Title: Assessment of Tapentadol API Abuse Liability with the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System

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Complete Title: Assessment of Tapentadol API Abuse Liability with the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System

Running Head: Tapentadol API Abuse Liability

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Authors TJC, SPK and MWP are compensated for participation on the RADARS System Scientific Advisory Board, and DHHA contracts with these authors’ institutions for the operation of RADARS System programs that provided some of the data for this study.
HIGHLIGHTS:

- Abuse liability of tapentadol API is compared to those of other Scheduled opioids.
- Population-level event rates of tapentadol API abuse were lower than comparators.
- Drug-availability adjusted event rates of tapentadol abuse were low but not lowest.
- Public health burden of tapentadol API appears to be low.

ABSTRACT

Tapentadol, a Schedule II opioid with a combination of μ-opioid activity and norepinephrine reuptake inhibition, is used for the management of moderate to severe acute and chronic pain. Its dual-mechanism of action is thought to reduce opioid-related side effects that can complicate pain management. Since approval, tapentadol has been tracked across multiple outcomes suggesting abuse liability, and a pattern of relatively low, although not absent, abuse liability has been found. This retrospective cohort study further details the abuse liability of tapentadol as an Active Pharmaceutical Ingredient (API) when both immediate-release and extended-release formulations were on the market together (4Q2011 to 2Q2016). Tapentadol (API) was compared to tramadol, hydrocodone, morphine, oxycodone, hydromorphone, and oxymorphone across Poison Center, Drug Diversion and Treatment Center Programs Combined data streams from the RADARS System. Findings suggest the public health burden related to tapentadol to date is low, but present. Event rates of abuse per population-level denominators were significantly lower than all other opioids examined. However, when adjusted for drug availability, event rates of abuse were lower than most CII opioids studied, but were not the lowest. Disentangling these two sets of findings further by examining various opioid formulations, such as extended-release and the role of abuse-deterrent formulations, is warranted.

Perspective:

This article presents the results from an examination of tapentadol API across the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System: a broad and carefully designed postmarketing mosaic. Data to date from Poison Center, Drug Diversion and Treatment Centers Combined suggest a low, but present public health burden related to tapentadol.
Keywords:

Prescription drug abuse; Prescription opioid abuse; Prescription opioid analgesic; Tapentadol abuse liability; API; Human; Pain management
Introduction

Tapentadol is a CII centrally-acting analgesic consisting of a combination of μ-opioid activity and norepinephrine reuptake inhibition which is thought to enhance moderate to severe acute and chronic pain relief with fewer opioid-related side effects\(^29,30\). Tapentadol immediate-release (IR; NUCYNTA) was approved by FDA in December 2008 and the extended-release (ER) formulation (Nucynta® ER) was approved in August 2011. Tapentadol ER is formulated with an INTAC™ crush-resistant matrix\(^17\).

Since its approval, tapentadol IR has been tracked across multiple outcomes suggestive as potential signals of abuse liability. Between 3Q2009 and 2Q2011, Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program data revealed that intentional exposures to tapentadol were minimal (0.003 to 0.02 cases per 100,000 population). A low public health impact of tapentadol intentional exposure was inferred from the per population-level outcome\(^11\).

However, when examined as rate per 1,000 unique recipients of dispensed drug (URDD), rates of intentional exposures of tapentadol hovered around 0.30 per 1,000 URDD, which were similar to oxycodone, higher than hydrocodone, and lower than tramadol. At the same time, data gathered from RADARS System Treatment Center Programs Combined indicated rates of tapentadol IR abuse were low but variable (remaining close to 0 per 100,000 population)\(^11\). Rates of tapentadol IR non-medical use in college students were also reported to be low (0.7%)\(^10\). This set of findings was interpreted as being driven by varying degrees of market penetration of tapentadol IR across different geographic regions and experimentation with this newly available opioid\(^11\).

