


Misuse of Tramadol in the United States: An Analysis of the National Survey of Drug Use and Health 2002-2017

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ABSTRACT

OBJECTIVE: To analyze the rates of misuse - that is, use in any way not directed by a doctor - of products containing oral tramadol, a Schedule IV opioid, from the National Survey of Drug Use and Health (NSDUH), as compared to comparator Schedule II opioids (morphine, oxycodone, and hydrocodone) and alprazolam, a commonly prescribed Schedule IV controlled substance in the U.S.

METHODS: The NSDUH is a congressionally mandated household survey that collects information on tobacco, alcohol, and drug use, mental health and other health-related issues in the US. A cross-sectional surveillance study design was used to examine lifetime and past year misuse of oral tramadol and comparators of interest among NSDUH respondents aged 12 years or older. Based on when particular data were available, the past-year misuse analysis includes NSDUH data from 2015 to 2017, and the lifetime misuse analysis includes NSDUH data from 2002 to 2014.

RESULTS: In 2015 to 2017, past-year misuse of oral tramadol was approximately 4% of the total number of prescriptions, versus 7% to 8% for all of the comparators when adjusted for drug availability. In 2002 to 2014, lifetime misuse of oral tramadol remained at 1.5% or less over the 13-year period, and was lower than reported for hydrocodone (6%) and oxycodone (4%), respectively. Comparison of oral tramadol and alprazolam showed misuse of tramadol was also much lower than alprazolam. Too few reports of tramadol misuse by injection ($n = 7$) were reported, versus 570, 1096, and 32 reports of injection of morphine, oxycodone, and hydrocodone, respectively, during the 16-year analysis period to allow for any population-based estimation. Only morphine has an intravenous formulation available and tramadol was not available as an intravenous formulation in the U.S. during that time period.

CONCLUSIONS: This analysis shows a low prevalence of oral tramadol misuse, relative to other commonly prescribed opioids, in a nationally representative sample of noninstitutionalized US residents. Estimates of reported oral tramadol misuse have remained relatively stable over time and are substantially lower than those reported for comparators when adjusted for prescription volume. Reports of oral tramadol misuse are also much less than alprazolam, another Schedule IV drug.

KEYWORDS: tramadol, opiates, alprazolam, misuse, NSDUH

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Introduction

Tramadol is a centrally acting opioid analgesic with two mechanisms of action including weak activation of the μ opioid receptor by the parent drug, more potent activation by its primary metabolite (M1), and inhibition of the reuptake of serotonin and norepinephrine. These two distinct mechanisms function serve to make tramadol an effective analgesic with a good tolerability profile.¹ Tramadol is structurally related to codeine, and like codeine, there is a substitution of the methyl group on the phenol ring that imparts a relatively weak affinity for opioid receptors. The opioid component of tramadol-induced analgesia comes primarily from key metabolite M1. Due to the metabolic delay in formation of M1, tramadol is considered an atypical opioid with less abuse liability than conventional opioids.^{2,3}

Oral tramadol was approved by the Food and Drug Administration (FDA) in 1995 for moderate to moderately severe pain in adults. Oral tramadol is a Schedule IV

controlled substance versus other opioids which are Schedule II controlled substances in the U.S. The scheduling difference reflects the understanding that tramadol does not carry the same abuse potential as Schedule II opioids, as supported by studies that have shown that the human abuse potential of tramadol appears to be different from and lower than other opioid analgesic medications.^{2,3}

However, some have been calling federal governing bodies to consider reclassifying tramadol based on observational studies^{4,5} suggesting that patients receiving tramadol had similar to somewhat higher risks of prolonged opioid use compared with those receiving other short acting opioids. Those studies did not evaluate if persistent treatment for pain may be the driver for continued use, if physicians choose to prescribe tramadol due to its known less abuse potential; or if misuse or abuse was actually responsible for continued use (which, ultimately, is the key question relating when assessing abuse risk).



