

# Factors influencing the selection of hydrocodone and oxycodone as primary opioids in substance abusers seeking treatment in the United States



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## ABSTRACT

The purpose of the present study was to identify the factors that influence the selection of hydrocodone and oxycodone as primary drugs of abuse in opioid-dependent subjects ( $n = 3520$ ) entering one of 160 drug treatment programs around the country. Anonymous, self-administered surveys and direct qualitative interviews were used to examine the influence of demographic characteristics, drug use patterns, and decision-related factors on primary opioid selection. Our results showed that oxycodone and hydrocodone were the drugs of choice in 75% of all patients. Oxycodone was the choice of significantly more users (44.7%) than hydrocodone (29.4%) because the quality of the high was viewed to be much better by 54% of the sample, compared to just 20% in hydrocodone users, who cited acetaminophen as a deterrent to dose escalation to get high and hence, its low euphoric rating. Hydrocodone users were generally risk-averse women, elderly people, noninjectors, and those who prefer safer modes of acquisition than dealers (ie, doctors, friends, or family members). In contrast, oxycodone was a much more attractive euphorogenic agent to risk-tolerant young, male users who prefer to inject or snort their drugs to get high and are willing to use more aggressive forms of diversion. Prevention and treatment approaches, and pain physicians, should benefit from these results because it is clear that not all drug abusers share the same characteristics, and the decision to use one drug over another is a complex one, which is largely attributable to individual differences (eg, personality, gender, age, and other factors).

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## 1. Introduction

Prescription opioid abuse has reached epidemic levels in the past 15 years [4,17,20,23,24,26,28,30,32,33,44]. While most opioid classes have seen increases in their misuse, hydrocodone and oxycodone products are by far the most prevalent drugs of choice among prescription opioid abusers [2,7,12,21,27,37,42,45]. Given that a percentage of any prescribed opioid is diverted for misuse [6,13,29], it follows that there are large amounts of hydrocodone and oxycodone readily accessible to those who choose to misuse them because they are the 2 dominant opioids used for pain management within general medicine and dentistry [19,37,41]. Accessibility, coupled with the high affinity of hydrocodone and oxycodone for the  $\mu$ -opioid receptor mediating pain relief and euphoria, would seemingly be able to fully explain their popular-

ity. However, despite reports of pharmacological, physiological, and subjective similarities between oxycodone and hydrocodone in preclinical and clinical laboratory studies [34,40,46], evidence is emerging that suggests there are differences between those who use oxycodone and hydrocodone products. For example, it has been shown that, despite its very high abuse rates among prescription opioid abusers, hydrocodone is viewed as less attractive than oxycodone by active abusers when measured by the Opioid Attractiveness Scale [3]. Oxycodone users are also more likely to tamper with their drugs in order to inhale or inject their drug, a concern that led to the introduction of an abuse-deterrent formulation for OxyContin (Purdue Pharma, Stamford, CT, USA) [11].

Understanding differences between those who select hydrocodone and oxycodone as their drug of choice for nontherapeutic purposes is important for 2 reasons: 1) given their indication for acute pain, established safety profiles, and well-entrenched role in pain medicine, physicians may benefit from a characterization of risk factors for those likely to abuse one drug over another [5,26,43], particularly when deciding what prescription opiate

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would best fit the patient at hand; and 2) understanding the motivational differences between those who abuse either drug could better inform prevention and treatment strategies. In the present study we used quantitative methods (ie, a standardized, self-administered survey used extensively in past research [9–11,14]) to better understand the similarities and differences between hydrocodone and oxycodone users in 3520 patients entering drug treatment programs around the country with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) diagnosis of prescription opioid dependence. However, as an important adjunct, we also used an ethnographic approach to mitigate the limitations of any structured survey, particularly an anonymous, self-administered one, such as incomplete or ambiguous answers and an inability to ask follow-up questions.

## 2. Methods

### 2.1. Study sample

The term “Key Informants” has been used for decades in sociological research [18,22,31,39], and in this study, is defined as treatment center directors or their designees, who had daily contact with patients who met DSM-IV criteria for opioid abuse/dependence. This on-going nation-wide survey, termed the Survey of Key Informants’ Patients (SKIP) program, is a key element of the postmarketing surveillance system: the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system [8]. Briefly, SKIP consists of over 150 treatment centers, both public and privately funded, and balanced geographically with urban, suburban, and rural patients. Each treatment center was asked to recruit patients/clients to complete an anonymous survey who: 1) were 18 years or older; 2) met DSM-IV criteria for substance abuse with a primary drug that was a prescription opioid; and 3) used prescription opioid drugs to get high within 30 days of entering treatment. Due to the strict requirements placed on adolescent research that include parental consent and careful monitoring of the adolescent patient’s privacy, those under the age of 18 years were not included in the study program to ease the burden of program administration on the vast network of Key Informants.

To supplement and add context to the structured SKIP survey, we recruited 200 patients who had previously completed the SKIP survey and indicated by a mail-in postcard provided with the survey that they were willing to give up their anonymity to participate in a follow-up study, dubbed Researchers and Participants Interacting Directly (RAPID). Based on the reflexive nature of ethnographic research, the purpose of this program was 2-fold: 1) to be able to contact participants with questions that can be answered within a short time period to establish real-time data; and 2) to quickly ask follow-up questions based on SKIP and RAPID analyses. Participants were directed to a brief online survey, and upon completion of SKIP and RAPID data analyses, follow-up questions were developed and e-mailed to participants to further expand upon results found in these surveys.