Subsequent post-marketing studies investigating abuse of both tapentadol IR and ER formulations found low relative risk of past month abuse of tapentadol (an aggregate of IR+ER) between 1Q2011 and 3Q2012 in substance abusers seeking treatment\(^3\). However, when IR and ER formulations were examined separately, the relative risk of tapentadol IR abuse did not differ from that of fentanyl IR. Further, the relative risk of tapentadol ER abuse did not differ from that of hydromorphone ER,
suggesting a degree of abuse liability in both 3, even though messages posted by recreational drug users during the same time period revealed low levels of interest in tapentadol (ER+ IR 24. Although message posting in itself may not be a reliable source of abuse liability, it can be considered to provide a signal or insight into agents that may, or in the case of tapentadol, may not be particularly sought after for non-medical use. Meanwhile, studies of drug diversion, identified as cases opened by drug diversion investigators in the US between 3Q2009 and3Q2014 12, 13, the price paid for illicitly obtained tapentadol15, or the number of cases that are submitted to the National Forensic Laboratory Information System (NFLIS) 32, 32, 32, 22, 2, 33, 3, 3 have generally reported low or non-existent levels of illicit buying or selling of tapentadol.

To date, a pattern of relatively low, although not absent, abuse liability of ER and IR tapentadol has been documented. As a multi-modal opioid, tapentadol is a new and unique molecule, but little has been written about its abuse liability as an entity, either with behavioral pharmacology models 28 or within the postmarketing framework 4-7. As such, the purpose of this paper is to investigate the abuse liability of tapentadol as an active pharmaceutical ingredient (API) during the time that both IR and ER have been on the market together (4Q2011 through 2Q2016) to determine whether the abuse liability of tapentadol as an API remains one of the lowest of scheduled opioid compounds. Tapentadol API refers to any mention of tapentadol (ER, IR, or formulation not known).

Methods

Data sources

The RADARS System Programs

These analyses employ data from the RADARS System which provides post-marketing surveillance data regarding prescription medication abuse, misuse, and diversion to various stakeholders including regulatory agencies, policy making organizations, and pharmaceutical companies. The RADARS System is comprised of a mosaic of programs that gather data from several unique populations along
the spectrum of drug abuse. Rates of abuse and diversion of tapentadol-containing products were compared to products containing oxycodone, hydrocodone, oxymorphone, hydromorphone, morphine, and tramadol.

Comparators were chosen based upon their scheduling, market share and use characteristics. Tapentadol is a Schedule II opioid, and most comparators were also Schedule II. Oxycodone and hydrocodone were chosen as references because they are widely prescribed, oxymorphone and hydromorphone were chosen as comparators because they have similar market shares as tapentadol (internal IMS data) and morphine was chosen because it is a standard reference drug. In addition, the Schedule IV opioid tramadol was selected because it is a low potency, mixed-action opioid.

The RADARS System Poison Center Program obtains data from individuals within the general population and from healthcare providers who are seeking advice regarding potential toxic exposures, including exposures to prescription opioids and stimulants. For the calculation of rates, an event is defined as a mention of a product within a drug group by exposures identified as intentional abuse cases. Intentional abuse cases are exposures “resulting from the intentional improper or incorrect use of a substance where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect [http://www.ncbi.nlm.nih.gov/pubmed/26624241].” The Poison Center Program detects product-specific prescription drug abuse and misuse in near real-time. Poison Center data associate strongly with other measures of national prescription opioid exposures, such as emergency department visits 16 and national vital statistics 14, as well as with clinician ratings of intentional abuse 27. As of the second quarter 2016, the Poison Center Program collected data from 50 out of 55 regional US Poison Centers covering 48 states, including urban, suburban, and rural regions. In second quarter 2016, 91% of poison centers participated in the program and 94% of the US population resided in areas covered by these centers. Investigators
at each participating poison center collect data using a nationally standardized electronic health record. In addition to the institutional review board (IRB) approvals from each participating regional poison center, this study protocol was granted exempt status by the Colorado Multiple Institutional Review Board.