This current study aims to provide a different perspective by analyzing the rates of misuse (defined as use in any way not directed by a doctor) of products containing oral tramadol, as compared to other commonly prescribed opioids (morphine, oxycodone, and hydrocodone) and alprazolam, a commonly prescribed Schedule IV drug indicated for anxiety in the U.S. The rationale for choosing these comparators is described in the Methods section.

Data were obtained from the National Survey of Drug Use and Health (NSDUH), an annual, cross-sectional, population-based survey of self-reported alcohol, drug and tobacco use among non-institutionalized persons (≥ 12 years old). In a 2016 presentation, FDA highlighted the NSDUH as a source of “self-reported behavior of abuse” which provides national estimates on the non-medical use of pain relievers.⁶ This is a reasonable assumption because a significant subset of misuse, which has a broad definition, is likely to be abuse, defined by the FDA as “the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect”.⁷

Intravenous tramadol is currently under review by the Food and Drug Administration as a treatment for moderate to moderately severe pain, and thus an understanding of the comparative abuse of oral tramadol is needed to provide context for potential IV tramadol abuse. Because oral tramadol is a Schedule IV opioid, IV tramadol is expected to be given the same scheduling. The current study sheds light on “misuse” directly for oral tramadol, and therefore, is informative in assessing the abuse potential of both oral and intravenous tramadol as compared to Schedule II opioids, and to another drug in the same scheduling classification (Schedule IV) as tramadol.

Methods

The NSDUH is conducted each year by the Substance Abuse and Mental Health Services Administration⁸ (SAMHSA). NSDUH is congressionally mandated to provide annual prevalence estimates of reported use and misuse of tobacco, alcohol and drugs for the nation as a whole.⁹ It is a comprehensive nationwide survey enrolling people aged 12 or older and is highly representative of the US population not experiencing homelessness or institutionalization with minimal duplication of the same respondent(s) across years.^{10,11} The purpose of the NSDUH is to provide data that support prevention and treatment programs, to monitor substance use trends, to estimate the need for treatment, and to inform public health policy. As the NSDUH is a self-reported questionnaire, people are self-reporting misuse, and thus this is not a diagnosis from a health-care professional.

Since 2015, misuse was defined in NSDUH as use in any way not directed by a doctor, including use without a prescription of one’s own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.¹²

This study was a cross-sectional surveillance study designed to examine past-year and lifetime reports of misuse of oral tramadol and comparator products among NSDUH respondents. Commonly prescribed Schedule II opioids including morphine, oxycodone, and hydrocodone were also analyzed as comparators for context. An additional analysis compared estimates of reports of oral tramadol misuse with another Schedule IV drug, alprazolam. These comparators were chosen to provide an appropriate framework for the data. In the U.S., as with tramadol, morphine, oxycodone and hydrocodone are commonly prescribed opioid medicines. Morphine, oxycodone and hydrocodone are considered conventional opioids in that they are pure mu agonists, each a Schedule II controlled substances based on current understanding that they carry a high potential for abuse. Because there is not another widely prescribed opioid medicine in Schedule IV, alprazolam was chosen as a comparator with that schedule designation, as it is widely prescribed in the U.S. and provides a context for comparison within the same schedule.

Based on the survey question, reports of past-year misuse of oral tramadol and comparators from 2015 to 2017 are available. Results were adjusted for drug availability to provide a better framework. In the context of the study, drug availability was expressed as the volume of total prescriptions in the U.S. per year (obtained from Symphony Health). To better understand the trends, the analysis also included lifetime misuse reports (collected in the survey prior to 2015) of tramadol and comparators from 2002 to 2014.

Descriptive analyses using the public-use dataset were conducted to estimate reported oral tramadol misuse during the past year (any and in combination with other opioid analgesics) for the overall population and stratified by numerous demographic factors including age, race, and gender for 2015, 2016 and 2017. Reported “any oral tramadol misuse” during the past year was comprised of “oral tramadol only” and “oral tramadol in combination” with all other opioid analgesics [including heroin] where the sum of these two subgroups sums to the total of “any oral tramadol misuse” group.

