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ORIGINAL RESEARCH

Evaluation of Abuse Deterrent Formulations of Oxycodone Products: Real-World Data from an Enriched Population of Substance Users Assessed with the Addiction Severity Index-Multimedia Version (ASI-MV®)

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Purpose: The study purpose was to evaluate real-world data on routes of administration (ROAs) employed for nonmedical use (NMU) of XTAMPZA ER compared to other oxycodone extended-release (ER) and oxycodone immediate-release (IR) formulations in a population of adults assessed for substance use.

Patients and Methods: A cross-sectional observational study was conducted among adults assessed for substance use and treatment planning using the Addiction Severity Index-Multimedia Version (ASI-MV®) from July 2016 through December 2023. Demographic and substance use history data were summarized to characterize the sample. The primary outcome measure was the prevalence of past 30-day non-oral NMU, assessed first by using Pearson's chi-square to test differences in prevalence, then by calculating the proportional reporting ratios (PRR) to determine if specific non-oral ROAs were more or less likely to be used for XTAMPZA ER NMU versus comparators.

Results: The prevalence of non-oral ROA cases was significantly higher among other oxycodone ER cases (2221/4935, 45.0%) and oxycodone IR cases (10,598/20,394, 52.0%) compared to XTAMPZA ER cases (31/141, 22.0%)(X^2=29.43, p<0.0001 and X^2=50.41, p<0.0001, respectively). Compared to other oxycodone ER, XTAMPZA ER had a 33% lower risk of snorting (PRR: 0.67, 95% CI: 0.47, 0.95) and a 63% lower risk of injecting (PRR: 0.37, 95% CI: 0.19, 0.71). Compared to oxycodone IR, XTAMPZA ER had a 46% lower risk of snorting (PRR: 0.54, 95% CI: 0.38, 0.77) and a 66% lower risk of injecting (PRR: 0.44, 95% CI: 0.23, 0.86).

Conclusion: Opioid medications can provide valuable patient benefits with risks best mitigated by using formulations associated with lower likelihood of NMU, particularly via higher-risk non-oral ROAs. These study findings suggest that XTAMPZA ER has a lower risk of NMU via non-oral ROA compared to other oxycodone ER and oxycodone IR products in an enriched population of substance users.

Keywords: pain management, opioid, nonmedical use, substance abuse treatment, real-world data, abuse deterrent formulations, routes of administration

Introduction

Promising trends in reductions of drug overdose fatalities have been reported in the United States (US). These include a 4% decrease in the overall age-adjusted rate between 2022 and 2023 with a 33.3% decline in deaths involving heroin, a 17.1% decline in deaths involving natural and semisynthetic opioids (prescription opioids), and a 2.2% decline in deaths involving synthetic opioids other than methadone (primarily fentanyl and fentanyl analogs).[1] Another provisional report of drug overdose fatality data discovered a 24% overall decline from September 2023 to September 2024.[2]

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While significant reductions in deaths involving prescription opioids have been reported, there has been a continued effort to reduce nonmedical use (NMU) of prescription opioids in the US. NMU is any deviation from legitimate medical use (defined as use of one's own prescription medication from a healthcare provider only in the manner in which it was prescribed, including using via the intended route of administration (ROA)). This is challenging considering that in 2023, almost one in four (24.3%) American adults suffered from chronic pain and 8.5% suffered from high impact chronic pain (pain that often restricts life or work activities).[3] Pain management is among the most common reasons adults seek medical care and has been associated with anxiety and depression[4] and decreased quality of life.[5] These patients and their providers often rely on prescription opioid therapies as part of their treatment plan. Restrictions on opioid prescribing have reduced the supply of these medications, however mixed results are reported in relation to the associated positive and negative effects on the intended patient population, the majority of which use their medications appropriately. The updated CDC guidelines for opioid prescribing noted unintended impacts of the original guidelines on patient health and encouraged patient-centric pain management going forward (with opioids and other therapies).[6] This is important as healthcare providers balance treatment of chronic pain with mitigation of opioid-related risks.

Numerous interventions have been implemented to curb opioid NMU. However, only abuse deterrent formulations (ADFs) are product-specific and intended to deter use by non-oral ROAs (eg, snorting, smoking, injecting). Non-oral ROAs have been associated with a higher likelihood of life-threatening events and death.[7] The Abuse-Deterrent Opioids – Evaluation and Labeling Guidance for Industry, published by the US Food and Drug Administration (FDA) in April 2015,[8] defines abuse-deterrent properties as those shown to meaningfully *deter* abuse, even if they do not fully *prevent* abuse.