The RADARS System Drug Diversion Program conducts a quarterly survey of law enforcement investigators on the diversion of prescription opioid and stimulant products in their jurisdictions. Diversion officers represent municipal police departments, multi-jurisdictional drug task forces, county sheriffs’ departments, regulatory agencies such as state medical and pharmacy boards, state police agencies, prosecutors’ offices, and departments of health. Drug diversion officers submit data on the number of new documented drug diversion cases within their jurisdiction for specific prescription products of interest. While formal comparative analyses have not been conducted, similar patterns of diversion are observed within the RADARS mosaic between RADARS and NFLIS estimates, and have been noted between RADARS diversion findings and other national surveys.

In the second quarter 2016, the Drug Diversion Program collected data from 205 out of 250 participating agencies in 48 states (all states except Hawai‘i; this is a response rate of approximately 82% participating agencies). Approximately 38% of the population falls with the coverage area. Coverage is most complete in the mid-Atlantic and Plains states, with New England and California also having substantial coverage (maps available in the Dart et al., 2015 supplement). For the calculation of rates, an event represents the number of newly opened written complaints or reports involving products within the drug group of interest. The Drug Diversion Program study protocol was deemed to be non-human subject research by NOVA Southeastern University’s IRB.

The RADARS System Treatment Center Programs Combined is comprised of both the Opioid Treatment Program and the Survey of Key Informants’ Patients Program. Each newly admitted patient is offered the opportunity to complete a standardized self-administered
questionnaire that solicits information on specific prescription and illegal opioid products abused in the past month. Both programs use a common core questionnaire allowing data to be combined. For the calculation of rates, an event is an endorsement of past month use to get high with a product within the drug group of interest. Treatment Centers Combined data have strong associations with national Treatment Episodes Data Set.

In the second quarter 2016, 59 of 74 participating methadone maintenance treatment programs provided at least one survey to the Opioid Treatment Program. The 59 centers are in 30 states. Respondents are primarily from the coasts and in the mid-Atlantic states. The Opioid Treatment Program study protocol was reviewed and approved by the IRB of the National Development and Research Institutes, Inc.

As of the second quarter 2016, The Survey of Key Informants’ Patients Program involved 129 substance abuse treatment programs in 46 states, representing approximately 48% of the US population. Approximately 78% of the patients who are asked complete a valid version of the survey, and they receive modest compensation for doing so. SKIP data include representation from urban, suburban, and rural centers, with coverage being fairly consistent across the lower 48 states, excluding Montana, which does not currently have any representation, while California, Nevada, Utah, Texas, Wisconsin and South Carolina having lighter than average coverage. The Survey of Key Informants’ Patients Program study protocol was reviewed and approved by Washington University in St. Louis IRB.

**Denominators**

Three denominators were used in the present analyses: population, total number of prescriptions dispensed, and total number of dosage units dispensed.

Population estimates were calculated by assuming linear growth between 2000 and 2010 US census and was extrapolated using this same rate of change from October 1, 2011 to June 30, 2016. For
any given year quarter, the total population covered by the RADARS System programs is computed in this manner and this number is used as the denominator when calculating population rates.

QuintilesIMS™ Government Solutions, Inc., a subsidiary of QuintilesIMS™ Health Inc. (Atlanta, Georgia) obtains product and geographically specific data from a sample of roughly 50% of retail pharmacies in the US (SDI database, generated by QuintilesIMS™ Government Solutions, Inc.). QuintilesIMS Health uses a complex proprietary projection methodology to extrapolate from the observed data to the universe of all retail prescriptions in the US. The study uses national estimates from QuintilesIMS Health for total prescriptions dispensed and total dosage units dispensed at the three-digit ZIP code level for products of interest. For any given quarter, the total of prescriptions and the total of dosage units in the three-digit ZIP codes covered by the RADARS System Programs were used as the denominators when calculating drug utilization rates.