For context, descriptive analyses were also performed with the other Schedule II opioid comparators (ie, morphine, hydrocodone, oxycodone) and for another Schedule IV comparator (alprazolam). For example, “any morphine” reported misuse (comprised of “morphine only” and “morphine in combination” with other opioid analgesics (including heroin)). The groups were not mutually exclusive due to the combination groups (eg, there were respondents reporting morphine use in the “oral tramadol in combination” group and there were respondents reporting oral tramadol use in the “morphine in combination” group). Importantly, the combination groups did not mean that the drugs were used simultaneously on one occasion, but rather that respondents reported misusing that particular drug during the past year.

In addition, reports of misuse by injection of tramadol and comparator opioids were examined from 2002 to 2017.

Table 1. Reported past-year misuse as a percentage of total prescriptions (2015-2017) by product (Source: NSDUH, Symphony Health).

OPIOID	PARAMETER	2015	2016	2017
Tramadol	Any misuse (n)	1 787 180	1 644 875	1 699 088
	Any misuse as a % of those reporting use	9.6%	8.6%	9.2%
	Number of prescriptions	41 432 884	40 024 216	37 108 843
	Any misuse as a % of prescriptions	4.3%	4.1%	4.6%
Morphine	Any misuse (n)	684 758	562 711	524 847
	Any misuse as a % of those reporting use	9.2%	8.4%	8.7%
	Number of prescriptions	8 490 114	8 224 136	7 609 560
	Any misuse as a % of prescriptions	8.1%	6.8%	6.9%
Oxycodone	Any misuse (n)	4 310 809	3 964 528	3 788 907
	Any misuse as a % of those reporting use	15.2%	14.6%	14.2%
	Number of prescriptions	51 196 554	50 333 009	46 442 560
	Any misuse as a % of prescriptions	8.4%	7.9%	8.2%
Hydrocodone	Any misuse (n)	7 132 805	6,995,523	6,184,708
	Any misuse as a % of those reporting use	12.2%	12.8%	12.0%
	Number of prescriptions	93 966 773	86 124 804	75 897 828
	Any misuse as a % of prescriptions	7.6%	8.1%	8.2%

Respondents were asked whether they had ever injected heroin, cocaine, or other commonly-injected drugs. Respondents were not asked specifically about injection of tramadol; however, they were able to write in injected drugs that were not specifically included in previous questions (eg, Ultram, tramadol). Too few reports of tramadol misuse by injection (n = 7) were reported to conduct any formal analysis.

All estimates were weighted to the US population using weights provided by SAMHSA. More information on weighting can be found in the NSDUH 2017 Person-Level Sampling Weight Calibration Report.¹³

Results

Oral tramadol versus comparator opioids

2015 to 2017 (Past-year Misuse). Starting in 2015, NSDHU collected data on reported past-year misuse among individuals reporting past-year use of oral tramadol, morphine, oxycodone, and hydrocodone. An estimated 1.6 to 1.8 million Americans reported any (alone or in combination) past-year misuse of oral tramadol, versus 0.5 to 0.7 million for morphine, 3.8 to 4.3 million for oxycodone, 6.2 to 7.1 million for hydrocodone during the 3-year period.

To put the misuse data into context, the misuse data were analyzed against prescription volume data provided by Symphony Health (one of the largest integrated repositories of healthcare data in the US) (Table 1). The calculation of

misuse as a percent of total prescriptions provides insight as to how often these drugs may be misused relative to availability. The data from 2015 to 2017 consistently demonstrated that reported misuse of oral tramadol was at approximately 4% of total prescriptions versus approximately 7- to 8% reported for each of the Schedule II comparator opioids. Any past-year misuse as a percent of prescriptions is illustrated in Figure 1.

2002 to 2014 (Any lifetime misuse). Data from 2002 to 2014 indicate that any lifetime misuse, defined as having misused the product at least once during the lifetime, increase slightly over the time period for all four opioids. However, estimates of any lifetime misuse of oral tramadol consistently remained at 1.5% or less (0.4% in 2002 to 1.5% in 2013) of the population. In contrast, any lifetime misuse of hydrocodone and of oxycodone were much higher than those of oral tramadol at > 6% (6.0% in 2002 to 9.9% in 2012) and > 4% (4.8% in 2005 to 6.5% in 2014), respectively (Figure 2). Although morphine appears similar to tramadol on this parameter, it is comparable to other Schedule II opioids when adjusted for availability.