Postmarket evaluation of ADF opioids has been generally positive. One study documented reduction in abuse, therapeutic errors, and accidental exposures involving ADF opioids reported to US poison centers.[9] Another group of studies found reductions in prevalence of overall abuse and abuse via non-oral ROAs with ADF opioids in adults evaluated for substance use.[10–12] One additional study reported a reduction in drug diversion of ADF medications[13] and another reported a reduction in healthcare utilization and associated healthcare costs (eg, opioid-related emergency department visits and hospitalizations) of ADF opioids.[14,15]

Within the marketed opioid medications, oxycodone-containing products are available in ADF and non-ADF formulations, allowing for evaluation of the effectiveness of an ADF. As of 2013, all extended-release (ER) oxycodone products marketed in the US must have abuse-deterrent properties.[16] On the contrary, immediate-release (IR) oxycodone products are not required to have abuse-deterrent properties and to date, the only ADF IR oxycodone product is Roxybond™ which was approved by the FDA in 2017. The first ADF to receive FDA labeling was OxyContin® (oxycodone HCl extended-release tablets, Purdue Pharma L.P., Stamford, CT) in 2010. This labeling included a statement that the formulation is expected to make abuse via injection difficult and expected to reduce abuse by the intranasal ROA.[17] XTAMPZA ER (oxycodone extended-release, Collegium Pharmaceutical, Stoughton, MA) was approved in April 2016 and includes ADF labeling that states that the formulation is expected to make abuse by injection difficult and expected to reduce abuse via the oral and intranasal ROAs.[18] The FDA labeling is different between these two ER ADFs because while both are intended to preserve the prolonged release mechanism and prevent immediate access to the full amount of active ingredient, they use different technology. OxyContin uses RESISTEC™, a polyethylene oxide matrix that hardens the tablet and becomes viscous in aqueous solutions which aids in resistance to syringe aspiration. XTAMPZA ER uses the DETERx® microsphere-in-capsule technology in which the oxycodone is homogenously dispersed within hydrophobic, waxy microspheres with each microsphere acting as an independent drug delivery system.

The published literature provides consistent evidence suggesting lower risk of misuse, abuse (particularly via non-oral ROAs), diversion, product tampering, severity of clinical outcomes, and opioid-related healthcare costs with XTAMPZA ER relative to other ADF opioids.[11,12,15,19–22] The reported differences appeared to be sustained throughout the first five years that XTAMPZA ER was on the US market (2016–2021), however the opioid landscape is constantly evolving and ongoing surveillance is warranted. Hence, the objective of this study was to extend the surveillance period through 2023 and evaluate real-world data on NMU via non-oral ROAs of XTAMPZA ER compared to other oxycodone ER formulations and oxycodone IR formulations in a population of adults assessed for substance use.

Materials and Methods

A cross-sectional observational study was conducted to evaluate NMU by ROA among adults aged 18 years or older assessed for substance use and treatment planning using the Addiction Severity Index-Multimedia Version (ASI-MV®) assessment. The study groups included those who reported NMU of (1) XTAMPZA ER, (2) other oxycodone ER (excluding XTAMPZA ER), or (3) oxycodone IR. Individuals could report NMU of more than one product therefore these groups are not mutually exclusive. The primary outcome measure was past 30-day NMU stratified by ROA.

Data Source

The ASI-MV is a modified version of the original Addiction Severity Index (ASI), a clinical intake assessment designed for use upon admission to drug and alcohol treatment with demonstrated reliability and validity.[23–26] The ASI-MV is used in a variety of clinical settings, including inpatient and outpatient treatment facilities.

The ASI-MV has good test-retest reliability, discriminant validity, and criterion validity.[23] In addition to the original ASI domains (medical, employment/financial support status, alcohol use, drug use, legal, family/social status, and psychiatric status), the ASI-MV also collects patient characteristics, substance use and treatment history, and use of pharmaceutical substances via product-specific questions about use, past 30-day NMU, ROA, and sources of procurement. Specific medications are identified by presenting screens with images, text and audio including medication names and slang/street names, so that respondents are better able to differentiate between various products that they report having used. NMU was identified with the use of an algorithm of responses to several questions to identify any deviation from legitimate medical use (use of one's own prescription medication from a healthcare provider only in the manner in which it was prescribed, including using the intended ROA). The definition of NMU as captured by ASI-MV and used in this study includes both abuse (intentional, non-therapeutic use of a drug even once to achieve a desirable psychological or physiological effect) and misuse (intentional therapeutic use of a drug in an inappropriate way).