Data analysis

Plots of quarterly abuse and diversion rates were generated for descriptive purposes. Event rates are calculated by dividing the sum of events from October 2011 through June 2016 by the sum of the population or prescriptions dispensed or drug units dispensed within the 3-digit ZIP codes covered by a particular program in a given quarter. Rates therefore reflect a quarterly average where quarters with larger denominators have greater influence on the overall average. Population rates are scaled per 1,000,000 individuals, while drug utilization rates are scaled per 10,000 prescriptions dispensed and per 100,000 dosage units dispensed. Confidence intervals (CIs) for the cumulative analyses are calculated using the exact Poisson method. Rate ratios compare the cumulative rate of abuse or diversion for each opioid to that of tapentadol and are calculated using a saturated Poisson regression. The natural log of each denominator enters the model as an offset variable to calculate rates. Rate ratios are depicted on the logarithmic scale to account for the wide range of values among comparator products. Rate ratios greater than 1 mean the comparator product is abused or diverted more than tapentadol whereas ratios
less than 1 mean the comparator product is abused or diverted less than tapentadol. Comparator product rate ratios with 95% CIs that cross 1 do not differ from tapentadol, and comparator products with overlapping 95% CIs do not differ from one another.

Results

Poison Center Program.

Rate per 1,000,000 population

From October 2011 through June 2016 there were 87 mentions of tapentadol products by intentional abuse exposure cases reported to participating poison centers. Figure 1A presents the Poison Center Rate of Intentional Abuse per 1,000,000 population by quarter. Rates of tapentadol intentional abuse were the lowest among all products and ranged from 0.007 to 0.036 during this period.

Average quarterly rate (event rate) of intentional abuse of tapentadol per 1,000,000 population was 0.015 (95% CI: 0.012 to 0.019) (Table 1, Upper Panel). Event rates of intentional abuse were greatest for oxycodone (1.302, 95% CI: 1.272 to 1.332), followed by hydrocodone (1.255, 95% CI: 1.226 to 1.284), tramadol (0.521, 95% CI: 0.502 to 0.540), morphine (0.275, 95% CI: 0.262 to 0.289), hydromorphone (0.137, 95% CI 0.127 to 0.147) and oxymorphone (0.114, 95% CI: 0.106 to 0.124). Rate ratios per 1,000,000 population of intentional abuse calculated between tapentadol and comparators revealed that comparators were intentionally abused from 7.414 times (oxymorphone) to 84.322 times (oxycodone) the rate of intentional abuse of tapentadol at the population level (Table 1, Upper Panel; Figure 2A).

Rate per 10,000 prescriptions dispensed
Figure 1B presents the Poison Center rate of intentional abuse per 10,000 prescriptions dispensed by quarter. Rates of tapentadol intentional abuse ranged from 0.088 to 0.453 during this period. Average quarterly rate (event rate) of intentional abuse of tapentadol per 10,000 prescriptions dispensed was 0.207 (95% CI: 0.166 to 0.255) which was neither the largest nor smallest event rate (Table 1, Middle Panel). Event rates of intentional abuse were greatest for oxymorphone (1.168, 95% CI: 1.079 to 1.261) and lowest for hydrocodone (0.131, 95% CI: 0.128 to 0.134). Rate ratios of intentional abuse per 10,000 prescriptions dispensed calculated between tapentadol and comparators revealed that hydrocodone and tramadol were intentionally abused less than tapentadol (0.632 and 0.769 times the rate of tapentadol intentional abuse), whereas the remainder of comparators were abused from 1.356 (oxycodone) to 5.651 (oxymorphone) times the rate of intentional abuse of tapentadol (Table 1, Middle Panel; Figure 2B).

Rate per 100,000 dosage units dispensed

Figure 1C presents the Poison Center rate of intentional abuse per 100,000 dosing units dispensed by quarter. Rates of tapentadol intentional abuse ranged from 0.012 to 0.066 during this period. Average quarterly rate (event rate) of intentional abuse of tapentadol per 100,000 dosing units dispensed was 0.028 (95% CI: 0.023 to 0.035) which was neither the largest nor smallest event rate of intentional abuse (Table 1, Lower Panel). Event rates were greatest for oxymorphone (0.166, 95% CI: 0.153 to 0.179), and lowest for hydrocodone (0.020, 95% CI: 0.019 to 0.020). Rate ratios of intentional abuse per 100,000 prescriptions dispensed calculated between tapentadol and comparators revealed that hydrocodone and tramadol were intentionally abused less than tapentadol (0.703 and 0.766 times the rate of tapentadol abuse), whereas the remainder of comparators were abused from 1.275 (oxycodone) to 5.886 (oxymorphone) times the rate of intentional abuse of tapentadol (Table 1, Lower Panel; Figure 2C).