### 2.2. Patient/subject confidentiality

Completed SKIP survey instruments were identified by a unique case number and sent directly to Washington University in St. Louis by the respondent. Key Informants did not see the detailed responses of their patients/clients and there was no link between the data provided in the SKIP and RAPID programs. Protocols were approved by the Washington University in St. Louis Institutional Review Board.

### 2.3. Measures

#### 2.3.1. Primary opioid

SKIP respondents were asked to identify the opioid used most in the past 30 days to get high (ie, their primary drug) stratified by opioid compound (buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol). To assess satisfaction with an individual’s actual primary drug, respondents were asked “If cost, availability and access to opioids was not a problem, and you could have any opioid drug you wanted, which would you prefer?” Respondents then wrote in their “preferred opioid,” which was grouped into one of the following categories: hydrocodone, oxycodone, high potency opioids (hydromorphone, oxymorphone, methadone, morphine and fentanyl), other opioids (buprenorphine, tapentadol, and tramadol), and illicit opioids (opium, heroin).

#### 2.3.2. Sociodemographic variables

The SKIP survey included the following sociodemographic variables: 1) sex (male/female); 2) age (continuous then subsequently divided into 1 of 4 groups; 18–24, 25–34, 35–44 and 45 years and over); 3) race/ethnicity (White, African American, Latino/a, other race); 4) area of residence (large urban, small urban, suburban, rural); 5) source of income (employed, public assistance, friends/family, other); 6) health care coverage (none, private/dependent, Medicare/Medicaid/military, other); and 7) level of education completed (“some college” or higher level, any level below “some college”).

#### 2.3.3. Primary drug abuse patterns

Variables on the SKIP survey relating to an individual’s use of their primary drug included: routes of administration (oral [swallow/chew/sublingual]; inhalation [snort/smoke]; injection); methods of diversion (friend/relative; dealer; doctor; emergency department; stole; forged prescription); intent of opioid use (alter mood/escape from life/get high; treat pain; treat other medical or psychiatric issues; other); and the single, main reason for primary drug selection (makes me feel better than other drugs; easiest to get; safer to use than other drugs; only thing available; cheapest; other). Respondents were also asked for the average amount of money spent per week to obtain their primary drug.

#### 2.3.4. RAPID survey

Respondents were asked to name their primary opioid of abuse and then describe in an open-ended format why they chose that particular opioid as their primary drug. To assess exposure and decision-making factors related to a variety of opioid types, respondents were then asked if they had ever abused any hydrocodone, oxycodone, hydromorphone, fentanyl, buprenorphine, or tapentadol products. For each drug endorsed that was not their primary drug, respondents were then asked to describe why that drug was not, or did not become, their primary opioid of abuse.

#### 2.3.5. RAPID follow-up

Based on SKIP and RAPID analyses, respondents were re-contacted by e-mail to answer 2 follow-up questions: “If a drug was available that contained 100% hydrocodone, and NO combination drug (ie, acetaminophen, ibuprofen), would you be more likely, less likely, or no more or less likely to use hydrocodone to get high?”; and “Has the change in formulation of OxyContin, in which the pill is harder to crush and dissolve, made you more likely, less likely, or no more or less likely to use OxyContin to get high?” Respondents were then asked, in an open-ended format, to explain their answers in their own words.

## 2.4. Data analyses

Descriptive analyses were used to assess prevalence rates of primary opioids of abuse as a function of total responses and by quarter-year, as well as gender, age group, race/ethnicity, and “preferred opioid” for the entire SKIP sample. To assess the generalizability of our sample population, we accessed the Substance Abuse and Mental Health Services Administration’s (SAMHSA) Treatment Episode Data set (TEDs) for 2010 [38], which gathers demographic and drug use data on those entering treatment for substance abuse around the country. Using those individuals over the age of 18 years with a primary substance of abuse coded as “other opioids” (than heroin), we calculated prevalence rates for sex, age group, and race/ethnicity to compare with those found in the SKIP analysis. Using a report from SAMHSA’s 2011 National Survey of Substance Abuse Treatment Services (N-SSATS) [36], we also compared rates of public vs privately funded treatment centers across the country with those reported by our Key Informant Network. Locations of Key Informant sites and respondents were mapped by 3-digit zip code using Microsoft MapPoint North America 2006 (Microsoft Corporation, Redmond, WA, USA).

Due to their high rates of abuse compared to other opioids, subsequent analysis in both SKIP and RAPID datasets was restricted to those who selected hydrocodone (1) or oxycodone (0) as a primary opioid of abuse. Variables were transformed into binary measures (1/0) and cross-tabulations were used to assess prevalence rates. Bivariate logistic regression models reported as odds ratios (OR) with 95% confidence intervals were used to predict the influence of sociodemographic characteristics and drug use patterns on primary opioid selection. The significance level was set at  $P < 0.01$  for all comparisons. Data were analyzed using IBM SPSS Statistics v20 (IBM, Armonk, NY, USA).

Word frequencies from open-ended questions in the RAPID program and subsequent follow-ups, set for the 100 most frequently mentioned words excluding “hydrocodone,” “oxycodone,” and stop words (ie, “a” and “the”), were used to understand the motivations for selecting hydrocodone or oxycodone as a primary drug of abuse. Thematic analyses using NVivo version 9 (QSR International, Burlington, MA, USA) were also used to code open-ended responses and develop themes surrounding the decision-making factors involved in the exclusion of other opioids as primary drugs of abuse.