A single ASI-MV assessment may report past 30-day NMU of multiple products within one study group or NMU of products from multiple study groups. For example, one assessment could report past 30-day NMU of XTAMPZA ER, other oxycodone ER, and oxycodone IR products. To address this aspect of real-world use, NMU was evaluated at the *assessments* level and at the *mentions* level. NMU *mentions* include the total number of past 30-day NMU reports of the opioid products within a study group (ie, the sum of reports). When evaluating NMU at the *assessments* level, a binary variable (Yes/No) is constructed in which each assessment is either assigned as reporting NMU of the study group (Yes) or not reporting NMU of the study group (No). Thus, the count of NMU *mentions* will be greater than the count of NMU *assessments* for the comparator oxycodone study groups. As the XTAMPZA ER study group includes only one product, the counts of NMU *mentions* and *assessments* will be the same. It is possible for a unique individual to complete more than one assessment over time. In this instance, the first assessment completed by the individual during the given quarter was retained and any subsequent assessments in that quarter were removed from the analysis dataset.

Data Analysis

The study period included ASI-MV assessments collected from 01 July 2016 through 31 December 2023. XTAMPZA ER was launched in June of 2016 and added to the ASI-MV in Q3 2017, allowing for a one-year market transition before data regarding this product were collected. One year of baseline data was included for comparator groups to account for this transition. Demographics and substance use history were summarized and compared between study groups using Pearson's chi-square test (or Fisher's exact test for comparisons with small cell size) for categorical data (demographics, ROA) and Wilcoxon rank sum tests for ordinal data (domain severity ratings). Statistical significance was determined for tests where $p<0.05$.

Nonparametric statistics were used to compare past 30-day NMU by ROA. The primary benefits of nonparametric testing are that they can accommodate smaller sample sizes, they do not require any assumptions about the underlying probability distribution of the data, and they appropriately use categorical data.[27–29] This was assessed first by using Pearson's chi-square to test differences in the volume of cases with non-oral ROA between XTAMPZA ER and comparator groups. Next, the proportional reporting ratios (PRR) were calculated to determine if specific ROAs were

more or less likely to be used for XTAMPZA ER NMU versus comparator groups. PRR is a commonly used method to assess disproportionality in pharmacovigilance surveillance data and has been deemed a validated method in drug safety research and surveillance for signal detection.[30,31]

Using XTAMPZA ER as the reference group, the PRR was calculated for (a) any non-oral ROA (snorted, smoked, injected) versus any oral ROA (swallowed whole, chew then swallowed, dissolved like a cough drop, dissolved in liquid then drank), (b) any non-oral route versus swallowed whole, (c) snorted versus swallowed whole, and (d) injected versus swallowed whole. An individual assessment may include reported NMU of more than one oxycodone product by more than one ROA, hence ROAs are not mutually exclusive. Each mention of a product and ROA was used to calculate the ratios. Statistical significance was reached if the 95% confidence interval (CI) for the PRR did not include 1.0. Analyses were conducted using SAS statistical software version 8.3 (SAS Institute, Cary NC, USA).

Secondary analysis of existing de-identified clinical data was determined to be exempt from institutional review board review by the New England Institutional Review Board (now part of the WCG IRB). All data accessed complied with relevant data protection and privacy regulations.

Results

From 01 July 2016 through 31 December 2023, 879 sites located in 46 states contributed a total of 341,851 adult assessments to the ASI-MV network (Figure 1). A total of 67,855 (19.8%) of the 341,851 assessments included self-reported past 30-day NMU of a prescription opioid. Of these, 141 (0.2%) reported XTAMPZA ER NMU, 4935 (7.3%) reported other oxycodone ER NMU, and 20,394 (30.1%) reported oxycodone IR NMU (Table 1). The majority (97.9%) of assessments that reported XTAMPZA ER NMU also reported NMU of other prescription opioids, including 38.3% that also reported other oxycodone ER and 87.9% that also reported oxycodone IR.

The distribution of demographics was similar between the XTAMPZA ER and comparator groups except for race; Hispanic/Latino race was reported by a greater proportion of the XTAMPZA ER group (12.8%) compared to the other oxycodone ER and oxycodone IR groups (7.5% and 7.6%, respectively) (Table 1). Those reporting XTAMPZA ER NMU were more likely to have a current pain problem than both comparator groups and more likely to report past 30-day illicit drug use than the oxycodone IR group. Otherwise, historical drug use was similar among the study groups. Other notable differences were that, relative to the oxycodone IR group, a greater proportion of the XTAMPZA ER group had severity ratings in the alcohol, employment, family and medical domains that reflected moderate, considerable, or extreme problems (Table 2). Further, the XTAMPZA ER group had a higher proportion of moderate/considerable/extreme legal severity ratings than the other oxycodone ER group and the oxycodone IR group.