Data on misuse via injection

The NSDUH data included too few reports of tramadol use by injection to allow for reliable estimates or statistical comparisons with other drugs. In total, there were 7 total reports of misuse of tramadol by injection over the 16 year period

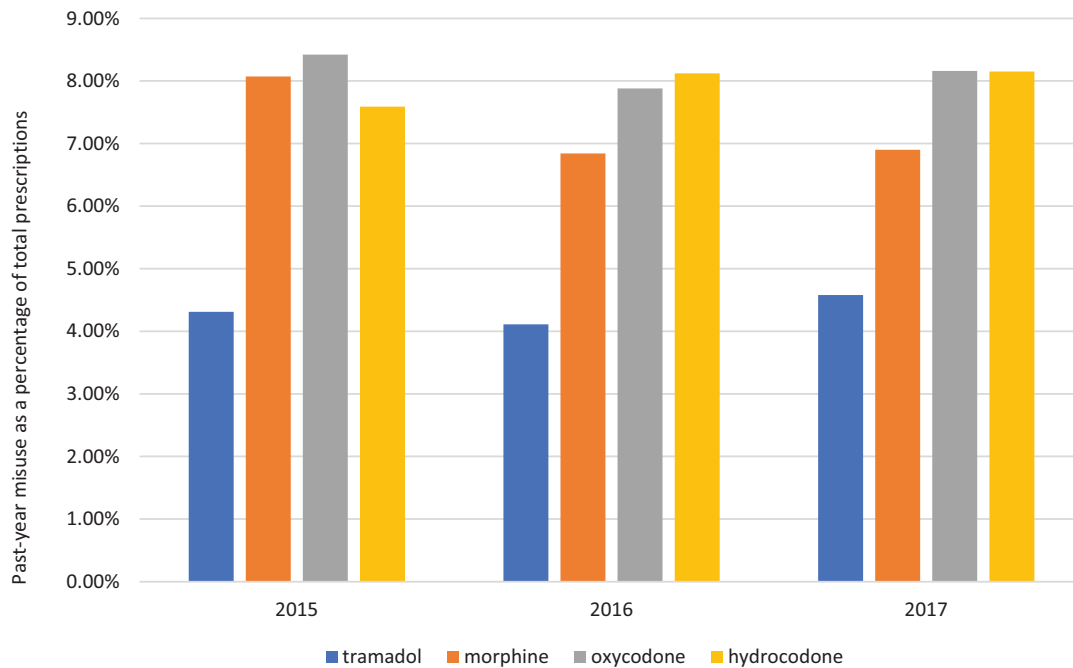


Figure 1. Reported past-year misuse as a percentage of total prescriptions (2015-2017) (Source: NSDUH, Symphony Health).

