. Heroin (diamorphine) has been classified as a Schedule I drug under the Controlled Substances Act (CSA) since its inception. The USA has always taken a hard-line approach with this particular substance in contrast to other nations (e.g., Switzerland, Germany, Canada) that permit its use for both analgesic and maintenance of addiction purposes. Given that the abuse liability of oxycodone appears comparable to that of heroin, and given that heroin-dependent individuals around the nation nearly unanimously allege that oxycodone was their "gateway" to heroin use, we propose at least a discussion of reclassifying oxycodone as a Schedule I drug. Multiple other opioid agents are available for the co-treatment (within a multimodal regimen, having failed more conservative means) of legitimate severe acute pain scenarios as well as for chronic pain scenarios.

The argument might be raised that such "sacrifice" (of a therapeutic agent) would increase suffering at an individual and population level. We would reply first of all by pointing out again that while on the one hand such consideration is undoubtedly true in terms of psychological (and even physical) distress from "cutting off" America's drug of choice, professional society recommendations [71–74] are unanimous in their advisory stance against chronic opioid therapy for chronic non-cancer pain. Furthermore, we argue that hamstringing primary prevention of opioid dependence, with its manifest virulence and pathogenicity (to apply epidemiologic terms) for the sake of such misguided secondary/tertiary prevention approach to pain may well comprise sacrifice of naïve individuals including future generations, which we know are far more susceptible to the development of addiction [75, 76].

The argument might also conceivably be made that elimination of oxycodone would further shift abuse patterns/drug of choice to heroin, as has been seen already with reduction/elimination of OxyContin. To that allegation, we would respond that first of all the prescription of any opioid besides methadone (in a federally-licensed opioid treatment program) or buprenorphine (by DATA 2000-waived clinicians) for the purpose of harm reduction, i.e., heroin abuse prevention is illegal. Secondarily, we would argue that perpetuation of oxycodone manufacture, distribution and prescription in the face of strong evidence for addiction-specific harms outweighing benefit is no different than the strategy of supervised clean-needle heroin provision, an approach almost universally disfavored in this country.

In the defensive against opioid dependence with its ever-increasing grim morbidity and mortality statistics, strategic and operational level considerations such as the National Pain Strategy, efforts targeting adverse childhood experiences, etc. are paramount and long overdue. At a tactical ("boots on the ground") level, individual clinicians need training and facilitation in implementing practices performed on a daily basis to combat the problem, such as the mandated use of Prescription Monitoring Programs, restricted prescription durations, and referral thresholds. A specific tactical approach we have adopted within our practice over the past several years has been restriction of the prescription of oxycodone to a 7-day postoperative prescription of combination oxycodone/acetaminophen regimens with rapid transition to an alternate agent (e.g., tapentadol or morphine) for subsequent weaning/discontinuation of opioid therapy. The other rare situation we prescribe it for is imminently terminal abdominal malignancy situations owing to theoretical improved efficacy/rationality in abdominal pain stemming from its presumed increased kappa opioid receptor (KOR) affinity [77, 78] and the preponderance of KOR within the gut. In both situations, the prescription is given only after considerable discussion with the patient regarding our assessment of oxycodone's disproportionate abuse liability, other adverse psychological effects, and hyperalgesia.

In situations where we "inherit" patients using oxycodone regularly, we advise that for all of the reasons detailed herein that we do not prescribe the drug for the treatment of chronic pain; we will offer them a transition to another agent (e.g., oxymorphone, which they are already exposed to by virtue of the metabolism of oxycodone, or preferably tapentadol which shows significantly lower abuse liability [79–81]. If severe pain with a clear organic basis, refractory to more conservative multimodal therapy cannot be demonstrated, we have no recourse but to offer the patient immediate discontinuation of oxycodone with palliation of withdrawal symptoms by means of clonidine, promethazine, gabapentin, etc. and a trial of buprenorphine, exactly as is done for heroin.

## Conclusions

Oxycodone possesses pharmacologic qualities that render it the prescription opioid most liable to abuse, dependence, and addiction. The risks of any long-term prescription outweigh the benefits, and it should not be prescribed on a chronic basis, if at all.

### Compliance with Ethical Standards

**Conflict of Interest** Heath McAnally and Daniel Remillard declare no conflict of interest. Alan Kaye is on the speaker bureau for Merck and Depomed, Inc.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
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