Oral ROAs were most commonly reported across all study groups (Table 3). The proportion of non-oral ROA cases was significantly higher with other oxycodone ER cases (45.0%) and oxycodone IR cases (52.0%) compared to XTAMPZA ER cases (22.0%)(X^2=29.43, $p<0.0001$ and X^2=50.41, $p<0.0001$, respectively). Snorting was the most reported non-oral ROA in all study groups, followed by injecting. Compared to other oxycodone ER, XTAMPZA ER had a 40% lower risk of NMU via non-oral ROAs (PRR: 0.60, 95% CI: 0.45, 0.80), a 33% lower risk of snorting (PRR: 0.67, 95% CI: 0.47, 0.95), and a 63% lower risk of injecting (PRR: 0.37, 95% CI: 0.19, 0.71) (Figure 2). Compared to oxycodone IR, XTAMPZA ER had a 46% lower risk of NMU via non-oral ROAs (PRR: 0.54, 95% CI: 0.41, 0.72), a 46% lower risk of snorting (PRR: 0.54, 95% CI: 0.38, 0.77), and a 66% lower risk of injecting (PRR: 0.44, 95% CI: 0.23, 0.86). All differences were statistically significant (CI did not include 1.0).

Discussion

Ongoing efforts to prevent prescription opioid NMU are important considering the need for effective and safe pain therapies. ADF formulations are a product-specific innovation, and some may be more effective than others at deterring use via non-oral ROAs. This is impactful since opioid abuse via non-oral ROAs has been associated with a higher likelihood of life-threatening events or death.[7] Considering the primary goal of an ADF is to deter manipulation of the drug to be used via non-oral ROAs, ROAs should be considered as a primary outcome in assessing their effectiveness. In this study, XTAMPZA ER had a reduced risk of NMU via non-oral ROAs, snorting, and injecting compared to other oxycodone ER and oxycodone IR. These findings were statistically significant even with the relatively small number of