## 3. Results

### 3.1. Characteristics of key informants and SKIP respondents

Fig. 1 shows the regional distribution of participating Key Informants ( $n = 160$ ) and their opioid-dependent patients/clients completing a survey stratified by the 3-digit zip code of the treatment centers (blue) and patient/client residences (red). Coverage rates represent a mix of treatment centers in urban, suburban, and rural areas across the country. Table 1 compares the demographic profile of SKIP survey respondents ( $n = 3520$ ) to that of opiate-dependent clients who provided data to the SAMHSA-sponsored TEDS ( $n = 154,568$ ) [38], as well as the breakdown of publicly and privately funded treatment centers from SAMHSA’s 2011 N-SSATS [36]. N-SSATS treatment centers were predominantly private, whereas those acting as Key Informants in the SKIP program were more evenly distributed between privately and publicly funded centers. In terms of patients’ gross demographic features, the samples were comparable, but there was a slightly higher population of non-Whites in the SKIP sample. Thus, our relatively small sample ( $n = 3520$ ) seems representative of much larger ( $n = 154,568$ ) databases.

### 3.2. Primary drug selection

Oxycodone and hydrocodone had the highest rates of primary opioid selection, with oxycodone selected by 44.7% of the total sample and hydrocodone second at 29.4%. Far fewer participants selected any other opioid as their primary drug. Although the introduction of an OxyContin abuse-deterrent formulation in the third quarter of 2010 led to a significant drop in the use of OxyContin, from 35.6% prior to its introduction, to 12.8% 3 years later, the overall impact on total oxycodone users was not sufficiently large enough to change the rank of order of abuse rates; oxycodone products remained more popular than hydrocodone products. Oxycodone (55.5%) and hydrocodone (19.4%) were also the opioids most preferred by participants when considering an ideal world where accessibility and cost were irrelevant. However, hydrocodone users were more likely than oxycodone users to prefer a different drug (38.7% vs 15.4%, OR 3.486,  $P < 0.001$ ), most often choosing oxycodone (68.9%). On the other hand, the small group of oxycodone users that would switch generally chose higher potency (53.3%) or illicit opioids (20.1%).

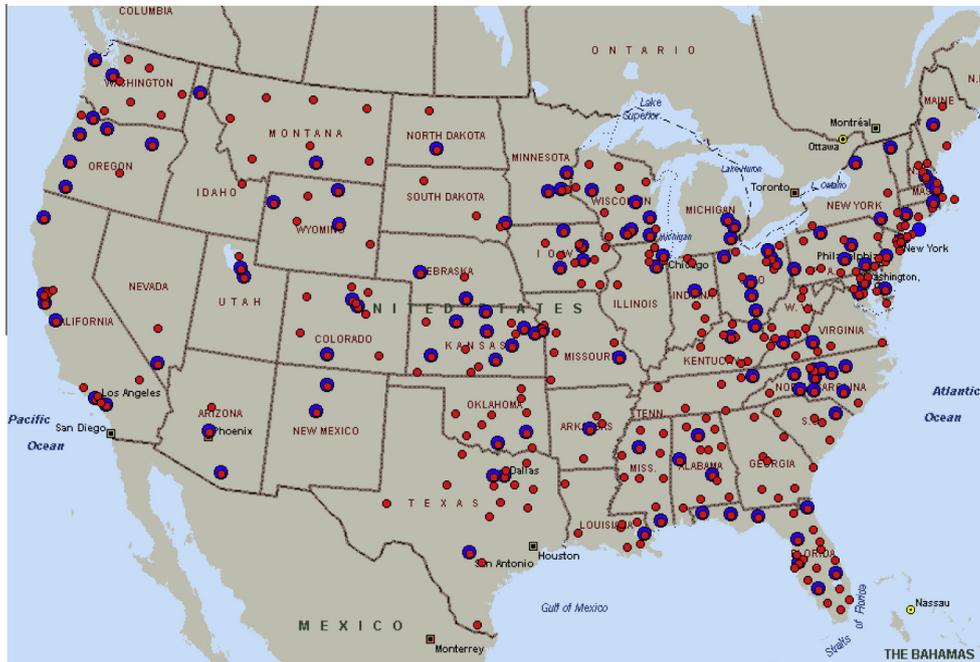
### 3.3. Demographics and patterns of primary drug use

Table 2 summarizes the sociodemographic characteristics of individuals selecting either hydrocodone or oxycodone as a primary opioid. Primary hydrocodone users were more likely to be female (OR 1.326) and more likely to include African Americans (OR 1.634) and Latinos (OR 1.932). In terms of age, there was an inverse relationship between the 2 drugs: relative to oxycodone, hydrocodone was used much less often in 18–24-year-olds (OR 0.573), but those over the age of 45 years were twice as likely to use hydrocodone as oxycodone (OR 2.094). There were no other significant differences observed in employment status, income, health care/insurance, or area of residence. Table 3 shows that hydrocodone users were far more likely to use the oral route of administration (OR 8.092) and were less likely to inject (OR 0.165) or snort (OR 0.198) their drug than oxycodone users. Hydrocodone users were also less likely to use a dealer (OR 0.333) than oxycodone users, whereas they were more likely to use a doctor’s prescription (OR 1.918) or to forge a prescription for their drug (OR 1.803).