Drug Diversion.
Rate per 1,000,000 population

From October 2011 through June 2016 there were 58 reports of tapentadol diversion. Figure 3A presents the rates of Drug Diversion per 1,000,000 population by quarter. Rates of tapentadol diversion were the lowest among all products and ranged from 0.000 to 0.070 during this period.

Average quarterly rate (event rate) of diversion was 0.029 (95% CI: 0.022 to 0.038) for tapentadol (Table 2, Upper Panel). Drug diversion rates were greatest for oxycodone (9.234, 95%CI: 9.101 to 9.368) and hydrocodone (7.656, 95%CI: 7.535 to 7.779). Rate ratios reveal that comparators were diverted from 23.172 (oxymorphone) to 316.862 (oxycodone) times the rate of tapentadol diversion per 1,000,000 population (Table 2, Upper Panel; Figure 4A).

Rate per 10,000 prescriptions dispensed

Figure 3B presents the rates of Drug Diversion per 10,000 prescriptions dispensed by quarter. Rates of tapentadol diversion were similar to tramadol and ranged from 0.000 to 0.794 during this period. Average quarterly rates (event rates) of diversion per 10,000 prescriptions dispensed were lowest for tapentadol and tramadol (0.334 and 0.335, 95% Event Rate CIs overlap) (Table 2, Middle Panel). Drug diversion rates were greatest for oxymorphone (6.183, 95% CI: 5.856 to 6.522) and hydromorphone (5.427, 95%CI: 5.221 to 5.638). Rate ratios reveal that comparators significantly different from tapentadol were diverted from 2.613 (hydrocodone) to 18.507 (oxymorphone) times the rate of tapentadol diversion per 10,000 prescriptions dispensed (Table 2, Middle Panel; Figure 4B).

Rate per 100,000 dosage units dispensed

Figure 3C presents the rates of Drug Diversion per 100,000 dosing units dispensed by quarter. Rates of tapentadol diversion were similar to tramadol and ranged from 0.000 to 0.1027 during this
period. Average quarterly rates (event rates) of diversion per 100,000 dosage units dispensed were lowest for tapentadol and tramadol (0.045 and 0.047, respectively; 95% Event Rate CIs overlap) (Table 2, Lower Panel). Drug diversion rates were greatest for oxymorphone (0.860, 95%CI: 0.814 to 0.907) and hydromorphone (0.620, 95%CI: 0.596 to 0.644). Rate ratios reveal that comparators significantly different from tapentadol were diverted from 2.957 (hydrocodone) to 19.308 (oxymorphone) times the rate of tapentadol diversion per 100,000 dosage units dispensed (Table 2, Lower Panel; Figure 4C).

Treatment Center Programs Combined.

Rate per 1,000,000 population

From October 2011 through June 2016 there were 744 endorsements of past month use to get high with tapentadol products. Figure 5A presents the Treatment Centers Combined rates of past-month use to get high per 1,000,000 population by quarter. Rates of past-month use of tapentadol to get high were the lowest among all products and ranged from 0.115 to 0.472 during this period.

Average quarterly rate (event rate) of reported use for getting high within the past month with tapentadol per 1,000,000 population was the lowest rate during the study period (0.245, 95%CI: 0.228 to 0.263) (Table 3, Upper panel). Rate of reported use for getting high in the past month was greatest for oxycodone (12.969; 95% CI: 12.841 to 13.097) and hydrocodone (10.102, 95%CI: 9.989 to 10.216). Rate ratios reveal that comparator use for getting high in the past month ranged from 3.475 (tramadol) to 52.972 (oxycodone) times the rate of tapentadol use per 1,000,000 population (Table 3, Upper panel; Figure 6A).

