

ORIGINAL REPORT

Patterns of abuse and routes of administration for immediate-release hydrocodone combination products

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Abstract

Purpose: Prescriptions for hydrocodone immediate-release (IR) combination products have recently decreased, yet they represent the majority of opioid prescriptions dispensed and are commonly abused analgesics among both adults and adolescents. Little data exist to understand the contribution of IR products to the problem of prescription opioid abuse. This study aimed to better understand abuse patterns for hydrocodone IR combination products among adult and adolescent substance abusers.

Methods: This cross-sectional study examines abuse prevalence (including abuse adjusted for prescription volume and morphine milligram equivalents) and abuse characteristics for hydrocodone IR combination products and other prescription opioids among separate samples of adults and adolescents assessed for substance abuse problems or entering treatment from January 2012 through June 2015.

Results: Results indicate higher abuse for hydrocodone IR combination products than other opioid categories per 100 assessments but lower per prescriptions dispensed. Hydrocodone IR combination products had similar abuse prevalence to all extended-release and long-acting opioids when considering abuse measured per morphine milligram equivalents dispensed. An upward trend in hydrocodone IR combination product abuse was observed among adult substance abusers comparing the period prior to and after Drug Enforcement Administration rescheduling of these products in October 2014. Most individuals reported oral abuse of hydrocodone IR combination products, but snorting, reported by 23% of hydrocodone IR combination product abusers, also appears to be a route of abuse that may have public health relevance.

Conclusions: Given their high prescription volume, hydrocodone IR combination products, even at a relatively low prevalence of abuse, may contribute substantially to the overall problem of prescription opioid abuse. Additional public health interventions, including development of abuse-deterrent formulations for these types of opioid products may aid in reducing their abuse.

KEYWORDS

abuse-deterrent formulations, hydrocodone, NAVIPPRO, opiates, prescription opioids, route of administration

A portion of these data were presented at PAINWeek 2015 in Las Vegas, Nevada, September 2015.

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1 | INTRODUCTION

Abuse of prescription opioid medications is a significant and pervasive public health problem in the United States affecting the adult and adolescent populations. Of the 21.5 million Americans 12 years or older with a substance use disorder in 2014, 1.9 million involved prescription pain relievers.¹ Further, in 2014, 467 000 adolescents were current non-medical users of pain relievers, with 168 000 reporting a past year prescription pain reliever use disorder.¹ While the problem is multifaceted, one contributing aspect is overprescribing of these medications and the resulting availability for these products to be diverted for purposes of misuse and abuse. Over a 10-year period from 2000 to 2010, prescriptions of opioid analgesics increased by 104%, with prescribing rates among adolescents and young adults nearly doubling during this time.²

While opioid prescribing stabilized from 2010 to 2012,³ and more recently prescriptions for hydrocodone immediate-release (IR) combination products have decreased from approximately 125 to 90 million from 2011 through 2015, these products alone still represent the largest category of opioid prescriptions dispensed nationwide (approximately 37%).^{4,5} Hydrocodone is also one of the more commonly abused opioid medications among adults.⁶⁻⁸ Further, hydrocodone IR combination products have also been reported as one of the most common drugs involved in prescription overdose deaths.⁹ Recently published data from US poison control centers indicate that for intentional exposures among adolescents specifically, hydrocodone is the most frequently reported misused or abused drug.¹⁰

Several interventions and nationally based efforts have been implemented to lessen the burden of prescription opioid abuse. Strategies to address the prescription opioid abuse epidemic include controls and monitoring of appropriate prescribing practices through implementation of state-wide prescription monitoring programs^{11,12} increased efforts to improve prescriber education related to safe opioid prescribing¹³ and more recently, efforts to expand access to and funding for medication-assisted substance abuse treatment services.¹⁴ The US Food and Drug Administration (FDA) has also taken specific steps to improve the safe use of prescription opioids by implementing a class-wide risk evaluation and mitigation strategy for extended-release (ER) and long-acting (LA) opioid products. In addition, black box safety warnings for both ER and IR pain medications were issued to highlight the risks of misuse, abuse, overdose, and death due to these products.¹⁵ The FDA also encouraged pharmaceutical companies to develop new drug technologies and abuse-deterrent formulations (ADFs) that address opioid abuse.

In October 2014, the Drug Enforcement Administration (DEA) rescheduled hydrocodone IR combination products from a schedule 3 controlled substance to schedule 2 resulting in certain restrictions in prescribing and dispensing of these opioid medications.¹⁶ While the rescheduling is expected to result in lower abuse and diversion of these products, it is important to understand and characterize their associated patterns of abuse to be able to examine the impact of this change and potential future changes in the opioid landscape. Moreover, hydrocodone IR combination products still remain the most widely prescribed and available opioid products. In addition, although lifetime abuse of IR opioids is at least as prevalent as abuse of ER opioids, nearly all currently marketed opioids with FDA-approved

KEY POINTS

- While the number of prescriptions for hydrocodone IR combination products has recently decreased, these products still represent the majority of opioid prescriptions dispensed in the United States and are commonly abused by both adults and adolescents. Lifetime abuse of immediate-release opioids is at least as prevalent as abuse of extended-release opioid products, but little data exist to understand their contribution to the problem.
- Postmarket surveillance data were used to examine patterns in abuse prevalence and ROA for hydrocodone IR combination products among 2 high-risk populations of adults and adolescents assessed for substance abuse treatment.
- Abuse prevalence was higher for hydrocodone IR combination products than other opioid categories but was lower than other opioid categories per prescriptions dispensed. Hydrocodone IR combination products had similar abuse prevalence to all ER/LA opioids when considering abuse measured per MME dispensed.

abuse-deterrent product labels are ER products. To further understand abuse of hydrocodone IR combination products, we examined their pattern of abuse among 2 high-risk populations of adults and adolescents assessed for substance abuse treatment problems relative to other opioid compounds including IR and ER products as well as ADF and non-ADF opioid formulations currently on the market.

2 | METHODS

2.1 | Sample description

This study was a cross-sectional design that examined data from adults (ages 18 and older) and adolescents (primarily ages 13 to 18) assessed for substance-abuse problems using 2 data sources from NAVIPPRO®, a public health surveillance system for monitoring patterns and trends in substance abuse including prescription medication use and abuse.¹⁷ We examined prevalence of past 30-day abuse of hydrocodone IR combination products in comparison to other prescription opioids among separate samples of adults who completed an ASI-MV® (Addiction Severity Index – Multimedia Version) assessment and adolescents who completed a CHAT® (Comprehensive Health Assessment for Teens) assessment. Data were examined across a 3.5-year period from January 1, 2012, through June 30, 2015, with a specific focus on the 18-month period before and after the change in scheduling of hydrocodone IR combination products from schedules 3 to 2 (ie, January 2014 through June 2015).

Both the ASI-MV and CHAT assessments are structured, self-administered, computerized interviews that measure the severity of a range of problem areas associated with drug and alcohol abuse and are used for clinical assessment and treatment planning on admission to drug and

alcohol treatment.¹⁸⁻²⁰ Data were drawn from 831 facilities located within the United States that participate by contributing data to the ASI-MV network and 180 facilities that contribute data on adolescents.

