4-1-2018

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NSUWorks Citation

Vosburg, S. K., Severtson, S., Dart, R. C., Cicero, T. J., Kurtz, S. P., Parrino, M. W., & Green, J. L. (2018). Assessment of Tapentadol API Abuse Liability with the Researched Abuse, Diversion and Addiction-Related Surveillance System. *The Journal of Pain: Official Journal of the American Pain Society, 19* (4), 439-453. https://doi.org/10.1016/j.jpain.2017.11.007

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 19, No 4 (April), 2018: pp 439-453
Available online at www.jpain.org and www.sciencedirect.com

Assessment of Tapentadol API Abuse Liability With the Researched Abuse, Diversion and Addiction-Related Surveillance System

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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 immediate-release as well as extended-release formulations were on the market together (fourth quarter of 2011 to second quarter of 2016). Tapentadol (API) was compared with tramadol, hydrocodone, morphine, oxycodone, hydromorphone, and oxymorphone across Poison Center, Drug Diversion, and Treatment Center Programs Combined data streams from the Researched Abuse, Diversion and Addiction-Related Surveillance 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 Schedule II opioids studied, but were not the lowest. Disentangling these 2 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 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.***

Key words: *Prescription drug abuse, prescription opioid abuse, prescription opioid analgesic, tapentadol abuse liability, active pharmaceutical ingredient, human, pain management.*

Received June 28, 2017; Revised October 18, 2017; Accepted November 29, 2017.

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System is supported by subscriptions from pharmaceutical manufacturers for surveillance, research and reporting services. The RADARS System is the property of Denver Health and Hospital Authority (DHHA), a political subdivision of the State of Colorado. Denver Health retains exclusive ownership of all data, databases, and systems. Subscribers do not participate in data collection or analysis, nor do they have access to the raw data. Depomed is a RADARS System subscriber. Scientists from Depomed reviewed the draft manuscript for propriety information, however, all final content decisions were made by the RADARS System.

S.K.V. is a scientific consultant with RADARS System and received compensation for preparation of this article. S.K.V. has consulted with Grünenthal, USA. T.J.C., S.P.K., and M.W.P. 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. S.G.S., R.C.D. and J.L.D. are employees of DHHA.

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1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2017.11.007

Tapentadol is a Schedule II 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.[30,31] Tapentadol immediate-release (IR; Nucynta; Depomed, Newark, CA) was approved by the U.S. Food and Drug Administration (FDA) in December 2008 and the extended-release (ER) formulation (Nucynta ER; Depomed) was approved by the FDA in August 2011. Tapentadol ER is formulated with an Intac (Grünenthal, Aachen, Germany) crush-resistant matrix.[17]

Since its approval, tapentadol IR has been tracked across multiple outcomes suggestive as potential signals of abuse liability. Between the third quarter of 2009 and the second quarter of 2011, Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program data revealed that intentional exposures to tapentadol were minimal (.003 to .02 cases per 100,000 population). A low public health effect 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, rates of intentional exposures of tapentadol hovered around .30 per 1,000 unique recipients of dispensed drug, 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 nonmedical use in college students were also reported to be low (.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 postmarketing studies investigating abuse of tapentadol IR as well as ER formulations reported low relative risk of past month abuse of tapentadol (an aggregate of IR + ER) between the first quarter of 2011 and the third quarter of 2012 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] although 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 nonmedical use. Meanwhile, studies of drug diversion, identified as cases opened by drug diversion investigators in the United States between the third quarter of 2009 and the third quarter of 2014,[12,13] the price paid for illicitly obtained tapentadol,[15] or the number of cases that were submitted to the National Forensic Laboratory Information System[33] have generally reported low or nonexistent 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 multimodal 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[29] or within the postmarketing framework.[4-7] As such, the purpose of this study was to investigate the abuse liability of tapentadol as an active pharmaceutical ingredient (API) during the time that IR as well as ER were on the market together (fourth quarter of 2011 through the second quarter of 2016) 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 use data from the RADARS System, which provides postmarketing 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 with products containing oxycodone, hydrocodone, oxymorphone, hydromorphone, morphine, and tramadol.

Comparators were chosen on the basis of 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 market shares similar to tapentadol (internal IMS Health 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 health care 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."[25] 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.[28] As of the second quarter 2016, the Poison Center Program collected data from 50 of 55 regional U.S. Poison Centers covering 48 states, including urban, suburban, and rural regions. In the second quarter of 2016, 91% of poison centers participated in the program and 94% of the U.S. 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 IRB.