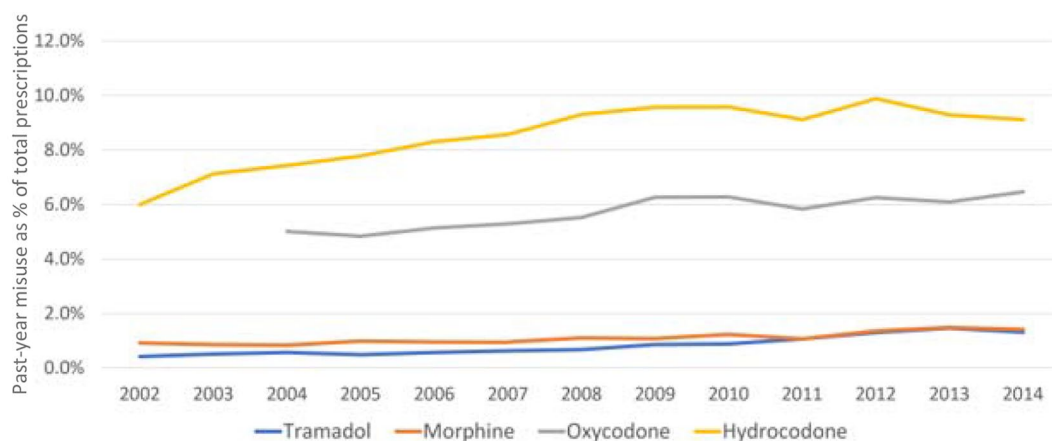


Figure 2. Percent of US Population reporting any lifetime misuse (at least once) of oral tramadol, morphine, oxycodone, and hydrocodone (2002-2014) (Source: NSDUH).

(2002-2017). There were 570 reports of misuse of morphine by injection, 1096 reports of misuse of oxycodone by injection, and 32 reports of misuse of hydrocodone by injection (Table 2). Tramadol was not available in the U.S. as an intravenous formulation during that time period, while only morphine had an intravenous formulation available in the U.S. during that time period.

Oral tramadol versus alprazolam

2015 to 2017 (Past-year misuse). Both tramadol and alprazolam are commonly prescribed Schedule IV drugs, the former for pain and the latter for anxiety. The number of respondents reporting misuse was 1.6 to 1.8 million for tramadol, versus 4.2 million for alprazolam. To put

the misuse data into further context, the misuse data were analyzed against prescription volume data provided by Symphony Health (Table 3). The calculation of misuse as a percent of total prescriptions provides insight as to how often these drugs may be misused relative to availability. In 2015 to 2017, alprazolam has approximately 9% misuse as a percent of the total number of prescriptions versus oral tramadol at approximately 4% (Figure 3).

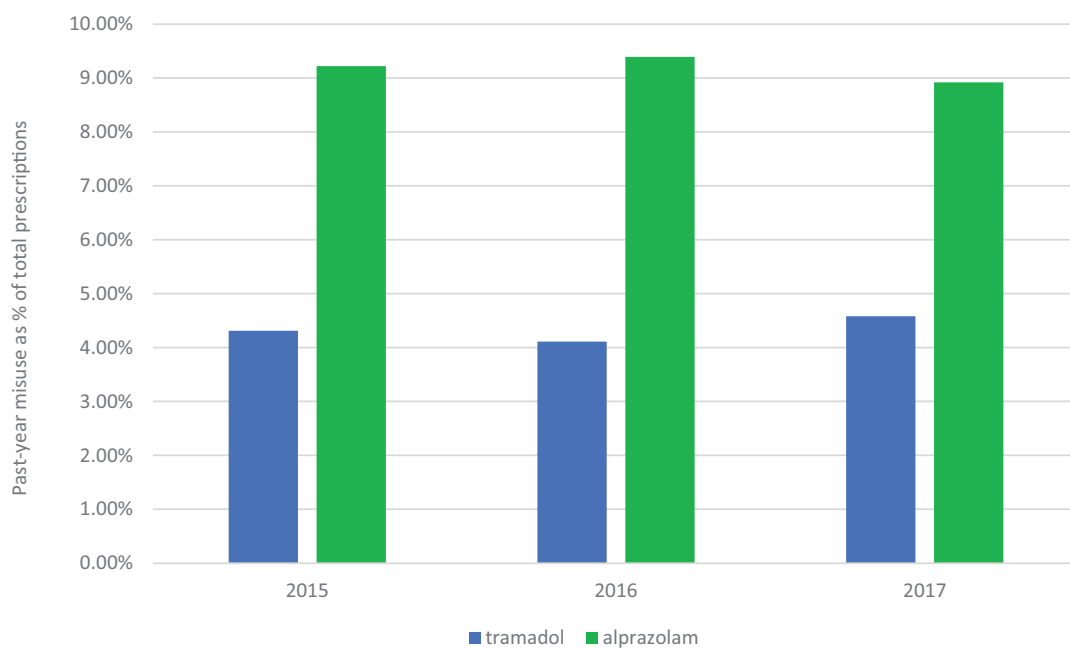
2012 to 2014 (Any lifetime misuse). Data from 2002 to 2014 indicate that any lifetime misuse of oral tramadol increased from approximately 0.4% to 1.5% from 2002 through 2014. Reported any lifetime misuse of alprazolam increased over the 13-year time period from 3.5% of the US population in 2002 to a maximum of 6.1% in 2014 (Figure 4).