2.2 | Measures/data analysis

Abuse and specific route of administration (ROA) for hydrocodone IR combination products and 6 other prescription opioid categories including oxycodone IR combination products, oxycodone IR single-entity products, all other IR opioid products, all ER/LA opioids, all ADF ER/LA opioids (product with approved ADF label or formulated to deter abuse without ADF label), and all non-ADF ER/LA opioids were captured via self-report during either the ASI-MV or CHAT assessment. Products included in the opioid groups examined are provided in Table 1. Abuse was defined as use of a prescription opioid product at least once within the past 30 days prior to assessment not prescribed to you or used in a way not intended for pain relief. Route of administration pattern was measured as the frequency and percent of individuals reporting a specific route of abuse among individuals who reported overall past 30-day abuse of the individual opioid categories reviewed (ie, proportion of abuse via oral route, snorting, or injection). Characteristics (eg, abuse severity and illicit drug use) of abusers of hydrocodone IR combination products were also examined.

Abuse prevalence was calculated first as the proportion of any past 30-day abuse for a particular opioid category among the study sample (the number of past 30-day abuse cases per 100 assessments where the denominator is equal to the total number of either adult or adolescent assessments). Two additional measures of abuse prevalence were calculated to account for differences in prescription volume across the opioid categories examined including (1) the number of cases of past 30-day abuse for a particular opioid category per 100 000 prescriptions dispensed and (2) the number of cases of past 30-day abuse for a particular opioid compound per 10 000 000 morphine milligram equivalents (MME) dispensed.

Abuse estimates presented as per 10 000 000 MME dispensed were derived using the total weight in milligrams dispensed for each opioid category multiplied by the morphine equivalence factor for each opioid compound.²¹ Weights for individual products were summed across all of the available product dosage strengths and across all products included in a specific opioid category. Prescription data for these analyses were obtained from IMS Health using the IDW (Integrated Data Warehouse) pain market prescription database. These data provide national level projected prescription tracking captured at the pharmacy level within the United States and include cash, Medicaid, and third-party transactions.

To examine changes in abuse prevalence and the possible impact of rescheduling of hydrocodone IR combination products in October 2014, an analysis of temporal trend in abuse was conducted using general estimating equation regression models to determine the probabilities of abuse prevalence over time for 2 denominators: (1) abuse per 100 assessments and (2) abuse per 10 000 000 MME. The models estimated period-specific slopes in the rate of abuse for a given opioid category per quarter in the period before and after rescheduling of hydrocodone IR combination products. Models were parameterized

TABLE 1 Listing of products included in opioid categories

Opioid Group	Product Included
Hydrocodone IR combination products (brand and generic formulations)	Lorcet Lortab Vicodin Vicoprofen Norco Other immediate-release hydrocodone combination product
Oxycodone IR combination products (brand and generic formulations)	Percocet Tylox Percodan Combunox Roxicet Other short acting oxycodone (includes other generic oxycodone IR combination products)
Oxycodone IR SE	OxyIR Roxicodone Other Roxicodone not shown
All other IR prescription opioids (both single-entity and combination excluding schedule 3 products)	Actiq Fentora Onsolis Dilaudid Other IR hydromorphone (includes generic hydromorphone IR products) MSIR Other IR morphine Opana Generic IR oxymorphone Nucynta
All ER/LA opioids (both ADF and non-ADF products excluding patch and buprenorphine products)	Original/old OxyContin Reformulated/new OxyContin Xartemis XR Other non-combination ER oxycodone Other ER oxycodone w/ acetaminophen Exalgo MS Contin KADIAN AVINZA Oramorph SR EMBEDA Other ER morphine not shown Original/old Opana ER Reformulated/new Opana ER Generic ER oxymorphone (Actavis) Generic ER oxymorphone (Impax) Other generic ER oxymorphone not shown Nucynta ER Zohydro ER
All ADF ER/LA opioids ^a	Reformulated OxyContin Xartemis XR Exalgo EMBEDA Reformulated Opana ER Nucynta ER
All non-ADF ER/LA opioids (excluding patch and buprenorphine products)	Original OxyContin Other non-combination ER oxycodone Other ER oxycodone w/ acetaminophen MS Contin KADIAN AVINZA

(Continues)

TABLE 1 (Continued)

Opioid Group	Product Included
	Oramorph SR
	Generic ER morphine products
	Original Opana ER
	Generic ER oxycodone (Actavis)
	Generic ER oxycodone (Impax)
	Other generic ER oxycodone
	Zohydro ER

Abbreviations: ADF, abuse-deterrent formulation; ER, extended release; IR, immediate release; LA, long acting; SE, single entity.

^aADF ER/LA Opioids category includes opioid products with abuse-deterrent labeling approved by the FDA and products with ADF properties or formulations intended to deter abuse but without approved ADF labeling by the FDA.

where the fixed effects included a categorical indicator variable for period, a time covariate (measured in calendar quarter units), and the interaction of both fixed effects. A log-binomial model was used to estimate changes in linear trends in abuse per 100 assessments across each of the 4 years examined. A log-Poisson model was used to estimate changes in linear trends in abuse per 10 000 000 MME dispensed. The number of assessments and prescription volume, defined as MME, were treated as offsets in the models.²² Analyses for trend were performed for the adult sample only. Trend analyses were not feasible among the adolescent sample due to small sample size across the period examined.

3 | RESULTS

3.1 | Sample demographics

The adult sample consisted of 226 357 assessments from 831 sites in 45 states within the United States during January 2012 through

June 2015. Demographically, the adult sample was primarily individuals of younger age (59% between 18 to 34 years) and male (64%). The majority of adults in the sample were Caucasian race (62.1%) (Table 2). Overall, 60% of the adult sample were prompted to enter substance abuse treatment via the criminal justice system and nearly 33% reported a chronic pain problem. Approximately 23% reported that they had abused a prescription opioid within the past 30 days. In general, adult prescription opioid abusers within the sample had a similar demographic profile to the total sample with the exception that a lower percentage was prompted to enter treatment by the criminal justice system (36%) and a higher percentage reported a problem with pain (approximately 50%). The adolescent sample consisted of 12,906 assessments from 180 sites in 26 states within the United States. Approximately 80% of the adolescent sample was between 15 to 18 years old. Sample demographics for adolescents were similar to that of adults where a higher percentage of were male (68.2%) and Caucasian (67.8%) (Table 1). The majority were enrolled in public school (72.4%) and 35% reported being in a controlled environment (such as juvenile justice/detention center, mental health facility, or treatment setting) within the past 30-days.