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, multijurisdictional 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. Although formal comparative analyses have not been conducted, similar patterns of diversion are observed within the RADARS mosaic[20] between RADARS and National Forensic Laboratory Information System estimates,[32,33] and have been noted between RADARS diversion findings and other national surveys.[21]

In the second quarter of 2016, the Drug Diversion Program collected data from 205 of 250 participating agencies in 48 states (all states except Hawaii; this is a response rate of approximately 82% of 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[12]). 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 nonhuman subject research by Nova Southeastern University's IRB.

The RADARS System Treatment Center Programs Combined is comprised of the Opioid Treatment Program as well as 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 the national Treatment Episodes Data Set.[23]

In the second quarter of 2016, 59 of 74 participating methadone maintenance treatment programs provided at least 1 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.[12] 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 of 2016, The Survey of Key Informants' Patients Program involved 129 substance abuse treatment programs in 46 states, representing approximately 48% of the U.S. population. Approximately 78% of the patients who are asked complete a valid version of the survey, and they receive modest compensation for doing so. Survey of Key Informants' Patients 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, whereas 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, 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 U.S. 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, GA) obtains product and geographically specific data from a sample of approximately 50% of retail pharmacies in the United States (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 United States. The study uses national estimates from QuintilesIMS Health for total prescriptions dispensed and total dosage units dispensed at the 3-digit ZIP code level for products of interest. For any given quarter, the total of prescriptions and the total of dosage units in the 3-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, whereas 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 >1 indicate the comparator product is abused or diverted more than tapentadol whereas ratios <1 indicate 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 each other.

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. Fig 1A presents the Poison Center Rate of Intentional Abuse per 1,000,000 population according to quarter. Rates of tapentadol intentional abuse were the lowest among all products and ranged from .007 to .036 during this period.

Average quarterly rate (event rate) of intentional abuse of tapentadol per 1,000,000 population was .015 (95% CI = .012–.019; Table 1, top section). Event rates of intentional abuse were greatest for oxycodone (1.302, 95% CI = 1.272–1.332), followed by hydrocodone (1.255, 95% CI = 1.226–1.284), tramadol (.521, 95% CI, .502–.540), morphine (.275, 95% CI, .262–.289), hydromorphone (.137, 95% CI, .127–.147), and oxymorphone (.114, 95% CI, .106–.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, top section; Fig 2A).

Rate Per 10,000 Prescriptions Dispensed

Fig 1B presents the Poison Center rate of intentional abuse per 10,000 prescriptions dispensed according to quarter. Rates of tapentadol intentional abuse ranged from .088 to .453 during this period. Average quarterly rate (event rate) of intentional abuse of tapentadol per 10,000 prescriptions dispensed was .207 (95% CI = .166–.255), which was neither the largest nor smallest event rate (Table 1, middle section). Event rates of intentional abuse were greatest for oxymorphone (1.168, 95% CI, 1.079–1.261) and lowest for hydrocodone (.131, 95% CI, .128–.134). Rate ratios of intentional abuse per 10,000

Table 1. Poison Center: Rates of Intentional Abuse per 1,000,000 Population, Rate Ratios and 95% CIs for Tapentadol API and Comparators

	Event Rate	*Lower 95% CI*	*Upper 95% CI*	*Rate Ratio*	*Lower95% CI*	*Upper 95% CI*
Drug (API)	*Rates and Rate Ratios of Intentional Abuse Per 1,000,000 Population, 95% CIs*					
Tapentadol API	**.015**	**.012**	**.019**	**1**		
Oxymorphone API	.114	.106	.124	7.414	5.927	9.274
Hydromorphone API	.137	.127	.147	8.851	7.091	11.047
Morphine API	.275	.262	.289	17.816	14.356	22.110
Tramadol API	.521	.502	.540	33.736	27.258	41.753
Hydrocodone API	1.255	1.226	1.284	81.276	65.788	100.411
Oxycodone API	1.302	1.272	1.332	84.322	68.256	104.169
	Rates and Rate Ratios of Intentional Abuse Per 10,000 Prescriptions Dispensed, 95% CIs					
Hydrocodone API	.131	.128	.134	.632	.512	.781
Tramadol API	.159	.153	.165	.769	.622	.952
Tapentadol API	**.207**	**.166**	**.255**	**1**		
Oxycodone API	.280	.274	.287	1.356	1.098	1.675
Morphine API	.374	.356	.393	1.811	1.459	2.248
Hydromorphone API	.534	.497	.573	2.584	2.071	3.226
Oxymorphone API	1.168	1.079	1.261	5.651	4.517	7.069
	Rates and Rate Ratios of Intentional Abuse Per 100,000 Dosage Units Dispensed, 95% CIs					
Hydrocodone API	.020	.019	.020	.703	.569	.868
Tramadol API	.022	.021	.022	.766	.619	.947
Tapentadol API	**.028**	**.023**	**.035**	**1**		
Oxycodone API	.036	.035	.037	1.275	1.032	1.575
Morphine API	.052	.050	.055	1.862	1.500	2.310
Hydromorphone API	.062	.057	.066	2.184	1.750	2.726
Oxymorphone API	.166	.153	.179	5.886	4.705	7.362

NOTE. Data are organized by rate of intentional abuse. Also see Fig 1.