Rate per 10,000 prescriptions dispensed
Figure 5B presents the rates of past-month use of tapentadol to get high per 10,000 prescriptions dispensed by quarter. Rates of tapentadol use to get high ranged from 1.584 to 6.065 during this period. Average quarterly rates (event rates) of reported use for getting high within the past month with tapentadol per 10,000 prescriptions dispensed was 3.162 (95%CI: 2.939 to 3.398) which was neither the largest nor smallest event rate (Table 3, Middle Panel). Rate of reported use for getting high in the past month was greatest for oxymorphone (29.450; 95% CI: 28.881 to 30.027) and hydromorphone (21.240, 95%CI: 20.924 to 21.559) and lowest for tramadol (0.264; 95% CI 0.254 to 0.274). Rate ratios reveal that comparator use for getting high in the past month ranged from 0.083 (tramadol) to 9.313 (oxymorphone) times the rate of tapentadol use (Table 3, Middle Panel; Figure 6B).

Rate per 100,000 dosage units dispensed

Figure 5C presents the rates of past-month use of tapentadol to get high per 100,000 dosing units dispensed by quarter. Rates of tapentadol use to get high ranged from 0.219 to 0.823 during this period. Average quarterly rate (event rate) of reported use for getting high within the past month with tapentadol per 100,000 dosing units dispensed was 0.436 (95%CI: 0.405 to 0.468) which was neither the largest nor smallest event rate (Table 3, Lower Panel). Rate of reported use for getting high in the past month was greatest for oxymorphone (4.221; 95% CI: 4.140 to 4.304) and hydromorphone (2.471; 95%CI: 2.434 to 2.508) and lowest for tramadol (0.036; 95% CI 0.034 to 0.037). Rate ratios reveal that comparator use for getting high in the past month ranged from 0.082 (tramadol) to 9.686 (oxymorphone) times the rate of tapentadol use (Table 3, Lower Panel; Figure 6C).

Discussion

The purpose of this report was to evaluate the abuse liability of the tapentadol API from October 2011 through June 2016. When evaluated per 1,000,000 population across Poison Center, Drug Diversion and Treatment Center Programs Combined data streams, tapentadol was the least-mentioned API, with rates being less than 0.5 cases per 1,000,000 population across all data streams during this
time period. These data suggest a low overall public health burden associated with abuse or diversion of tapentadol.

When adjusted for drug utilization, i.e., per 10,000 prescriptions dispensed and per 100,000 dosage units dispensed, tapentadol abuse liability was generally low compared to other opioids, but present, nonetheless. Reports varied by data stream.

Evaluation of Drug Diversion data revealed that rates of tapentadol diversion did not differ from those of tramadol, both of which had the lowest rates of drug diversion among all comparators. Tramadol, scheduled as a CIV opioid with pharmacology including mu-receptor agonism and norepinephrine and serotonin reuptake inhibition\textsuperscript{25}, is recognized for low-to-modest abuse liability and relatively low levels of abuse and diversion\textsuperscript{34, 9, 36}. It is possible that the low diversion rate of tapentadol across all denominators is because tapentadol is less likely to be accessed through the illicit markets that are usually attended to by law enforcement and more likely to be diverted through other distribution systems, however, this remains to be determined. Low rates of tapentadol diversion have also been supported in existing literature\textsuperscript{6, 11, 13, 24} suggesting that to-date, this is a stable finding.

Evaluation of Treatment Center Programs Combined and Poison Center data when adjusted for drug utilization revealed similar patterns between the two data streams. Tapentadol had neither the highest nor lowest reported rates of use to get high in the past month (TC) or intentional abuse (PC). Across both data sets, rates of tapentadol abuse were greater than tramadol and hydrocodone, with a more pronounced difference in the Treatment Centers Combined. In particular, when adjusting for drug utilization and interpreting the longitudinal data presentation, recent Treatment Centers Combined data suggest a slight increase in use of tapentadol to get high.