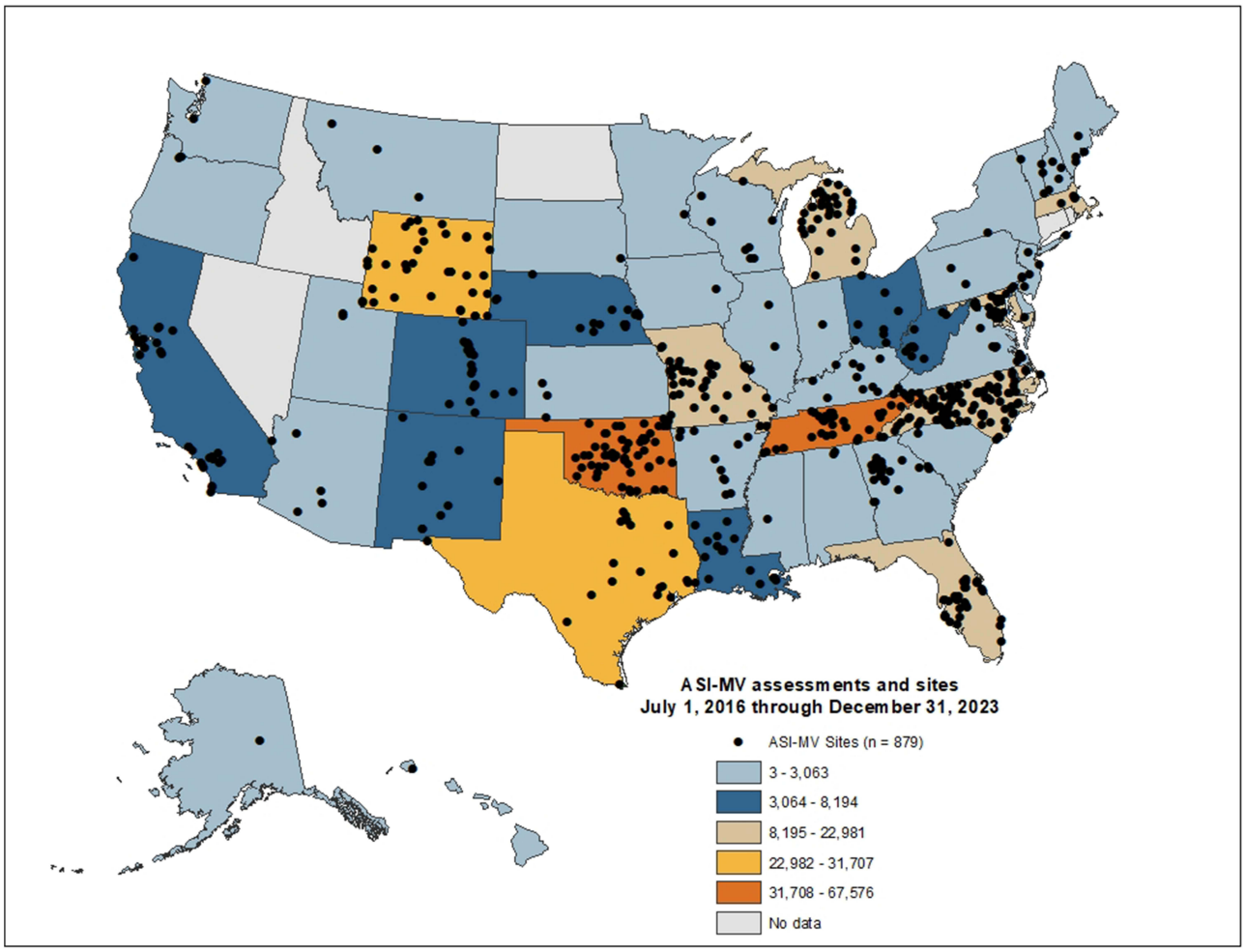

Figure 1 Geographic Distribution of ASI-MV Assessments and Sites, by State (01 July 2016 through 31 December 2023).
Notes: Figure 1 displays the number of ASI-MV assessments submitted by state location of site; with black dots representing the zip code location of site. It is possible to have more than one site in the same zip code or city in which case the dots will be superimposed on the map.
Abbreviation: ASI-MV, Addiction Severity Index-Multimedia Version.

XTAMPZA ER NMU mentions. A previous study analyzed ASI-MV data through 2019 and reported a statistically significant difference in the proportion of non-oral versus oral ROAs between XTAMPZA ER and other oxycodone ER (X^2=18.57, p<0.001) and oxycodone IR (X^2=52.47, p<0.001) with mixed results for the PRR analysis.[11] All PRRs favored XTAMPZA ER but not all were statistically significant, likely due to the small sample size for the XTAMPZA ER group (n=73). The current study included data through 2023 and a sample size of 141 for the XTAMPZA ER group, with all PRR analyses resulting in statistically significant differences. These findings suggest reduced risk with XTAMPZA ER even with increasing utilization.

Abuse profiles with specific evaluation by ROAs have also been evaluated using data from US poison centers and other substance use treatment center-based data sources with similar findings[12,22] Severtson et al 2020 reported that (1) non-oral abuse cases involving XTAMPZA ER were infrequent and occurred at lower rates than with oxycodone IR, other ADF ER opioids, and non-ADF ER opioids, and (2) while drug utilization increased during the study period, there was not an increase in abuse/misuse. Building upon this study, Severtson et al 2023 noted that as of 2021, which was almost 5 years since market introduction, no reports of use of XTAMPZA ER via injecting or snorting had yet been reported to participating poison centers.

It is possible that prescribing of these different oxycodone medications is differential, meaning prescribers may choose a particular medication for a patient with certain characteristics or risks, thus introducing a selection bias. The

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Table 1 Demographics and Substance Use History of Individuals Reporting Past 30-Day Nonmedical Use (NMU) from 01 July 2016 Through 31 December 2023