Table 2. Number of reports of injection (unweighted) of tramadol, morphine, oxycodone and hydrocodone from 2002 to 2017 (Source: NSDUH).

DRUG	YEAR NUMBER OF RESPONDENTS (PERCENT OF RESPONDENTS)																
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Tramadol	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	2 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.0%)	2 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Morphine	26 (0.0%)	30 (0.1%)	25 (0.0%)	38 (0.1%)	24 (0.0%)	29 (0.1%)	29 (0.1%)	32 (0.1%)	31 (0.1%)	51 (0.1%)	36 (0.1%)	42 (0.1%)	48 (0.1%)	34 (0.1%)	41 (0.1%)	54 (0.1%)	
Oxycodone	22 (0.0%)	23 (0.0%)	36 (0.1%)	48 (0.1%)	48 (0.1%)	57 (0.1%)	56 (0.1%)	89 (0.2%)	74 (0.1%)	98 (0.2%)	91 (0.2%)	112 (0.2%)	89 (0.2%)	93 (0.2%)	74 (0.1%)	86 (0.2%)	
Hydrocodone	0 (0.0%)	1 (0.0%)	1 (0.0%)	4 (0.0%)	0 (0.0%)	2 (0.0%)	2 (0.0%)	4 (0.0%)	1 (0.0%)	1 (0.0%)	2 (0.0%)	3 (0.0%)	2 (0.0%)	3 (0.0%)	3 (0.0%)	3 (0.0%)	
Total respondents	54079	55230	55602	55905	55035	55049	55110	55234	57313	58397	55268	55160	55271	57146	56897	56276	

Table 3. Reported past-year misuse of oral tramadol and alprazolam as a percentage of total prescriptions (2015-2017) (Source: NSDUH, Symphony Health).

DRUG	PARAMETER	2015	2016	2017
Tramadol	Any misuse (n)	1 787 180	1 644 875	1 699 088
	Any misuse as a % of those reporting use	9.6%	8.6%	9.2%
	Number of prescriptions	41 432 884	40,024,216	37,108,843
	Any misuse as a % of prescriptions	4.3%	4.1%	4.6%
Alprazolam	Any misuse (n)	4 242 532	4 400 878	4 211 257
	Any misuse as a % of those reporting use	24.0%	23.8%	23.3%
	Number of prescriptions	46 039 314	46,844 582	47 207 803
	Any misuse as a % of prescriptions	9.2%	9.4%	8.9%

**Figure 3.** Reported past-year misuse as a percentage of total prescriptions (2015-2017) (Source: NSDUH, Symphony Health).

Discussion

The strength of the NSDUH is in its randomized household survey design with its large number of respondents (close to 70,000 people), resulting in a highly representative sample of the U.S. community not experiencing homelessness or institutionalization.^{10,11} Thus, the NSDUH can be viewed as a reliable and robust source of data when assessing prescription opioid misuse.

However, there are some limitations with NSDUH, including “self-reporting” bias, exclusion of certain groups (institutionalized and homeless populations), and difficulty distinguishing between different types of “misuse”, for example, individuals who use someone else’s prescription opioids one time to relieve physical pain versus individuals who use someone else’s prescription opioids daily to get high.¹⁴

The calculation of misuse as a percent of total prescriptions provides insight as to how often these drugs may be misused relative to availability. From 2015 through 2017, estimates of reported “any past-year misuse” of oral tramadol represented approximately 4% of the total number of oral tramadol prescriptions, about half of those of comparator schedule II opioids (6.8–8.1%, 7.9–8.4%, and 7.6–8.2% for morphine, oxycodone, and hydrocodone respectively).