### 3.4. Reasons underlying primary drug selection

#### 3.4.1. SKIP data

Table 3 shows that while the vast majority (~90%) of users selected mood alteration as a motivation for using their primary drug, a significant fraction of participants – 50% to 60% – indicated that the treatment of pain was also a factor in their use, with slightly more endorsements from hydrocodone than oxycodone users (OR 1.399). The treatment of psychiatric and other medical issues was also endorsed with some frequency by both hydrocodone and oxycodone users (~37%). Table 3 also shows the breakdown of endorsements for the single most important reason a participant selected either oxycodone or hydrocodone as a primary opioid. While “makes me feel better than other drugs” (ie, quality of the high) and “easiest to get” were the 2 reasons most endorsed, collectively accounting for 75–85% of all responses, they were inverse in their proportions between the 2 drugs. Half of those using oxycodone indicated that the quality of the high was the major reason for selecting the drug as their primary one, whereas far fewer (19.2%) indicated this was the case for hydrocodone (OR 0.244). Instead “easiest to get” was more likely to be endorsed by those using hydrocodone (OR 2.470) than oxycodone. The cost of drugs seemed to be of minor concern in the selection of a primary opioid (2–4%): hydrocodone, whose users spent a mean of \$152.35 per



**Fig. 1.** Nationwide distribution of Key Informants and participants. Location by 3-digit zip code of Key Informant treatment centers (red circles,  $n = 160$ ) and patients who completed the Survey of Key Informants' Patients (blue circles,  $n = 3520$ ).

week to obtain the drug, was far cheaper than the \$340.79 spent per week by oxycodone users, yet oxycodone use predominated.

#### 3.4.2. RAPID data

Qualitative data from the RAPID program supported and amplified the results found in the SKIP analyses. Word frequencies, shown in Fig. 2 as tag clouds (ie, the larger the word, the more frequently found), show the different reasons provided by hydrocodone (Fig. 2A) and oxycodone users (Fig. 2B) in explaining their choice of primary drug. Hydrocodone users ( $n = 36$ ) had more frequent mentions of “pain,” receiving “prescriptions” from their doctor, and “easy to get,” suggesting not only that the availability of hydrocodone was a key motivator in its use, as was true in the SKIP analyses, but that pain played an influential role. Two responses illustrate this point:

“If I had medical insurance I would not need to buy it on the “streets” because I would be under a doctor’s care.”

“The good feeling for me was no pain and elevated feeling of being able to do anything without emotional or physical pain.”

Oxycodone users ( $n = 50$ ), despite also frequently mentioning “availability” and “easy to get,” had less about this in terms of pain management or receiving doctor’s prescriptions. In contrast to hydrocodone users, a large focus was placed on the “high” oxycodone “gave,” along with a variety of other key words relating to the effects of oxycodone, including: “strong,” “withdrawals,” “anxiety,” “feel,” “best,” and “euphoria.”

#### 3.5. Negative factors associated with other opioids

Given that opioids other than hydrocodone and oxycodone were rarely selected as primary drugs, we asked hydrocodone and oxycodone (primary drug) users if they had been exposed to other types of opioids, and if so, why those opioids did not become their primary drugs. Using thematic analyses, 7 distinct motivational categories were found to be involved in the decision process to not select a particular opioid as a primary drug of abuse

**Table 1**  
Comparison of SKIP and TEDs data.

	SKIP $n = 3520$	TEDs $n = 154,568$
Gender		
Male	47.2	53.8
Female	52.8	46.2
Age, years		
18–24	22.3	28.9
25–34	40.0	42.1
35–44	19.9	16.3
45+	17.8	12.7
Race/ethnicity		
White	80.8	88.8
African American	8.0	3.4
Latino	3.7	4.9
Other	7.6	2.9
	SKIP $n = 167$	N-SSATS $n = 13,720$
Treatment centers		
Private	53.0	87.9
Public	29.1	12.1
Both	17.9	–

SKIP, Survey of Key Informants' Patients program; TEDs, Treatment Episode Data set; N-SSATS, National Survey of Substance Abuse Treatment Services.

(Table 4). These categories included concern over safety/side effects, ineffective for intent of use, cost, maintenance, accessibility, route of administration, and unclear/unknown. Table 4 shows the reasons oxycodone users avoided hydrocodone and why hydrocodone users tended not to use oxycodone, even though it was often viewed as a better choice than hydrocodone. Most oxycodone users, who had far more experience with other opioids than hydrocodone users, indicated that hydrocodone was ineffective in terms of getting high, and there was also a serious concern about safety and side effects (eg, stomach issues, nausea). For example:

**Table 2**  
Demographics of opioid-dependent individuals entering treatment.

	Hydrocodone n = 912	Oxycodone n = 1350	Odds ratios <sup>†</sup> (Hydrocodone = 1)	95% CI (Lower, upper)
Female	57.8	50.8	1.326**	(1.117, 1.574)
Age, years				
18–24	16.1	26.4	0.573**	(0.433, 0.665)
25–34	36.4	42.3	0.778 <sup>†</sup>	(0.673, 0.969)
35–44	24	18.5	1.391 <sup>†</sup>	(1.133, 1.709)
45+	23.5	12.8	2.094**	(1.677, 2.614)
Race/ethnicity				
White	76	83.9	0.608**	(0.492, 0.751)
African American	10.3	6.6	1.634*	(1.205, 2.215)
Latino	4.7	2.5	1.932*	(1.215, 3.073)
Other	9.0	7.0	1.306	(0.958, 1.781)
Area of residence				
Large urban	17.9	20.6	0.841	(0.628, 1.127)
Small urban	30.0	31.5	0.932	(0.727, 1.195)
Suburban	23.2	21.9	1.074	(0.817, 1.413)
Rural	28.8	25.9	1.159	(0.896, 1.498)
Source of income				
Employed	43.5	43.1	1.016	(0.853, 1.209)
Public assistance	15.4	14.8	1.051	(0.825, 1.337)
Friends/family	25.1	28.6	0.836	(0.687, 1.017)
Other	16.1	13.6	1.219	(0.957, 1.554)
Health care coverage				
None	45.9	44.2	1.075	(0.878, 1.316)
Private/dependent	23.9	23.6	1.019	(0.804, 1.291)
Medicare/Medicaid/military	28.0	30.3	0.895	(0.717, 1.117)
Other	2.1	1.9	1.095	(0.536, 2.237)
Education				
Some college or higher	42.5	37.8	1.213	(1.020, 1.443)

CI, confidence interval.