3.2 | Abuse prevalence of hydrocodone IR combination products

Across the 3.5-year period examined, prevalence of abuse of hydrocodone IR combination products within the adult sample was highest (9.6 per 100 assessments) compared to all other opioid categories examined (range = 3.0 per 100 assessments for all other IR opioids to 8.0 per 100 assessments for oxycodone IR combination products). For adults, abuse prevalence for hydrocodone IR combination products was nearly twice that of all non-ADF ER/LA opioids (5.2 per 100

TABLE 2 Demographic characteristics of adults and adolescents assessed for substance abuse treatment

Response	Adults (N = 226 357)		Adolescents (N = 12 096)		
	n	%	n	%	
Age	<10 years		24	<1.0	
	10-14 years		2 378	19.7	
	15-18 years		9 626	79.6	
	>18 years		63	<1.0	
	18-24 years	50 961	22.5		
	25-34 years	82 930	36.6		
	35-54 years	80 063	35.4		
	>55 years	12 403	5.5		
Gender	Male	144 977	64.0	8 255	68.2
	Female	81 357	35.9	3 841	31.8
	Unknown	20	<1.0	0	0.0
Race	Caucasian	140 594	62.1	8 206	67.8
	African American	41 757	18.4	2 629	21.7
	Hispanic/Latino	29 952	13.2	1 419	11.7
	Other race	14 054	<1.0	1 349	11.1
Treatment prompted by criminal justice ^a	135 775	60.0	N/A	N/A	
Controlled environment [‡]	N/A	N/A	4 237	35.0	
Chronic medical problem	66 576	29.4	3 432	28.4	
Pain problem	73 995	32.7	2 357	19.5	

^aAdmission to substance abuse treatment required or encouraged by a judge, probation/parole officer, or other criminal justice official.

[‡]includes juvenile detention center, jail/prison, inpatient substance abuse, medical or mental health treatment, residential group home.

assessments) and nearly 3 times that of all ADF ER/LA opioids (3.5 per 100 assessments) (Figure 1). Among this sample of adults assessed for substance abuse treatment, the abuse prevalence of hydrocodone IR combination products relative to other prescription opioid categories remained the same annually across the 3.5-year period with abuse of hydrocodone IR combination products remaining higher than the other opioid categories examined including ADF ER/LA opioids and non-ADF ER/LA opioids.

The pattern of past 30-day abuse prevalence for hydrocodone IR combination products and the other opioid categories among adolescent substance abusers was similar to the adult sample where abuse prevalence of both hydrocodone IR combination and oxycodone IR combination products was higher than other opioid categories reviewed (Figure 2). To better understand the role of drug availability (number of prescriptions and amount of opioids dispensed) on abuse across the various opioid categories, prevalence of abuse measured as per 100 000 prescriptions dispensed and measured as per 10 000 000 MME dispensed were included in the analysis. Per prescriptions dispensed, abuse estimates for hydrocodone IR combination products was the lowest of all opioid categories for both adults and adolescents assessed for substance abuse treatment due to hydrocodone IR combination products having the highest volume of

prescriptions (Figures 3A,B). However, when considering the dosage and potency of the total prescriptions dispensed (MME dispensed) across the 6 opioid categories, abuse prevalence for hydrocodone IR combination products was comparable to ER/LA opioids (among adults 1.16 per 10 000 000 MME dispensed and 1.01 per 10 000 000 MME dispensed, respectively) (Figures 4A,B).

3.3 | Trend in abuse of hydrocodone IR combination products

Consistent with abuse patterns observed over the total 3.5-year period assessed, hydrocodone IR combination products also had the highest past 30-day abuse prevalence of the opioid categories examined during each quarter prior to and following hydrocodone rescheduling (Figure 5). However, both hydrocodone IR combination products and oxycodone IR combination products showed an overall pattern of decreasing prevalence across the first 5 quarters (Q1 2014 through Q1 2015), and a higher prevalence of abuse in the most recent quarter reviewed (Q2 2015). For hydrocodone IR combination products, abuse prevalence among adults ranged from 9.26 cases per 100 assessments during Q3 2014 to 8.78 cases per 100 assessments during Q1 2015 but was 10.53 cases per 100 assessments the following

FIGURE 1 Prevalence of past 30-day abuse per 100 assessments and 95% confidence intervals (95% CIs) among adults assessed for substance abuse treatment (1/1/2012 to 6/30/2015). ADF, abuse-deterrent formulation; ER, extended release; IR, immediate release; LA, long acting. [Color figure can be viewed at wileyonlinelibrary.com]

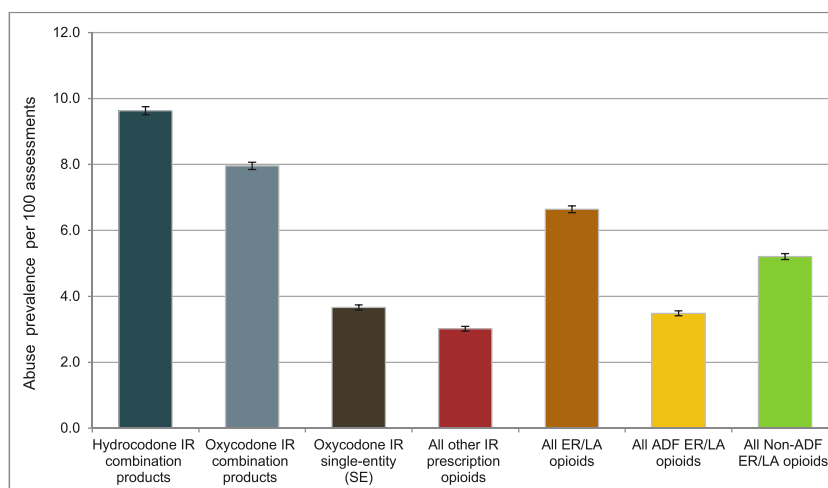
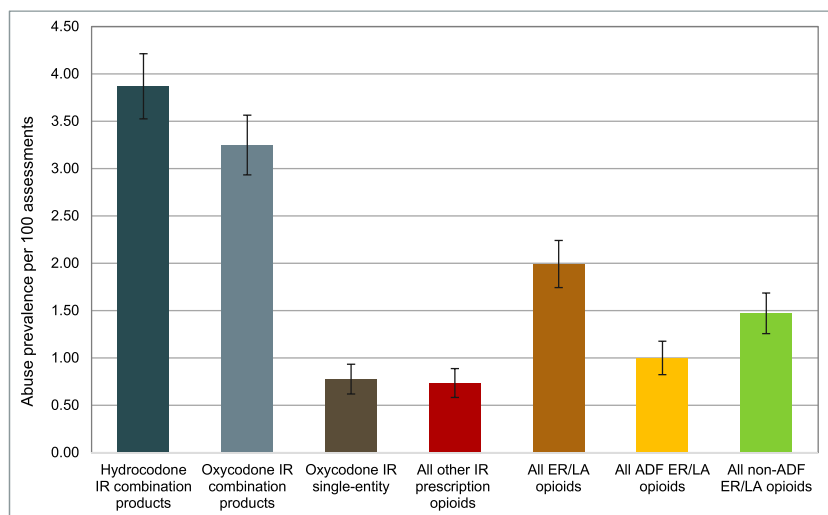
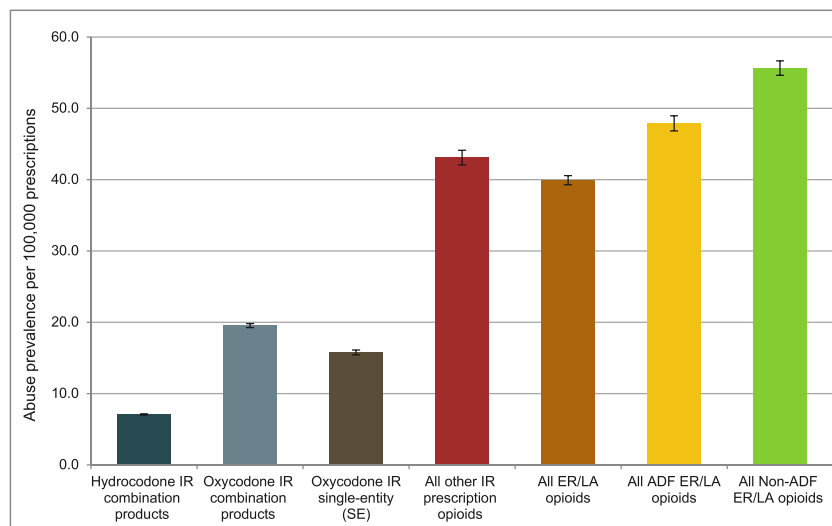
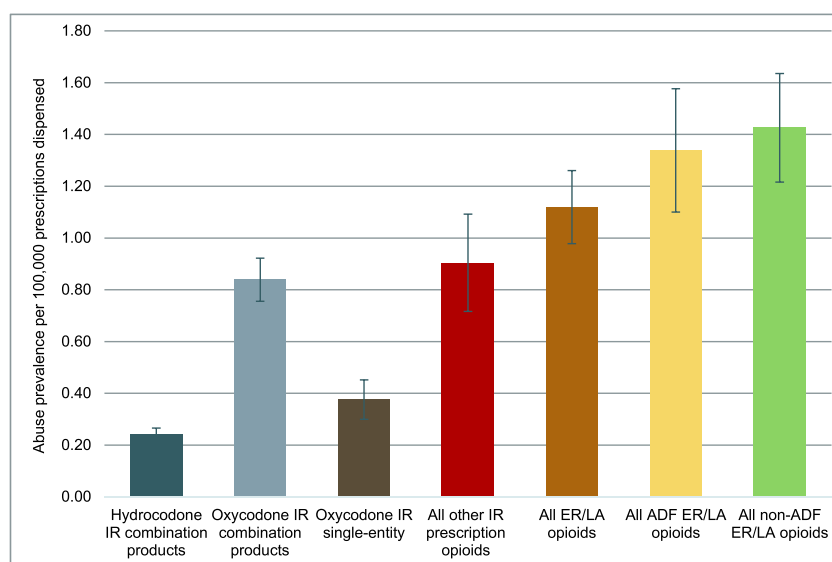