Furthermore, “any lifetime misuse” of tramadol (1.5% or less) between 2002 and 2014 was much lower than other commonly prescribed Schedule II opioids (6–9% for hydrocodone and 4% to 6% for oxycodone). The rate was similar to morphine; however, morphine may not be a suitable comparator as it is not widely prescribed as an oral opioid (due to poor bioavailability).¹⁵ The misuse data on morphine is

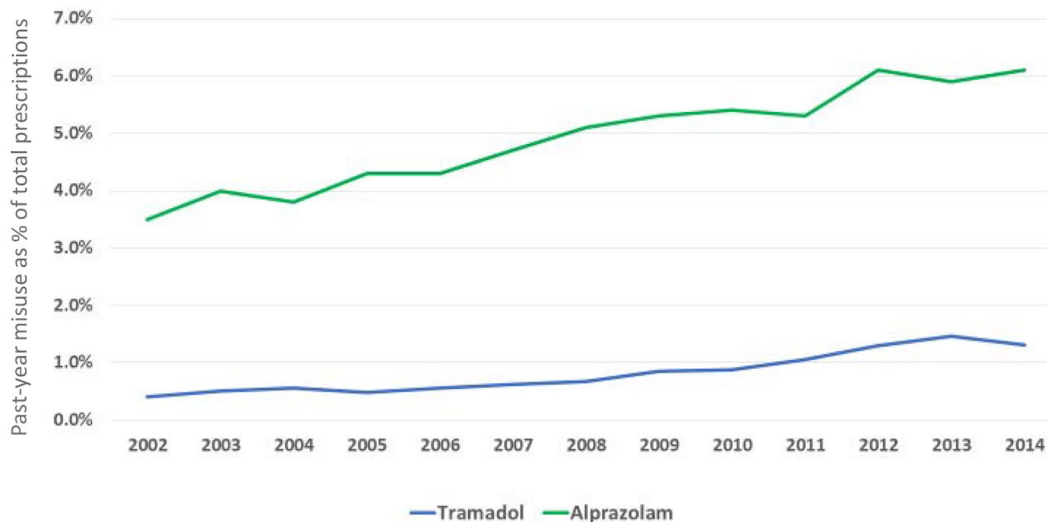


Figure 4. Percent of US Population Reporting any lifetime misuse (at least once) of oral tramadol and alprazolam (2002-2014) (Source: NSDUH).

comparable those of other Schedule II opioids when adjusted for availability.

These patterns are reinforced when the misuse of tramadol is compared to alprazolam, another Schedule IV drug. In addition, too few reports of tramadol misuse by injection were included in the 13-year analysis period to allow for any population-based estimation. Misuse of tramadol by injection, a formulation not available in the US, was virtually non-existent. It is unlikely in any case that oral tramadol would be diverted by drug abusers for use as intravenous injection, since compared to oral tramadol, injected tramadol results in less mu opiate effect as a result of slower onset and lower exposure to M1.¹⁶

It is important to note that the findings of the study are consistent with prior studies on tramadol. In randomized trials and other studies, the abuse potential for oral tramadol is low in comparison to more potent opioids such as morphine, oxycodone, and hydrocodone.^{3,17-21} Literature on diversion of tramadol indicates that it is also lower than other opioids.²²⁻²⁵

Conclusion

This analysis demonstrated a low prevalence of self-reported oral tramadol misuse (relative to other commonly prescribed opioids) in a large nationally representative sample of non-institutionalized US residents. Estimates of reported oral tramadol misuse have remained relatively stable over time and are substantially lower than those reported for comparators when adjusted for prescription volume. Reports of oral tramadol misuse are also much less than alprazolam, another Schedule IV drug.

Author Contribution

SAR contributed to the conceptualization and design of the study, the interpretation of the data, and writing of the manuscript.

BG contributed to the conceptualization and design of the study, the interpretation of the data, and writing of the manuscript.

MH contributed to the conceptualization and design of the study, the interpretation of the data, and writing of the manuscript.

LL contributed to the conceptualization and design of the study, the interpretation of the data, and writing of the manuscript

Authors' note

L Lu and SA Reines are employees of Avenue. M Harnett and B Goldsmith are paid consultants of Avenue.

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