This finding is surprising because, similar to tramadol, when adjusted for drug availability, hydrocodone has been found to have a relatively low abuse liability\textsuperscript{1, 11, 26}. The difference in relative rates may be a function of formulation, namely, much of the hydrocodone API in the present analysis
consists of immediate release combination hydrocodone/acetaminophen products, which for the majority of the time period studied were CIII substances; hydrocodone products without acetaminophen including Zohydro and Hysingla were approved by FDA in 2013 and 2014, respectively. Acetaminophen-containing products have resulted in adverse health outcomes that are thought to deter illicit use, although the effectiveness of this strategy can be debated. Regardless, a better understanding of this finding can be obtained by investigating these drugs as a function of their formulation (ER vs IR).

Rates of oxycodone abuse were also found to be significantly lower than tapentadol when adjusted for drug utilization in the Treatment Center Programs Combined data stream. This likely reflects, in part, the high proportion of combination oxycodone/acetaminophen products and to some extent the introduction of the abuse deterrent formulation of extended-release OxyContin which occurred in 2010. In addition to early studies that revealed drug abusers generally characterized the product as less desirable than the original OxyContin, postmarketing studies have identified general decreases in both the use and prescription of OxyContin.

However, this interpretation is not intended to minimize the appearance of recent increases in the rates of past-month use of tapentadol to get high in the Treatment Centers Combined data, but rather to provide context. The absolute numbers of past-month use to get high of tapentadol are much lower than other comparators by at least a factor of 10, suggesting less stable estimates of magnitude, and indeed, as depicted in the longitudinal data, tapentadol has had a variable pattern of abuse. The drug changed sponsors in April 2015 / 2Q2015 and recent increases in use to get high can be traced to that quarter. A similar pattern was observed in 2011, (after the introduction of the extended-release formulation) before levels of past-month use to get high decreased to similar low levels as tramadol. Thus, these data warrant continued observation.
While the RADARS data streams represent a broad and carefully designed surveillance system, the present findings must also be considered together with existing limitations. The Poison Center Program relies on spontaneous reports, therefore, the number of cases is underreported and drug identification may be inaccurate. Not all parts of the US have prescription drug diversion agencies, and thus data may also be subject to under-reporting. Lastly, Treatment Center Programs Combined data are also self-reported, and thus subject to limitations associated therewith.\(^\text{12}\)

Analyzing the abuse liability of an API has strengths and weaknesses. It is a broad concept that serves as an estimate of the impact of the molecule(s) of interest, regardless of the formulation (IR/ER; abuse-deterrent formulation/no abuse-deterrent formulation) or whether the molecule is packaged as a single-entity or combination-product. Although it lacks the specificity that an analysis of any one of these individual categories might provide, it yields relevant information about the general exposures resultant from the compound. It also removes potential product ascertainment bias among different formulations of the API.

In summary, these data suggest that the public health burden related to tapentadol, which occupies approximately 3% of the opioid market, is low, but present.

Event rates of abuse per the population-level denominator across the three data streams were significantly lower than all other opioids examined in this study, including CII opioids (hydrocodone, hydromorphone, oxycodone, oxymorphone and morphine). However, when adjusted for drug availability, these data also suggest that tapentadol has the potential for abuse. Event rates of abuse were lower than most CII opioids studied, but were not the lowest. Disentangling these two sets of findings further by examination of various opioid formulations, such as extended-release and the role of abuse-deterrent formulations, is warranted.
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References


Figure 1. **Poison Center: Intentional Abuse.** Quarterly rates of tapentadol and comparator opioid intentional abuse per 1,000,000 population (A), per 10,000 prescriptions dispensed (B) and per 100,000 dosing units dispensed (C) from 4Q2011 to 2Q2016.