FIGURE 2 Prevalence of past 30-day abuse per 100 assessments and 95% confidence intervals (95% CIs) among adolescents assessed for substance abuse treatment (1/1/2012–6/30/2015). ADF, abuse-deterrent formulation; ER, extended release; IR, immediate release; LA, long acting. [Color figure can be viewed at wileyonlinelibrary.com]





A



B

FIGURE 3 A, Prevalence of past 30-day abuse per 100 000 prescriptions dispensed and 95% confidence intervals (95% CIs) among adults assessed for substance abuse treatment (1/1/2012 to 6/30/2015). B, Prevalence of past 30-day abuse per 100 000 prescriptions dispensed and 95% confidence intervals (95% CIs) among adolescents assessed for substance abuse treatment (1/1/2012 to 6/30/2015). ADF, abuse-deterrent formulation; ER, extended release; IR, immediate release; LA, long acting. [Color figure can be viewed at wileyonlinelibrary.com]

quarter during Q2 2015. Past 30-day abuse for the category all other IR prescription opioids was lowest among the opioid categories reviewed, both overall (2.84 cases per 100 assessments during 2014 through Q2 2015) and quarterly (ranging from 3.10 cases per assessments during Q1 2014; to 2.78 cases per 100 assessments during Q2 2015).

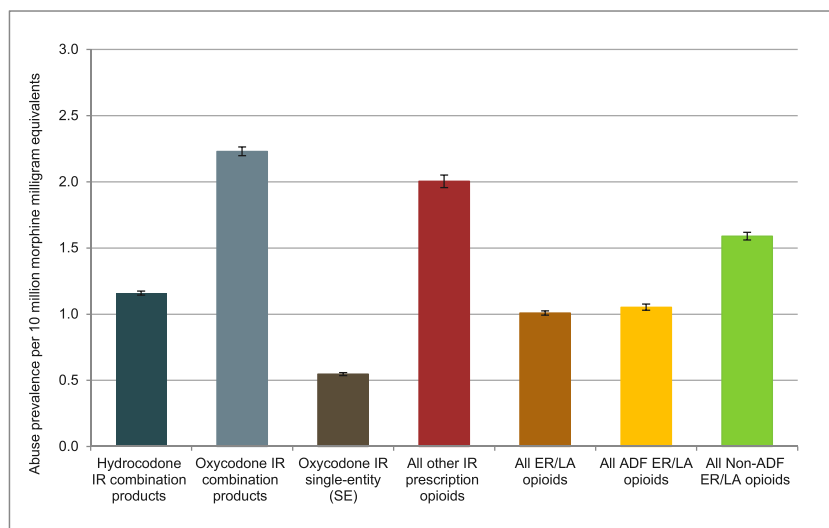
To further evaluate the patterns of abuse described above as well as to examine any potential change prior to and after the implementation of the DEA decision in early Q4 2014 to reschedule hydrocodone IR combination products and impose prescribing limits on these medications, a formal analysis of linear trend was conducted for the 3 quarters prior to and 3 quarters after rescheduling took effect. Trend analysis indicate that although quarterly estimates decreased by a factor of 0.98 during the 3 quarters prior to rescheduling, the change was not statistically significant ($P = .3595$) indicating essentially no change in the quarterly abuse estimates during Q1 2014 through Q3 2014.

After the rescheduling of hydrocodone IR combination products (Q4 2014 through Q2 2015), quarterly abuse estimates for hydrocodone IR combination products increased by a factor of 1.09 compared to the 3 prior quarters ($P < .0001$). Further, a relative