		Past 30-Day XTAMPZA ER NMU (n = 141)		Past 30-Day Other Oxycodone ER NMU (n = 4935)		Past 30-Day Oxycodone IR NMU (n = 20,394)		XTAMPZA ER versus Other Oxycodone ER	XTAMPZA ER versus Oxycodone IR
	Response	**n**	**%**	**n**	**%**	**n**	**%**	**p-value**	**p-value**
Gender	Male	69	48.9	2604	52.8	10,683	52.4	0.3691	0.4120
	Female	72	51.1	2331	47.2	9705	47.6		
	Unknown/no response	0	0.0	0	0.0	6	0.0		
Age	18–24 years	19	13.5	721	14.6	2939	14.4	0.4476	0.3498
	25–34 years	60	42.6	2029	41.1	8819	43.2		
	35–44 years	33	23.4	1316	26.7	5381	26.4		
	45–54 years	23	16.3	581	11.8	2229	10.9		
	55 + years	6	4.3	288	5.8	1026	5.0		
Race	Caucasian	100	70.9	3680	74.6	14,843	72.8	*0.0121*	*0.0020*
	African American	10	7.1	512	10.4	2478	12.2		
	American Indian/Alaskan Native	6	4.3	146	3.0	561	2.8		
	Asian	2	1.4	12	0.2	42	0.2		
	Pacific Islander/Native Hawaiian	0	0.0	0	0.0	0	0.0		
	Hispanic/Latino	18	12.8	368	7.5	1554	7.6		
	Other Race	5	3.6	217	4.4	916	4.5		
Marital Status	Married	28	19.9	1038	21.0	4568	22.4	0.9699	0.8194
	Separated, divorced, widowed	34	24.1	1185	24.0	4721	23.2		
	Never married	74	52.5	2682	54.4	10,978	53.8		
	Unknown/no response	5	3.6	30	0.6	127	0.6		
Employment Status	Professional	14	9.9	336	6.8	1308	6.4	0.3087	0.1671
	Administrative, clerical, sales	12	8.5	549	11.1	2396	11.8		
	Skilled or semi-skilled	49	34.8	1977	40.1	8292	40.7		
	Student	2	1.4	65	1.3	310	1.5		
	Homemaker	15	10.6	378	7.7	1595	7.8		
	Other manual/unskilled	23	16.3	597	12.1	2367	11.6		
	Did not work for pay last 3 years	5	3.6	254	5.2	1020	5.0		
	Disabled	12	8.5	374	7.6	1434	7.0		
	No occupation	7	5.0	370	7.5	1556	7.6		
	Unknown/no response	2	1.4	35	0.7	116	0.6		
Expected Treatment Modality	Residential/Inpatient	74	52.5	2764	56.0	10,804	53.0	0.1703	0.1562
	Outpatient/Non-Methadone	26	18.4	1020	20.7	4591	22.5		
	Methadone	22	15.6	439	8.9	1849	9.1		
	Drug Court	0	0.0	74	1.5	316	1.6		
	Probation/Parole	3	2.1	71	1.4	336	1.7		
	DUI/DWI	2	1.4	47	1.0	280	1.4		
	Other Corrections	0	0.0	33	0.7	162	0.8		
	Temporary Assistance for Needy Families (Welfare)	0	0.0	12	0.2	110	0.5		
	Other	14	9.9	475	9.6	1946	9.5		

(*Continued*)

Table 1 (Continued).

		Past 30-Day XTAMPZA ER NMU (n = 141)		Past 30-Day Other Oxycodone ER NMU (n = 4935)		Past 30-Day Oxycodone IR NMU (n = 20,394)		XTAMPZA ER versus Other Oxycodone ER	XTAMPZA ER versus Oxycodone IR
	Response	**n**	**%**	**n**	**%**	**n**	**%**	**p-value**	**p-value**
Current Pain Problem	Yes	96	68.1	2950	59.8	11,185	54.8	*0.0377*	*0.0012*
	No	44	31.2	1979	40.1	9183	45.0		
	Unknown/no response	1	0.7	6	0.1	26	0.1		
Criminal justice-Prompted Substance Use Treatment*	Yes	37	26.2	1158	23.5	4968	24.4	0.3046	0.4300
	No	98	69.5	3749	76.0	15,329	75.2		
	Unknown/no response	6	4.3	28	0.6	97	0.5		
Past 30-Day NMU of Other Prescription Opioid ±	Yes	138	97.9	4733	95.9	16,517	81.0	0.2424	*<0. 0001*
	XTAMPZA ER	–	–	*54*	*1.1*	*124*	*0.6*		
	Other oxycodone ER	*54*	*38. 3*	–	–	*4106*	*20. 1*		
	Oxycodone IR	*124*	*87. 9*	*4106*	*83. 2*	–	–		
	No	3	2.1	202	4.1	3877	19.0		
Past 30-day Marijuana Use	Yes	72	51.1	2458	49.8	10,038	49.2	0.8383	0.9464
	No	69	48.9	2477	50.2	10,356	50.8		
Past 30-day Illicit Drug Use (other than marijuana)**	Yes	107	75.9	3428	69.5	13,175	64.6	0.1019	*0.0052*
	No	34	24.1	1507	30.5	7219	35.4		
Past 30-day Heroin Use	Yes	57	40.4	2042	41.4	7231	35.5	0.8209	0.2191
	No	84	59.6	2893	58.6	13,163	64.5		
Lifetime Heroin Use	Yes	87	61.7	2986	60.5	10,941	53.7	0.7746	0.0560
	No	54	38.3	1949	39.5	9453	46.4		
Lifetime Injection of Any Drug	Yes	66	46.8	2520	51.1	8867	43.5	0.3189	0.4267
	No	75	53.2	2415	48.9	11,527	56.5		

Notes: *Admission to substance abuse treatment was required or encouraged of the respondent by a judge, probation or parole officer, or other criminal justice official. **Illicit drugs include heroin, cocaine, illicit amphetamines/methamphetamines, hallucinogens, inhalants, ecstasy, GHB, ketamine, K2, rohypnol, bath salts, and street fentanyl. ± Past 30-day NMU of Other Prescription Opioid is reported past 30-day NMU of any prescription opioid other than the opioid product(s) that comprise the study group. P-values were not generated for NMU overlap between study groups specifically. P-values represent results of Pearson's chi-square tests. Italics indicate statistical significance at $p<0.05$.