\* Statistically significant at  $P < 0.01$ .\*\* Statistically significant at  $P < 0.001$ .

† Variables were transformed into binary measures (1/0) and cross-tabulated with primary drug (hydrocodone = 1, oxycodone = 0).

**Table 3**  
Primary drug use patterns in opioid-dependent individuals entering treatment.

	Hydrocodone n = 912	Oxycodone n = 1350	Odds Ratios <sup>†</sup> (Hydrocodone = 1)	95% CI (Lower, upper)
Route of administration				
Oral	94.6	68.6	8.092**	(5.898, 11.101)
Inhalation	26.6	64.6	0.198**	(0.164, 0.239)
Injection	4.2	21.1	0.165**	(0.115, 0.235)
Method of diversion				
Friend/relative	58.2	59.4	0.952	(0.799, 1.135)
Dealer	53.2	77.3	0.333**	(0.276, 0.402)
Doctor	58.9	42.7	1.918**	(1.610, 2.286)
ED	23.7	18.6	1.360 <sup>†</sup>	(1.101, 1.680)
Stole	19.0	19.5	0.974	(0.782, 1.214)
Forged Rx	7.8	4.5	1.803 <sup>†</sup>	(1.253, 2.596)
Intent of opioid use				
Alter mood/escape/get high	84.3	90.3	0.581**	(0.433, 0.779)
Treat pain	59.8	51.6	1.399*	(1.151, 1.701)
Treat other issues	35.0	36.2	0.951	(0.777, 1.164)
Other	7.8	8.7	0.884	(0.621, 1.260)
Reason for PD selection				
Quality of high	19.2	49.4	0.244**	(0.182, 0.326)
Easiest to get	56.0	34.0	2.470**	(1.914, 3.188)
Safer than other drugs	11.9	7.8	1.605	(1.058, 2.436)
Only thing available	4.4	4.6	0.949	(0.520, 1.732)
Cheapest	4.4	2.2	2.015	(0.991, 4.098)
Other	4.1	2.1	2.048	(0.984, 4.263)

CI, confidence interval; ED, emergency department; Rx, prescription; PD, primary drug.

\* Statistically significant at  $P < 0.01$ .\*\* Statistically significant at  $P < 0.001$ .

† Variables were transformed into binary measures (1/0) and cross-tabulated with primary drug (hydrocodone = 1, oxycodone = 0).

**(A)**

able abuse **access** accomplish **addicted** affordability also anything appetite associated availability available away  
back basis became began **best** better biggest body bought built **buy** cant care cheapest chronic cost cramps dealing decreased dentist  
**doctor** doctors dont drug drugs **ease** easier easiest **easy** eat either elevated emotional emotionally  
**energy** euphoria even excess **feel** feeling fibromyalgia first friends gave **get** given gives good got  
health helped helps high hydromorphone including insurance internet issues knew let **like** liked lot low  
**made** mainly make many medical mellowed menstrual monthly morphine nausea need noticed nycynta **one** originally  
oxycodone **pain** physical **prescribed** prescriptions readily  
really **way**

**(B)**

able acquire actually **addicted** age ahold albeit alot also always anxiety **availability** available  
availability available **available** **back** bad became because **best** better biggest brings choice chose **chronic** cleaning  
confidance confidence **continued** craved day diagnosed didnt **doctor** done drive **drug** drugs ease eased easier easily  
**easy** effect emotional emotions energetic **energy** enough enuff erythematosis especially  
**euphoria** euphoric eventually every everywhere fall false far fast feb **feel** feelings fentanyl fiction find  
**first** floor free function functional **gave** **get** gives go going good got high  
hooked like liked lot **made** obtain opiates **pain** potency problems readily  
**started** strong things way withdrawals without work

**Fig. 2.** Reasons for primary drug selection. Word frequencies represented as tag clouds (ie, the larger the word, the more frequently found) showing the different reasons provided by hydrocodone (A) and oxycodone users (B) in explaining their choice of primary drug in their own words.

“It [hydrocodone] was initially my primary drug but as my tolerance increased I needed something stronger.”

“About all they did create stomach aches if taken when had nothing else because you would [have] to take so many in the hopes of happiness.”

Most hydrocodone users stated that oxycodone, despite its attractiveness as a euphorigenic agent, was not a drug of choice because of a lack of availability:

“It [oxycodone] was much harder to get a prescription for it, for some reason or another, doctors do not like prescribing it, from my personal experience. But occasionally, at the ER or Urgent Care, I would get a small quantity of it.”

Both oxycodone and hydrocodone users indicated a variety of factors involved in their decision-making process to not use other opioids. Higher-potency opioids were burdened with availability and safety issues, including concerns of overdose:

“That [fentanyl] was really hard to come by. And when I did find it, it was VERY expensive! But, I did have a “friend” that was prescribed them on a monthly (sometimes a few times a month via doctor shopping) basis. I did buy her patches occasionally, and the last time I did so I overdosed because I never wore the patches, I broke them open and ate the gel medicine instead. Very stupid move just for the record...”

But, despite the higher potency, a lack of “effectiveness” as a euphorigenic drug was also noted by some users.