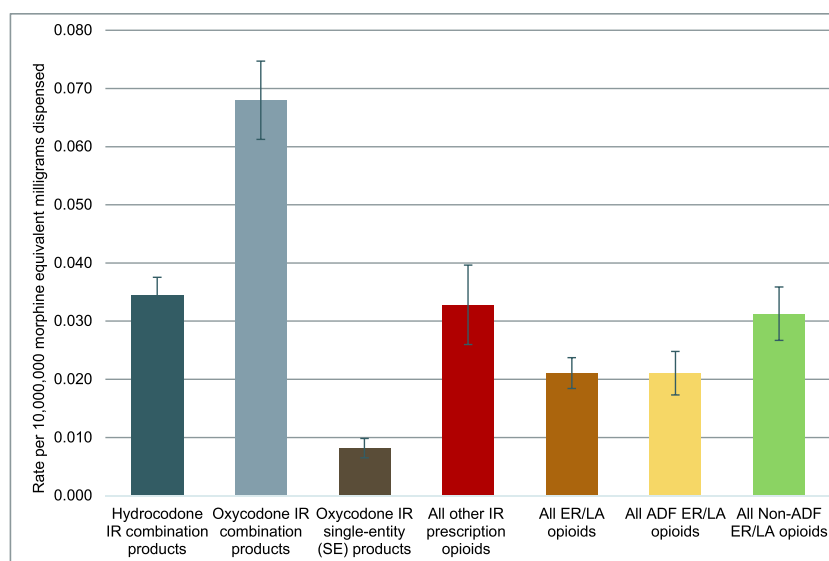
comparison of the differences in slopes over these periods indicated that the increase observed in hydrocodone IR combination products abuse during the postrescheduling period was significantly greater ($P < .0001$) in relation to the prerescheduling period whereas abuse of ER (both ADF and non-ADF formulations) and oxycodone IR single-entity products had significant downward trend in abuse after rescheduling (Figure 5). Similar results for trend were observed for modeled estimates of abuse of hydrocodone IR combination products per 10 000 000 MME where there was an increase in quarterly abuse prevalence after the rescheduling decision for these products. Comparison of quarterly estimates of abuse prevalence per morphine equivalent milligrams dispensed postrescheduling and prerescheduling indicates a statistically significant increase in abuse of hydrocodone IR combination products in the more recent period ($P \leq .0001$).

3.4 | Route of administration

A variety of ROAs was endorsed by both adults and adolescents who reported past 30-day abuse of hydrocodone IR combination products.



A



B

FIGURE 4 A, Prevalence of past 30-day abuse per 10 million morphine equivalent milligrams dispensed and 95% confidence intervals (95% CIs) among adults assessed for substance abuse treatment (1/1/2012 to 6/30/2015). B, Prevalence of past 30-day abuse per 10 million morphine equivalent milligrams dispensed and 95% confidence intervals (95% CIs) among adolescents assessed for substance abuse treatment (1/1/2012 to 6/30/2015). ADF, abuse-deterrent formulation; ER, extended release; IR, immediate release; LA, long acting. [Color figure can be viewed at wileyonlinelibrary.com]

Among the adult and adolescent substance abusers in this study, data reported for ROA were not mutually exclusive and individuals could indicate multiple routes for using a product. Hydrocodone IR combination products were indicated by adults as most often abused via the oral ROA (90.3%) with 23.4% reporting use via snorting and a very low level of abuse reported via other routes such as smoking or injection (<2.0%) (Figure 6; Figure S1A). Adolescents reported a similar pattern of ROA for these products with abuse primarily via the oral route (81.2%), although 42.5% reported snorting and less than 5% smoking or injection (Figure 6). While oral abuse of hydrocodone IR combination products was the predominant route of abuse among both adolescent and adult abusers of hydrocodone IR combination products, oral abuse was somewhat lower for adolescents compared to adults whereas the percentage of individuals who indicated snorting was higher for adolescents (adolescents 42.5% vs adults 23.4%).

Further, in absolute terms, the total number of individuals who reported snorting hydrocodone IR combination products (n = 5071) was similar to the frequency who report snorting of all non-ADF ER/LA opioids (n = 5326) and oxycodone IR combination products

(n = 4812) (Figures S1B and 2). Among adolescents, a greater number of individuals reported snorting as an ROA for both hydrocodone IR combination products (n = 200) and oxycodone IR combination products (n = 202) compared to the other opioid categories examined (n = 52 for oxycodone IR single-entity, n = 50 for ADF ER/LA opioids, and n = 97 for non-ADF ER/LA opioids) (Figure S2).

3.5 | History and severity of hydrocodone IR combination product abusers

An additional question of interest for this analysis was to examine characteristics of individuals who report abuse of hydrocodone IR combination products as it relates to their substance abuse profile or history as reported among adults entering or assessed for treatment. Review of characteristics of adult substance abusers within the study sample who reported past 30-day abuse of hydrocodone IR combination products alone compared to those who reported past 30-day abuse of hydrocodone IR combination products as well as abuse of

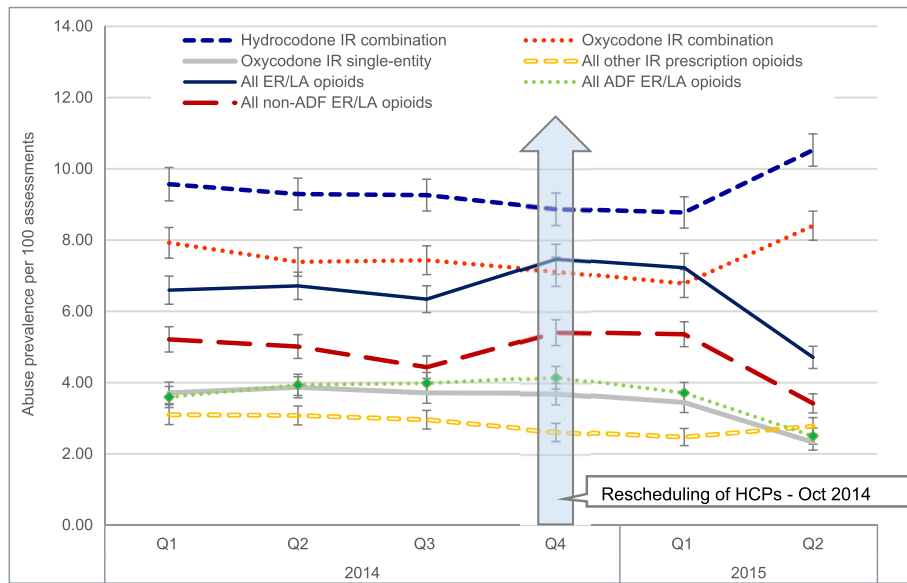
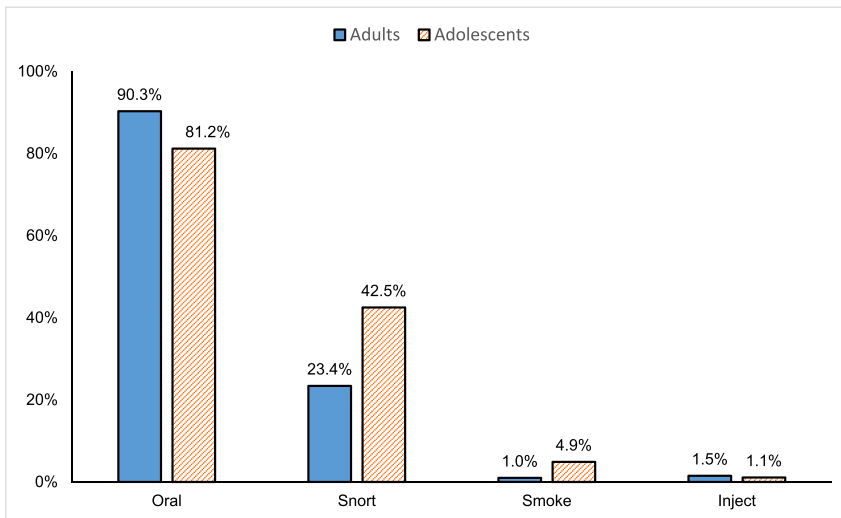
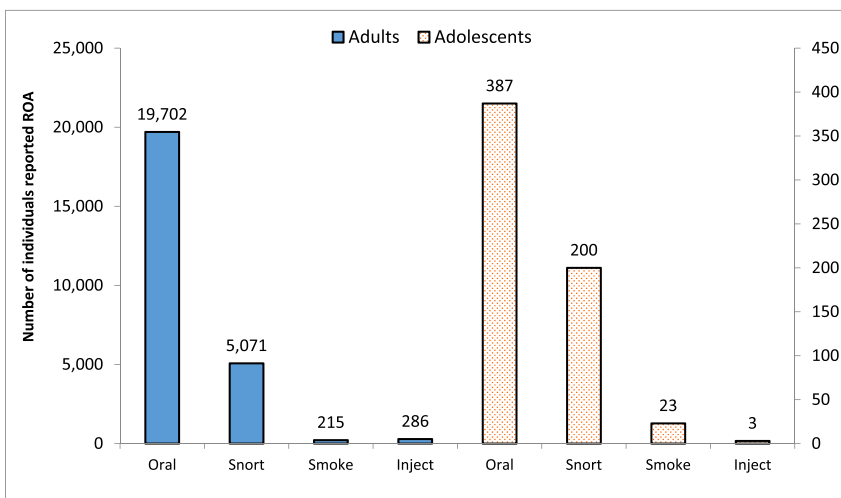