XTAMPZA ER group had higher alcohol, medical, family and employment severity ratings than oxycodone IR, a higher legal severity rating than other oxycodone ER and oxycodone IR groups, and higher likelihood of history of illicit drug use, yet XTAMPZA ER was still less likely to be used via non-oral ROAs. These real-world data findings are supported by the technology of the formulations as evaluated with premarket studies.[32–37] One such study, a comparative cross-over pharmacokinetic study,[32] found that crushed and intact XTAMPZA ER were bioequivalent and had lower peak plasma concentrations than crushed IR oxycodone, while crushed OxyContin exhibited a rapid increase in plasma oxycodone and was bioequivalent to IR oxycodone. This may help explain the differences in ROA profiles.

Limitations

As with any evaluations of real-world data, there are limitations to this study. While the ASI-MV uses photos and names of products, all assessments rely on self-report, including product selection and recall of ROA. The ASI-MV is not a nationally representative sample, hence it is unknown if these results are generalizable to all adults in the United States assessed for substance use and treatment planning. NMU of multiple opioid products, including products comprising one or more study groups, may be reported in a single assessment. The study included one year of baseline data for other

Table 2 Addiction Severity Index (ASI) Domain Severity Ratings* by Study Group

		Past 30-Day XTAMPZA ER NMU (n = 141)		Past 30-Day Other Oxycodone ER NMU (n = 4935)		Past 30-Day Oxycodone IR NMU (n = 20,394)		XTAMPZA ER versus Other Oxycodone ER	XTAMPZA ER versus Oxycodone IR
Domain	**Response**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value**	**p-value**
Alcohol Severity Rating	No real problem to slight problem	78	55.3	3346	67.8	14,538	71.3	0.0968	*0.0052*
	Moderate to considerable problem	37	26.2	1034	21.0	3911	19.2		
	Extreme problem	10	7.1	367	7.4	1264	6.2		
	Unknown/no response	16	11.4	188	3.8	681	3.3		
Drug Severity Rating	No real problem to slight problem	10	7.1	307	6.2	1706	8.4	0.0734	0.7543
	Moderate to considerable problem	55	39.0	1808	36.6	8326	40.8		
	Extreme problem	55	39.0	2490	50.5	9179	45.0		
	Unknown/no response	21	14.9	330	6.7	1183	5.8		
Employment Severity Rating	No real problem to slight problem	58	41.1	2259	45.8	10,414	51.1	0.3015	*0.0194*
	Moderate to considerable problem	64	45.4	2120	43.0	7984	39.2		
	Extreme problem	12	8.5	364	7.4	1243	6.1		
	Unknown/no response	7	5.0	192	3.9	753	3.7		
Family Severity Rating	No real problem to slight problem	61	43.3	2250	45.6	10,380	50.9	0.2049	*0.0129*
	Moderate to considerable problem	43	30.5	2007	40.7	7737	37.9		
	Extreme problem	26	18.4	470	9.5	1524	7.5		
	Unknown/no response	11	7.8	208	4.2	753	3.7		
Legal Severity Rating	No real problem to slight problem	66	46.8	2865	58.1	12,551	61.5	*0.0044*	*0.0001*
	Moderate to considerable problem	56	39.7	1692	34.3	6632	32.5		
	Extreme problem	7	5.0	78	1.6	216	1.1		
	Unknown/no response	12	8.5	300	6.1	995	4.9		
Medical Severity Rating	No real problem to slight problem	46	32.6	1928	39.1	9054	44.4	0.2857	*0.0204*
	Moderate to considerable problem	85	60.3	2725	55.2	10,315	50.6		
	Extreme problem	2	1.4	137	2.8	494	2.4		
	Unknown/no response	8	5.7	145	2.9	531	2.6		
Psychiatric Severity Rating	No real problem to slight problem	45	31.9	1750	35.5	8022	39.3	0.8335	0.1894
	Moderate to considerable problem	72	51.1	2613	53.0	10,488	51.4		
	Extreme problem	11	7.8	377	7.6	1240	6.1		
	Unknown/no response	13	9.2	195	4.0	644	3.2		

Notes: *Severity ratings are calculated for each of the seven biopsychosocial domains in the ASI-MV via an algorithm that is dependent upon responses to various questions. Interpretation of severity ratings is as follows: 0–1 = no problem; 2–3 = slight problem; 4–5 = moderate problem; 6–7 = severe problem; and 8–9 = extreme problem. P-values represent results of Wilcoxon Rank Sum tests, which excluded the unknown/no response category. Italics indicate statistical significance at p<0.05.