“I have tried these [hydromorphone]; it helped me to relax but didn’t get the high I wanted. I was chasing feelings of warmth – a cozy and over all state of well-being.”

For buprenorphine, its use was predominately for “maintenance” and hence was seen as less “effective” as a primary drug of abuse. Tapentadol had extremely low exposure rates, but 2 out of the 3 respondents who had tried tapentadol cited “safety” and

**Table 4**

Reasons other opioids were not selected as primary drugs.

	Hydrocodone	Oxycodone	Fentanyl	Hydromorphone	Buprenorphine	Tapentadol
Hydrocodone users (n = 36)						
Ever used to get high, n (%)	–	27 (75.0)	5 (13.9)	14 (38.9)	8 (22.2)	2 (5.6)
Reasons not primary drug <sup>a</sup>						
Concern over safety/side effects		4	1	1	3	1
Ineffective for intent of use		4	1	5	1	1
Cost		2	2		1	
Maintenance					2	
Accessibility		15	4	9	1	
Route of administration						
Unclear/unknown		3				
Oxycodone users (n = 50)						
Ever used to get high, n (%)	48 (96.0)	–	21 (42.0)	27 (54.0)	13 (26.0)	1 (2.0)
Reasons not primary drug <sup>a</sup>						
Concern over safety/side effects	10		3	3		
Ineffective for intent of use	29		3	4	9	
Cost			2	1		
Maintenance					3	
Accessibility	7		13	16		1
Route of administration	3			1		
Unclear/unknown	4		1	2	1	

<sup>a</sup> Hydrocodone and oxycodone users who “ever used” one of the given drugs to get high were asked to explain, in their words, why that drug did not become their primary drug of abuse. Thematic analysis was used to categorize responses into one or more of the developed themes, with the numbers above representing the number of participants that mentioned a particular theme in their response.

“ineffectiveness” as deterrents. As noted in the SKIP analyses, “cost” was rarely endorsed as a motivating or deterring factor in primary drug selection.

### 3.6. Impact of drug formulation

On the basis of these results, and because oxycodone and hydrocodone have varying formulations, we wanted to understand the role drug formulation played in primary drug selection. We posed a hypothetical question to participants in the RAPID study: “If a drug was available that contained 100% hydrocodone, and NO combination drug (ie, acetaminophen, ibuprofen), would you be more likely, less likely, or no more or less likely to use hydrocodone to get high?” The majority of participants (70%, n = 59/84) said this would make them more likely to use hydrocodone. Looking at word frequency distributions, “acetaminophen” was the most commonly cited word amongst these respondents, with “liver” also highly cited (Table 5), indicating an awareness and concern about the dangers of acetaminophen, which was either a deterrent, or constant fear, in their use of hydrocodone, particularly as tolerance developed, requiring higher doses to achieve euphoria. As one participant explained:

“In fact, one of the reasons I was abusing oxycodone in the end more than hydrocodone (despite the fact that I could afford hydrocodone more), was because I was too scared about the APAP (acetaminophen) damage to my liver. Now that I am clean, the thought is scary to me how much I did ingest there in the end, just to keep withdrawals away. I tried to keep under 1000 mg APAP per 4 hours, and under 3 to 4 K per day, but in the end, it didn’t matter to me when I was still getting sick at that dose (this was from taking generic 10/325 s Hydro/APAP). When I took oxycodone (in the form of the little blue 30-mg “roxy” pills, I did not worry for my liver...So, in a way, I guess had I gone on without getting clean, I may have overdosed from roxies rather than hydrocodone, since I felt (idiotically) that I could take more roxies at one time and get some kind of high...-though in the end I could not reach a high...just some excess energy, since too much of the 10/325 might send me in to APAP overdose for my liver.”

The purpose of the second question asked was to determine the impact of abuse-deterrent formulations on drug selection. Respondents were asked if the formulation change in OxyContin, designed to prevent abusers from easily tampering with the pill for intravenous/inhalation purposes, had made them more likely,

**Table 5**

Word frequencies based on RAPID follow-up questions (Q) and responses (R).

	Q: 100% hydrocodone* R: more likely (59/84)	Q: OxyContin ADF <sup>†</sup> R: less likely (43/77)	Q: OxyContin ADF <sup>†</sup> R: no more or less likely (32/77)
1	Acetaminophen (23)	Use (32)	Use (17)
2	High (21)	Heroin (16)	Drug (15)
3	Take (17)	Less (15)	Pill (11)
4	Likely (16)	Likely (14)	Still (11)
5	Drug (14)	Formulation (13)	Get (10)
6	Liver (14)	Drug (12)	Never (10)
7	Use (14)	High (11)	High (9)
8	Get (13)	Change (10)	Make (9)
9	Less (11)	Crush (10)	Formulation (8)
10	Much (11)	Get (10)	Just (8)
11	Pain (11)	New (10)	Likely (8)

RAPID, Researchers and Participants Interacting Directly study; ADF, abuse deterrent formulation.

\* Q: If a drug was available that contained 100% hydrocodone, and NO combination drug (ie, acetaminophen, ibuprofen), would you be more likely, less likely, or no more or less likely to use hydrocodone to get high?

<sup>†</sup> Q: Has the change in formulation of OxyContin, in which the pill is harder to crush and dissolve, made you more likely, less likely, or no more or less

less likely, or no more or less likely to abuse OxyContin. Respondents were split on this issue: nearly half indicated they were no more or less likely to use OxyContin (32/77), with some noting that they continued to inject/inhale OxyContin despite greater extraction efforts. However, word frequency distributions indicated that many of those who answered “no more or less likely” were oral users who “still” swallowed the “pill” and saw no need to change because of the formulation redesign, or they changed their route of administration from inhalation/injection to oral use and continued to use OxyContin.