FIGURE 5 Trend in prevalence of past 30-day abuse per 100 assessments and 95% confidence intervals (95% CIs) among adults assessed for substance abuse treatment before and after Drug Enforcement Administration rescheduling of hydrocodone IR combination products (HCPs). ADF, abuse-deterrent formulation; ER, extended release; IR, immediate release; LA, long acting. [Color figure can be viewed at wileyonlinelibrary.com]



A



B

FIGURE 6 A, Percent of route of administration for past 30-day abusers of hydrocodone immediate-release (IR) combination products among adults and adolescents in substance abuse treatment. Note: respondents selected multiple routes so that percentages do not add to 100%. B, Number of individuals reporting route of administration for past 30-day abuse of hydrocodone IR combination products among adults and adolescents in substance abuse treatment. ROA, route of administration. [Color figure can be viewed at wileyonlinelibrary.com]

other prescription opioid products shows that among abusers of hydrocodone products, approximately 44% report only abusing hydrocodone and no other prescription opioid. Nearly 80% of those who report using only hydrocodone IR combination products also report abusing at least 1 illicit substance in the past 30 days including 8% reporting past 30-day heroin abuse. Calculated drug-problem severity scores for these individuals also indicate that a large number of abusers of hydrocodone IR combination products have substance abuse problems considered significant or extreme (Figure S3). Because of a small sample size within subgroups of hydrocodone abusers, data regarding drug problem severity among adolescents were too limited to provide meaningful analysis.

4 | DISCUSSION

Results of this study indicate that across the period of January 2012 through June 2015, past 30-day abuse prevalence of hydrocodone IR combination products by both adults and adolescents assessed for substance abuse treatment was higher than any other opioid category reviewed. This pattern was similar when reviewed quarterly across the 6 quarter period (Q1 2014 to Q2 2015) where the level of past 30-day abuse of each of the opioid categories relative to each other remained the same. Our study also found large differences in the relative ranking of abuse prevalence for hydrocodone IR combination products when measured using the denominator of total prescriptions dispensed versus total MME. Abuse prevalence per total prescriptions dispensed was lower for hydrocodone IR combination products than other opioids examined, a result of the large prescription volume for hydrocodone IR combination products that far exceeds that of the other opioid categories. However, in total MME dispensed, abuse of hydrocodone IR combination products showed prevalence estimates similar to the level observed for all ER/LA opioids combined. Use of these two denominators was intended to provide different perspectives of abuse prevalence by adjusting for the amount of abusable (or "at-risk") product in 2 ways: total prescriptions—by definition, simply adjusts for the number of prescriptions dispensed for a particular opioid product, MME also considers the dosage, number of tablets dispensed, and potency of each opioid, and thus removes some of the distortion in prescription-level prevalence estimates that do not account for these product-specific differences.

A statistically significant upward trend in the slope and prevalence of abuse of hydrocodone IR combination products per 100 assessments and per 10 000 000 MME was observed when comparing the 3 quarters prior to and after rescheduling of these products in October 2014 but was not apparent for abuse of hydrocodone IR combination products per prescriptions dispensed. This suggests that despite a decrease of approximately 26.23 million total prescriptions dispensed after the DEA rescheduling to schedule 2,²³ among this population of adult substance abusers, abuse of hydrocodone may not be substantially declining. However, it bears noting that this increase in abuse was mostly confined to the most recent quarter of data reviewed (Q2 2015) and that future monitoring is required to provide a more robust interpretation of this observation.

There are notable differences in reported ROAs among prescription opioid analgesic formulations. The preferred ROA most likely reflects the level of attractiveness an abuser perceives for a certain drug, which is itself determined by a myriad of pharmacological, behavioral, and social factors.^{24,25} Furthermore, individual abusers often report using several different routes of abuse.^{26,27} In this study, the ROA pattern among both adults and adolescents who report abuse of hydrocodone IR combination products demonstrate that the predominant ROA for these opioids is the oral route (adults, 90.3%; adolescents, 81.2%) followed by snorting (adults: 23.4%, adolescents: 42.5%). Opioid products including hydrocodone IR combination products were consistently snorted by a high percentage of adolescents while the percentage of adults snorting these products varied more among the opioid categories (22.7-56.0%). The opioids most frequently snorted by adults were oxycodone IR single-entity products (56.0%) and non-ADF ER/LA opioids (43.5%). This pattern may be an indication of the experience level and risk behavior related to experimentation of these younger abusers compared to more sophisticated adult substance abusers whose ROA pattern reflect their abuse knowledge and experience when using certain opioids. Although the percentage of hydrocodone IR combination abusers who reported snorting was lower than other opioid categories, the absolute number of those who reported snorting of hydrocodone IR combination products was similar to the number reported for other prescription opioids typically reported with high levels of snorting (such as oxycodone IR single-entity and non ADF ER/LA opioids).