Figure 2. **Poison Center: Intentional Abuse.** Rate ratios of tapentadol and comparator opioid intentional abuse per 1,000,000 population (A), per 10,000 prescriptions dispensed (B) and per 100,000 dosing units dispensed (C) from 4Q2011 to 2Q2016. Tapentadol is the comparator and represented by the vertical line at 1.

Figure 3. **Drug Diversion.** Quarterly rates of tapentadol and comparator opioid drug diversion per 1,000,000 population (A), per 10,000 prescriptions dispensed (B) and per 100,000 dosing units dispensed (C) from 4Q2011 to 2Q2016.

Figure 4. **Drug Diversion.** Rate ratios of tapentadol and comparator opioid drug diversion per 1,000,000 population (A), per 10,000 prescriptions dispensed (B) and per 100,000 dosing units dispensed (C) from 4Q2011 to 2Q2016. Tapentadol is the comparator and represented by the vertical line at 1.

Figure 5. **Treatment Center Programs Combined: Past Month Use to Get High.** Quarterly rates of tapentadol and comparator opioid past-month use to get high per 1,000,000 population (A), per 10,000 prescriptions dispensed (B) and per 100,000 dosing units dispensed (C) from 4Q2011 to 2Q2016.

Figure 6. **Treatment Center Programs Combined: Past Month Use to Get High.** Rate ratios of tapentadol and comparator opioid past-month use to get high per 1,000,000 population (A), per 10,000 prescriptions dispensed (B) and per 100,000 dosing units dispensed (C) from 4Q2011 to 2Q2016. Tapentadol is the comparator and represented by the vertical line at 1.
Table 1. Poison Center. Rates of intentional abuse per 1,000,000 population, rate ratios and 95% confidence intervals for tapentadol API and comparators. Data are organized by rate of intentional abuse. Also see Figures 1A -1C.

<table>
<thead>
<tr>
<th>DRUG (API)</th>
<th>Event Rate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>Rate Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
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<td>9.274</td>
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<td>Hydromorphone API</td>
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<td>0.147</td>
<td>8.851</td>
<td>7.091</td>
<td>11.047</td>
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<th>Rate Ratio</th>
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<td>0.165</td>
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<th>Rate Ratio</th>
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<td>0.179</td>
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Table 2. Drug Diversion. Rates of diversion per 1,000,000 population, rate ratios and 95% confidence intervals for tapentadol API and comparators. Data are organized by rate of diversion. Also see Figures 2A -2C.

<table>
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<tr>
<th>DRUG (API)</th>
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<th>Rate Ratio</th>
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<th>Rate Ratio</th>
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Table 3. Treatment Center Programs Combined. Rates of past-month use to get high per 1,000,000 population, rate ratios and 95% confidence intervals for tapentadol API and comparators. Data are organized by past month rate of use. Also see Figures 3A-3C.

<table>
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<th>DRUG (API)</th>
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<th>Lower 95% CI</th>
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<th>Rate Ratio</th>
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<th>Upper 95% CI</th>
<th>Rate Ratio</th>
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</table>
Figure 1

Poison Center

A.

B.

C.

Year Quarter

Oxycodone
Hydrocodone
Hydromorphone
Morphine
Oxymorphone
Tramadol
Tapentadol
Figure 2

Poison Center

A.

B.

C.
Figure 3

Drug Diversion

A.

- Oxycodone
- Hydrocodone
- Hydromorphone
- Morphine
- Oxymorphone
- Tramadol
- Tapentadol

B.

C.

Year Quarter
Figure 4

Drug Division

A.

B.

C.
Figure 5

Treatment Centers Combined

A.

B.

C.
Figure 6

Treatment Centers Combined

A.

Tapentadol API

Tramadol API

Hydrocodone API

Morphine API

Hydromorphone API

Oxycodone API

Oxymorphone API

B.

Tapentadol API

Tramadol API

Hydrocodone API

Morphine API

Hydromorphone API

Oxycodone API

Oxymorphone API

C.

Tapentadol API

Tramadol API

Hydrocodone API

Morphine API

Hydromorphone API

Oxycodone API

Oxymorphone API