“I was a user that did shoot them but if I couldn’t do it that way then I would have just swallowed them. Yes the initial rush would not be there but I would still get the after-effects of it and wouldn’t be sick from withdrawals so it really wouldn’t have changed my usage, just the route administered.”

On the other hand, over half ( $n = 43/77$ ) indicated they were not only “less likely” to use OxyContin, but they often noted heroin and stronger, prescription opioids as replacement drugs. In fact, heroin was the second most frequently found word amongst all respondents (Table 5).

“Because of the change in the OxyContin formulation, I tried heroin for the first time. I did that in part because you couldn’t smoke or snort the OxyContin pills anymore so I resorted to something you could do that with. EVERY single person I know now that used pills, now uses heroin because of the change in formulation. Also, EVERY person I know that now uses heroin uses it intravenously. More people than I can count who I never thought would ever even try heroin are now shooting it up.”

“Switched to instant release oxycodone and morphines and hydromorphone.”

#### 4. Discussion

Our results indicate, as expected from earlier work, that oxycodone and hydrocodone products, the opioids most commonly used to control pain in the medical and dental fields [19,37,41], are likewise the most highly abused opioids [2,7,12,21,27,37,42,45]. Given that it has been shown that there is a direct relationship between the number of opioid prescriptions by health care providers and the magnitude of diversion to the illicit marketplace [6,13,29], accessibility is certainly a major feature attracting non-therapeutic users to these drugs. Moreover, both drugs have a long history of use for nontherapeutic purposes, and their patterns of use, side effects, and so forth, are well known and predictable to the well-informed drug sub-culture. While these data explain to some extent why oxycodone and hydrocodone are the primary drugs of more than 75% of those entering substance abuse treatment, it should not be assumed that the population of oxycodone and hydrocodone users is homogenous and uses these drugs interchangeably, even though nearly all respondents had used both drugs to get high in the past. On the contrary, despite reports of pharmacological, physiological, and subjective similarities between oxycodone and hydrocodone in preclinical and clinical laboratory studies [34,40,46], our data indicate that there are very substantial differences between those who use oxycodone and hydrocodone.

One of the major differences is that pure oxycodone is readily available as a stand-alone formulation in many dose forms, whereas hydrocodone is marketed only as a combination product, most commonly hydrocodone and acetaminophen in relatively small doses (usually 5 mg of hydrocodone and 325 mg of acetaminophen). Thus, there are many dose options available for oxycodone, which may enhance its popularity, most likely for those in whom dose escalation is the desired goal as tolerance developed.

However, the presence of acetaminophen in all hydrocodone products may be a much more important factor limiting its use relative to oxycodone. For example, we found through our direct patient interviews that the “adulteration” of hydrocodone with acetaminophen was a major factor limiting its use relative to oxycodone. For example, those opioid users who inhale or inject their drugs have a decided preference for oxycodone due to its intrinsic euphorogenic properties and, most importantly, freedom from the irritation of acetaminophen when used nasally or intravenously. Consequently, hydrocodone is almost exclusively taken orally, in large part because it is both easily accessible and perceived to be much safer since hydrocodone overdose deaths are less frequent than those attributable to oxycodone [35]. However, the considerable fear of acetaminophen toxicity, in terms of liver damage, greatly limits the amount of hydrocodone users feel comfortable taking orally to produce a high equivalent to that generated by oxycodone or to dose escalate as tolerance develops. This may influence the apparent “satisfaction” of users with their drug of choice to get high. Specifically, 54% of oxycodone users indicated that the high was superior to other drugs and was a major factor in its selection as a primary drug, whereas <20% of hydrocodone users indicated this was true. Furthermore, most oxycodone users indicated that their choice of oxycodone as a primary drug would persist, even in an ideal world in which cost and availability would not be factors in drug selection. This contrasts sharply with hydrocodone, where nearly half its users were willing to shift preferences, with most endorsing oxycodone products as their preferred alternative. While much of this difference can be attributed to acetaminophen toxicity, it is also possible that, despite preclinical and clinical studies that suggest equality between hydrocodone and oxycodone [34,40,46], users do easily discriminate between the 2, with oxycodone the clear choice.

The foregoing discussion raises 2 important, interrelated issues regarding opioid-acetaminophen combination drugs: first, one wonders, based on our results, whether compounds containing only hydrocodone would have much greater appeal than combination products; and second, if oxycodone was available only as a combination product with acetaminophen, would its use drop significantly? While there are no definitive data on this point, we speculate that opioid-acetaminophen products would generally have less significant abuse rates than opioid-only drug formulations. Interestingly, in December 2012, the U.S. Food and Drug Administration’s (FDA) Anesthetic and Analgesic Drug Products Advisory Committee voted against approval of Zohydro (Zogenix Inc, San Diego, CA, USA), which would have been the first hydrocodone-only product (extended release) available in the United States. The lack of an abuse deterrent formulation (ADF) of Zohydro, analogous to the new OxyContin ADF, was also a factor in this decision. It was clearly noted by the FDA, as shown in earlier published studies and the present results, that the ADF of OxyContin dropped its abuse rates significantly. There is no reason to believe that the same would not be true for other ADF formulations and, indeed, one could argue, as the FDA advisory group did, that, given the epidemic of prescription opioid abuse in this country, all extended-release opioid compounds, with their large reservoirs of pure opioid, should only be produced as an ADF.