There are several strengths and limitations to be considered when interpreting the analyses presented. We attempted to provide a broader public health perspective for understanding the potential burden of abuse of hydrocodone IR combination products relative to other prescription opioids by evaluating abuse prevalence using several denominators. Although the relative abuse level and ranking of hydrocodone IR combination products varied when different denominators were used, there is no single agreed upon denominator for which to measure abuse across the various subpopulations of abusers of prescription opioids.²⁸ Each calculation of abuse prevalence presented here provides a certain vantage point from which to assess abuse, and each of these measures has its own merits and drawbacks when viewed in isolation. For example, studies have indicated a relationship exists between the level of abuse of a drug and the amount of exposure or availability of a drug in the community.^{26,29-34} In the current analysis, abuse prevalence of hydrocodone IR combination products and comparison opioid categories were adjusted for prescribed availability of the products as a proxy for estimating exposure (ie, amount of product potentially available for abuse in the community). In this context, exposure or availability was measured in 2 ways: either per total prescriptions or per total MME dispensed for each product. These values represent abuse based on the total potentially abusable (at-risk) prescriptions circulating in a specified period (ie, cases per 100 000 prescriptions dispensed) or on the dosage and potency level of the opioid evaluated (ie, cases per 10 million MME dispensed). However, given that the number of prescriptions dispensed for hydrocodone IR combination products is much larger than for all other prescription opioids, reliance solely on use of total prescriptions as a denominator in the abuse prevalence estimates may

underestimate the true burden of abuse of these products. Prescriptions for hydrocodone IR combination products are typically of shorter duration than the other opioid categories, and these variations across opioid products are not accounted for when using prescription-level use as a denominator in abuse estimates. Furthermore, although a relationship between prescription volume and abuse has been observed, use of total prescriptions as a denominator assumes a linear or proportional relationship between abuse and a product's prescription volume. A recent analysis of abuse and prescription volume for different opioids suggests that it is possible that there is a point in prescription volume at which the abuse of a product does not proportionally increase with increasing prescriptions.³⁵ Therefore, it is important to consider empirical evaluation of the current assumptions underlying the relationship between prescription volume and abuse when used as a denominator. These aspects of prescription-based denominators underscore the major differences that can arise in abuse estimates between opioid products solely based on their various prescribing patterns. For this purpose, consideration of abuse expressed as absolute prevalence can provide additional perspective when comparing the abuse burden across individual opioids and between opioids classes.

Results presented here should be viewed in light of certain limitations. The current analyses were conducted among a sentinel population of individuals assessed for or entering substance abuse treatment. As such, they are not representative of all individuals who seek or do not seek treatment or of general population-based trends in prescription opioid abuse. Further, although the adult sample was large in terms of the number of treatment sites included and individuals assessed, the adolescent sample was of smaller sample size. Because both the ASI-MV and CHAT are convenience samples, meaning that the data are not collected as a random sample but provided from sites that participate in these surveillance networks by administering the assessment in their clinical settings, they are limited in geographic scope. For example, the ASI-MV has better representation in the West and South and a majority of data within the CHAT are from sites located in Missouri. Despite this, a strength of the present study includes the large and diverse sample that allows examination of abuse patterns among a sensitive population at high risk of prescription opioid abuse and likely with a high prevalence of tampering with these medications for abuse purposes. Although data from both the adult and adolescent study samples rely on self-report, they are validated clinical instruments³⁶⁻³⁹ that collect data as part of a clinical assessment rather than for pure research purposes. These data may therefore be more accurate as compared to self-report of substance use patterns in general population surveys since data collection occurs as part of patient treatment. Additionally, the data from the ASI-MV and CHAT constitute a uniform and systematic method of data collection over time and across sites with detailed questions that differentiate product-specific abuse and ROA in near real-time. This data collection procedure has been shown to be sensitive to detecting rapid changes in abuse patterns particularly in detecting more recent shifts in prescription opioid abuse after introduction ADFs to the market.^{31,40}

In summary, examination of abuse of hydrocodone IR combination products in 2 high-risk populations (adults/adolescents assessed for substance abuse treatment) indicated that abuse of these products

impacts a large number of prescription opioid abusers and occurs at a level of severity that represents considerable or extreme abuse behavior. Although proportionally most individuals report oral abuse of hydrocodone IR combination products, snorting also appears to be an ROA for these products that has public health relevance. Of particular public health relevance is the high percentage of snorting of hydrocodone IR combination products observed among adolescents in substance abuse treatment. Since no one standard denominator exists for which to assess prevalence or incidence of abuse of prescription opioid products across the various segments of abuser populations, evaluating abuse burden of hydrocodone should include examination of abuse not only adjusted for drug exposure (prescriptions dispensed) and amount of active pharmaceutical ingredient available but also absolute prevalence of abuse. The combined data can provide a better understanding of the magnitude of abuse of these products, which can in turn inform strategies to reduce their risk of abuse. Our findings suggest that frequently prescribed opioids, such as hydrocodone IR combination products, even at a relatively low prevalence of abuse, may contribute substantially to the overall problem of prescription opioid abuse. While new abuse-deterrent opioid products have been introduced to the market over the past few years, as of this writing almost all currently marketed ADF opioid products are ER or LA formulations with recent approval of an ADF version of IR single-entity oxycodone in April 2017. There is no hydrocodone IR combination product formulated with abuse-deterrent technology yet on the market. The findings of this study underscore the potential benefit that not only development of ADFs for IR opioids may have towards mitigating the public health burden of prescription opioid abuse but also the value of additional public health interventions for these types of opioid products.

ETHICS STATEMENT

These surveillance data from the ASI-MV were reviewed by the New England Institutional Review Board and determined as exempt from human subject research as they are a limited dataset in which subjects cannot be identified.

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CONFLICT OF INTEREST

Theresa A. Cassidy and Natasha Oyedele are employees of Inflexion Inc. Simon Budman is an employee and shareholder of Inflexion Inc. Travis Mickle and Sven Guenther are employees and shareholders of KemPharm Inc.