Table 3 Prevalence of Nonmedical Use (NMU) by Route of Administration

	Past 30-Day XTAMPZA ER NMU		Past 30-Day Other Oxycodone ER NMU		Past 30-Day Oxycodone IR NMU	
	n	**%**	**n**	**%**	**n**	**%**
Total NMU Assessments	**141**	**100.0**	**4935**	**100.0**	**20,394**	**100.0**
Any Non-Oral	31	22.0	2221	45.0	10,598	52.0
Oral	110	78.0	2714	55.0	9796	48.0
Chi-square, Any Non-Oral versus Oral Assessments (p-value)	**Index Group**		***29.43*** ***<0.0001***		***50.41*** ***<0.0001***	

(*Continued*)

Table 3 (Continued).

	Past 30-Day XTAMPZA ER NMU		Past 30-Day Other Oxycodone ER NMU		Past 30-Day Oxycodone IR NMU	
	n	%	n	%	n	%
Total Route Mentions*	**160**	**100.0**	**7528**	**100.0**	**55,518**	**100.0**
Any Oral	**110**	**68.8**	**4281**	**56.9**	**29,655**	**53.4**
Swallowed whole	75	46.9	2988	39.7	21,187	38.2
Chewed then swallowed	16	10.0	835	11.1	5514	9.9
Dissolved in mouth like a cough drop	15	9.4	309	4.1	2022	3.6
Drank after dissolved in liquid	4	2.5	149	2.0	932	1.7
Any Non-Oral	**36**	**22.5**	**3004**	**39.9**	**25,006**	**45.0**
Snorted	24	15.0	1699	22.6	17,008	30.6
Smoked	4	2.5	239	3.2	2120	3.8
Injected	8	5.0	1066	14.2	5878	10.6
Other Route	**14**	**8.8**	**243**	**3.2**	**857**	**1.5**

Notes: *Total route mentions are the total number of product/ROA combinations within each drug group/category that respondents reported for past 30-day NMU. Assessments may have reported multiple drugs and multiple routes in any category. Routes included swallowed whole, chewed then swallowed, dissolved in mouth like a cough drop, drank after dissolved in liquid, snorted, smoked, injected, and "other" route (unspecified). Multiple drugs and multiple ROAs for each drug could be selected by respondents for each product/comparator. All mentions of ROAs for each product/opioid group is included. Thus, the total number of routes may be greater than total NMU mentions. Italic font indicates statistically significant finding. Results in bold represent the collective categories of oral and non-oral ROAs while results in regular font represent subsets within each group (subsets are not mutually exclusive).
Abbreviations: ER, extended-release; IR, immediate-release; NMU, nonmedical use.

oxycodone ER and oxycodone IR NMU prior to the addition of XTAMPZA ER. The PRR is typically used for signal detection and these analyses are associative, thus a direct causal relationship cannot be established. Finally, the number of assessments reporting past 30-day NMU of XTAMPZA ER during the study period was relatively low with just three instances of XTAMPZA ER NMU alone (no other prescription opioid NMU reported in past 30-days), limiting evaluation of XTAMPZA ER NMU outside of polysubstance NMU. However, even with the overlap of opioids reported, differences were still discovered between study groups.

Figure 2 Proportional Reporting Ratios (PRR) of Routes of Administration: XTAMPZA ER NMU versus Comparator Groups. *Any Non-oral ROA includes snorted, smoked, and injected. Any Oral ROA includes swallowed whole, chewed then swallowed, dissolved in mouth like a cough drop, and drank after dissolved in liquid. ¥Italicized PRR values indicate statistical significance (confidence intervals did not include 1.0). PRR values <1.0 indicate a reduced risk for XTAMPZA ER versus comparator group.
Abbreviations: CI, confidence interval; ER, extended-release; IR, immediate-release; NMU, nonmedical use.

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Conclusion

XTAMPZA ER was associated with significantly lower rates of NMU via non-oral routes compared with other oxycodone formulations in a large, treatment-seeking population. Although limited by reliance on self-report and the inability to assign a causal relationship, these findings are consistent with the abuse deterrent properties of XTAMPZA ER. This real-world evidence supports the potential role of ADFs in reducing high-risk patterns of opioid misuse.

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Disclosure

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