The major question these data raise is why hydrocodone remains one of the most popular primary drugs despite its lower quality of high, potential for acetaminophen poisoning, and preference of its users for other opioids? Our data indicate that it is relatively inexpensive, easily accessible through physicians, friends, and families, and relatively safe to use, particularly by risk-averse users. For example, it is most commonly used in generally risk-averse women, elderly people, noninjectors, and those who prefer safer modes of acquisition than dealers (ie, doctors, friends, or family members). In contrast, oxycodone is a much more attractive

euphorogenic agent to risk-tolerant young, male users who prefer to inject or snort their drugs to get high and are willing to use riskier forms of diversion despite paying twice as much for oxycodone than hydrocodone. Prevention and treatment approaches should benefit from these results because it is clear that not all drug abusers share the same characteristics, and the decision to use one drug over another is a complex one, largely attributable to individual differences (eg, personality, gender, age, and other factors). Prescribing physicians should not only be aware of the potential for abuse, as many are, but that the selection of a primary drug is not a trivial concern and may determine which drug to prescribe and monitor for abuse. More work is needed to better characterize factors that could help physicians identify problematic patients on a more specific level.

Our studies support the claim that while the 8-factor analyses of abuse liability [1] required by the Controlled Substances Act is useful in assessing abuse potential [15,16,25,29], it will not always predict how a drug will behave when it is widely used in clinical practice [5,9,29,41]. While oxycodone and hydrocodone conform to their Schedule II status (Schedule III for hydrocodone combination products), other opioids predicted to have as much, or more, abuse potential, such as fentanyl, hydromorphone, morphine, oxymorphone – are rarely chosen by those who use opioids nontherapeutically to get high [9]. Much of this low usage may be due to FDA-mandated “black box” labels, or more likely, restricted use of these drugs to very controlled conditions, such as hospital settings. However, our results suggest that, aside from availability, these very potent opioids are still seemingly avoided for a variety of reasons: first, safety concerns about potency, overdose, or other undesirable effects; second, difficulty in dose-titration or extracting the active ingredient from its delivery device – for example, patch or an ADF; third, poor perceived quality of the high relative to other hard-to-get drugs.

The present data provide fairly compelling evidence that, although the main reason most of our participants are in treatment is for the use of opioid drugs to get high, there is one factor that should be examined in more depth: the importance of pain management as a motivating factor in the use of any opioid. Although getting high was the desire of nearly all users of both oxycodone and hydrocodone, 50–60% also indicated that the management of pain was an important factor. Moreover, the subset of RAPID participants who used hydrocodone as a primary drug, in addition to having far more associations with pain management than oxycodone users, also indicated that the “high” was not euphoria in the typical meaning of the word. Rather, the relief of pain resulted in an increase in mood and energy, and it was this that led them to use opioids to alter their mood. This response illustrates the strong confounding effect of pain management in the selection of a primary drug that has the dual effect of pain relief and euphoria. Based on these findings, more studies are needed in examining the role of pain in the misuse/abuse of specific opioid analgesics, particularly its real or perceived under-treatment, the economics of drug acquisition for pain, the incidence of abuse in chronic pain patients and, finally, whether pain management is as important as, or more important than, euphoria.

The importance of drug formulation on the misuse of opioids is considerable and, in addition to the discussion above, is also illustrated by the successful introduction of the ADF of OxyContin [11]. This formulation inhibits crushing the device for inhalation or solubilizing it for injection. As we have shown here and elsewhere [11], the popularity of OxyContin dropped precipitously with the introduction of the changed formulation. But there was an unfortunate consequence in that former OxyContin users did not stop opioid abuse, nor did they fall back to less potent opioids such as hydrocodone, but instead, shifted to heroin or stronger, prescription opioids, as the quotes from our qualitative studies

demonstrate. It should also be noted that our qualitative data indicated that the new formulation did not seem to deter those who use OxyContin orally, and in fact, merely shifted some from injecting and inhaling OxyContin to oral routes of administration.

There are limitations in our studies which should be kept in mind. Our population was exclusively those entering opioid abuse treatment clinics who obviously had severe abuse patterns. Thus, the applicability of our results to more recreational users, or users not likely to seek treatment, may be questionable. Furthermore, while our sample was large ( $n = 3530$ ), it was relatively small compared to other national databases (TEDS = 154,568) and thus, its representativeness could be questioned. However, our data show the gross demographics of prescription opioid users in both samples to be similar, suggesting that our results are relevant to the entire population of treatment clients. In addition, self-administered, structured surveys suffer from the limitations of any standardized instrument, such as ambiguous answers and incomplete data. While we recognize these limitations, the RAPID data are not as prone to such weaknesses and amplified and confirmed the observations gleaned from the SKIP survey. There is also the possibility that answers to some historical questions were impacted by poor recollection or that subjects misreported their drug use, though the assurance of confidentiality from their treatment providers likely mitigated this issue. Despite these limitations, we believe that a major strength of our approach was the joint use of SKIP and RAPID programs. The latter qualitative study added richness to the data, clarified ambiguities, and provided context to the issues identified in the SKIP study. We believe the combination of quantitative and qualitative data in epidemiological studies can lead to a better understanding of substance abuse than either approach alone and, therefore, would strongly endorse this approach in other studies.

### Conflict of interest statement

Authors Cicero and Surratt serve as consultants on the Scientific Advisory Board of the nonprofit postmarketing surveillance system, RADARS (Researched Abuse, Diversion and Addiction-Related Surveillance), which collects subscription fees from 14 pharmaceutical firms.

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