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REFERENCES

- Center for Behavioral Health Statistics and Quality. *Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health*; 2015. <http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf%5Cnhttp://www.samhsa.gov/data/>. Accessed October 4, 2016
- Fortuna RJ, Robbins BW, Caiola E, Joynt M, Halterman JS. Prescribing of controlled medications to adolescents and young adults in the United States. *Pediatrics*. 2010;126(6):1108-1116. <https://doi.org/10.1542/peds.2010-0791>.
- Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. *Am J Prev Med*. 2015;49(3):409-413. <https://doi.org/10.1016/j.amepre.2015.02.020>
- Center for Drug Evaluation and Research; Food and Drug Administration. FDA briefing document joint meeting of anesthetic and analgesic drug products advisory committee and drug safety and risk management advisory committee May 5, 2016.; 2016.
- IMS Health. Sub-national (ZIP-level) pain Market prescription tracking data. Longitudinal Prescription Data. 2015.
- Rosenblum A, Parrino M, Schnoll SH, et al. Prescription opioid abuse among enrollees into methadone maintenance treatment. *Drug Alcohol Depend*. 2007;90(1):64-71. <https://doi.org/10.1016/j.drugalcdep.2007.02.012>
- Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduct J*. 2011;8(1):29 <https://doi.org/10.1186/1477-7517-8-29>
- Volkow ND, McLellan AT. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA*. 2011;305(13):1346-1347. <https://doi.org/10.1001/jama.2011.369>
- CDC.gov. Prescription drug overdose: understanding the epidemic. *Prescr drug overdose Underst epidemic*. 2015. <https://www.cdc.gov/drugoverdose/epidemic/>. Accessed June 26, 2015.
- Zosel A, Bartelson BB, Bailey E, Lowenstein S, Dart R. Characterization of adolescent prescription drug abuse and misuse using the researched abuse diversion and addiction-related surveillance (RADARS®) system. *J Am Acad Child Adolesc Psychiatry*. 2013;52(2):196-204.e2. [10.1016/j.jaac.2012.11.014](https://doi.org/10.1016/j.jaac.2012.11.014)
- Delcher C, Wagenaar A, Goldberger BA, Cook RL, Maldonado-Molina MM. Abrupt decline in oxycodone-caused mortality after implementation of Florida's prescription drug monitoring program. *Drug Alcohol Depend*. 2015;150:63-68. <https://doi.org/10.1016>
- Rasubala L, Pernapati L, Velasquez X, Burk J, Ren Y-F. Impact of a mandatory prescription drug monitoring program on prescription of opioid analgesics by dentists. Narendran R, ed. *PLoS One*. 2015;10(8):e0135957 [10.1371/journal.pone.0135957](https://doi.org/10.1371/journal.pone.0135957)
- Alford DP, Zisblatt L, Ng P, et al. SCOPE of pain : An evaluation of an opioid risk evaluation and mitigation strategy continuing education program. *Pain Med*. 2015;n/a-n/a; [10.1111/pme.12878](https://doi.org/10.1111/pme.12878)
- Garunay M. President Obama is taking more steps to address the prescription drug abuse and heroin epidemic. <https://www.whitehouse.gov/blog/2016/03/29/president-obama-taking-more-action-address-prescription-drug-abuse-epidemic-0>. Accessed June 30, 2016.
- Food and Drug Administration. FDA announces enhanced warnings for immediate-release opioid pain medications related to risks of misuse, abuse, addiction, overdose and death. 2016. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm>.
- DOJ (U.S. Department of Justice). Schedules of controlled substances: rescheduling of hydrocodone combination products from schedule III to schedule II. United States; 2014:49661-49682.
- Butler SF, Budman SH, Licari A, et al. National addictions vigilance intervention and prevention program (NAVIPPRO): A real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiol Drug Saf*. 2008;17(12):1142-1154. <https://doi.org/10.1002/pds>
- McLellan AT, Kushner H, Metzger D, Angeriu M. The fifth edition of the addiction severity index. *J Subst Abuse Treat*. 1992;9(3):199-213.
- Butler SF, Redondo JP, Fernandez KC, Villapiano A. Validation of the Spanish addiction severity index multimedia version (S-ASI-MV). *Drug Alcohol Depend*. 2009;99(1-3):18-27. <https://doi.org/10.1016/j.drugalcdep.2008.06.012>
- Lord SE, Trudeau KJ, Black RA, et al. CHAT: development and validation of a computer-delivered, self-report, substance use assessment for adolescents. *Subst Use Misuse*. 2011;46(6):781-794. <https://doi.org/10.3109/10826084.2010.538119>
- Washington State Agency Medical Directors' Group. Interagency guideline on prescribing opioids for pain. 2015;(Accessed November 10, 2015). <http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf>.
- McCullagh P, Nelder JA. *Generalized linear models*. 2nd ed. Chapman & Hall/CRC: Boca Raton, Florida; 1989.
- Jones CM, Lurie PG, Throckmorton DC. Effect of US Drug Enforcement Administration's rescheduling of hydrocodone combination analgesic products on opioid analgesic prescribing. *JAMA Intern Med*. 2016;176(3):399 <https://doi.org/10.1001/jamainternmed.2015.7799>
- Gasior M, Bond M, Malamut R. Routes of abuse of prescription opioid analgesics: A review and assessment of the potential impact of abuse-deterrent formulations. *Postgrad Med*. 2016;128(1):85-96. <https://doi.org/10.1080/00325481.2016.1120642>
- Cicero TJ, Ellis MS, Harney J. Shifting patterns of prescription opioid and heroin abuse in the United States. *N Engl J Med*. 2015;373(18):1789-1790. <https://doi.org/10.1056/NEJMc1505541>
- Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduct J*. 2011;8(29):1-17. <https://doi.org/10.1186/1477-7517-8-29>
- Katz NP, Dart RC, Bailey E, Trudeau J, Osgood E, Paillard F. Tampering with prescription opioids: Nature and extent of the problem, health consequences, and solutions. *Am J Drug Alcohol Abuse*. 2011;37(4):205-217. <https://doi.org/10.3109/00952990.2011.569623>
- Secora AM, Dormitzer CM, Staffa JA, Dal Pan GJ. Measures to quantify the abuse of prescription opioids: A review of data sources and metrics. *Pharmacoepidemiol Drug Saf*. 2014;23(12):1227-1237. <https://doi.org/10.1002/pds.3711>
- Butler SF, Cassidy TA, Chilcoat H, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: Initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *J Pain*. 2012;9: <https://doi.org/10.1016/j.jpain.2012.08.008>
- Cassidy TA, Budman SH, Butler SF, Dasmahapatra P, Green TC. Abuse of prescription opioids and illegal drugs after introduction of abuse deterrent opioid formulations in the NAVIPPRO® surveillance network. In: *75th Annual CPDD Meeting (June 15 - 20)*. San Diego, CA; 2013.
- Cassidy TA, DasMahapatra P, Black RA, Wieman MS, Butler SF. Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. *Pain Med*. 2014;15(3):440-451. <https://doi.org/10.1111/pme.12295>
- Brownstein JS, Green TC, Cassidy TA, Butler SF. Geographic information systems and pharmacoepidemiology: Using spatial cluster detection to monitor local patterns of prescription opioid abuse. 2010;(April):627-637. [10.1002/pds](https://doi.org/10.1002/pds).
- Dart RC. Monitoring risk: post marketing surveillance and signal detection. *Drug Alcohol Depend*. 2009;105(Suppl):S26-S32. <https://doi.org/10.1016/j.drugalcdep.2009.08.011>
- Dasgupta N, Kramer ED, Zalman M-A, et al. Association between non-medical and prescriptive usage of opioids. *Drug Alcohol Depend*. 2006;82(2):135-142. <https://doi.org/10.1016/j.drugalcdep.2005.08.019>

35. Black RA, Butler SF, Cassidy TA, Thorley EM, Budman SH. An empirical evaluation of the assumptions underlying the relationship between volume and abuse for select ER and IR prescription opioid medications using the NAVIPPRO® ASI-MV® system. In: *PAINWeek September 8-12*. Las Vegas, NV; 2015.
36. Butler SF, Budman SH, Goldman RJ, et al. Initial validation of a computer-administered addiction severity index: The ASI-MV. *Psychol Addict Behav*. 2001;15(1):4-12. <http://www.ncbi.nlm.nih.gov/pubmed/11255937>
37. Butler SF, Cacciola JS, Budman SH, et al. Predicting addiction severity index (ASI) interviewer severity ratings for a computer-administered ASI. 1998;10(4):399-407.
38. Hendricks V, Kaplan C, VanLimbeek J, Geerlings P. The addiction severity index: reliability and validity in a Dutch addict population. *J ournal Subst Abus Treat*. 1989;6:133-141.
39. Kosten T, Rounsaville B, Kleber H. Concurrent validity of the addiction severity index. *J Nerv Ment Disord*. 1983;171(10):606-610.
40. Butler SF. Changes in abuse patterns following introduction of reformulated opioids observed in a surveillance system of substance abuse treatment centers. In: *75th Annual CPDD Meeting (June 15 - 20)*. San Diego, CA (June 15-20); 2013.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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