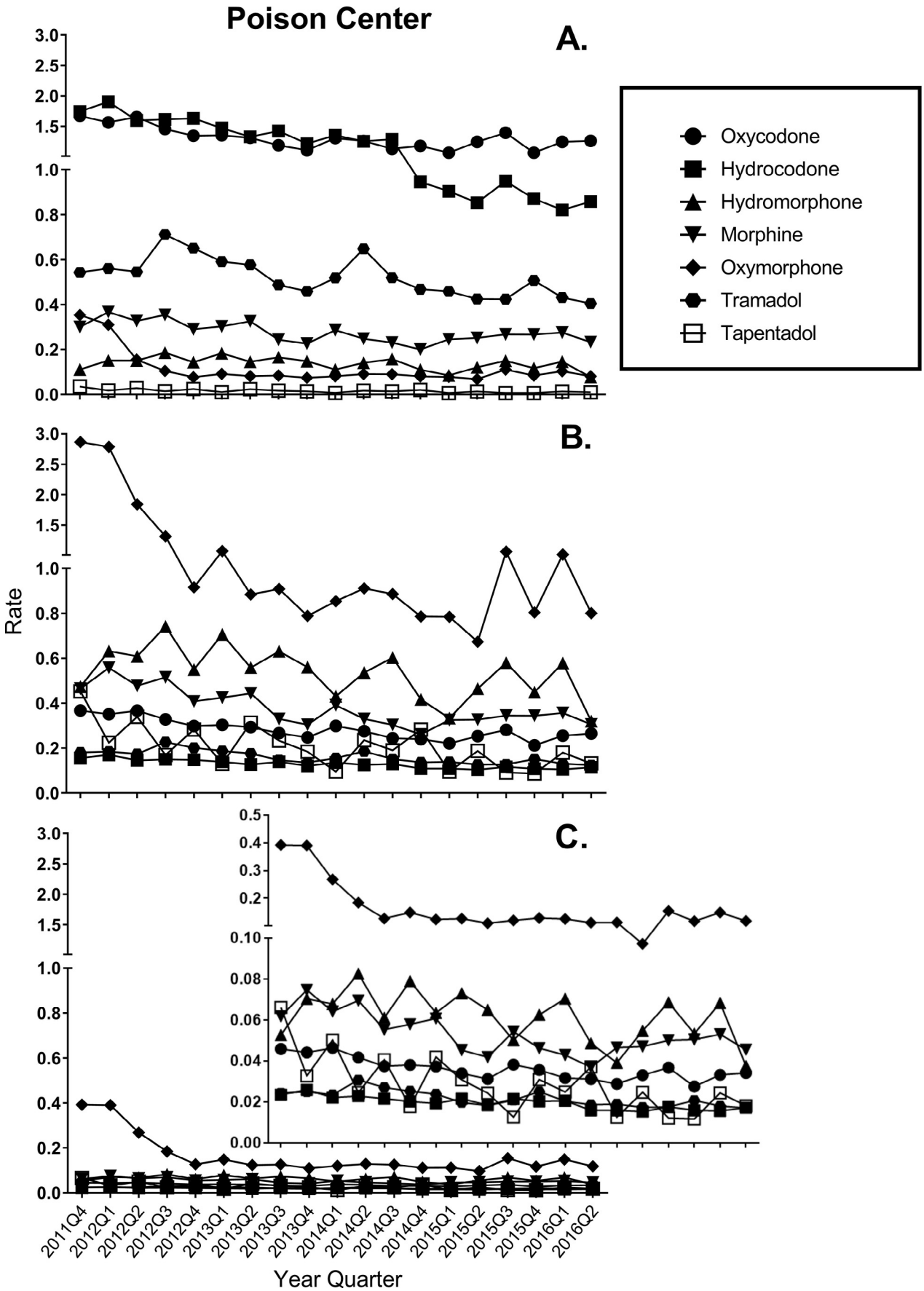

Figure 1. Poison Center: intentional abuse. Quarterly rates of tapentadol and comparator opioid intentional abuse per 1,000,000 population (**A**), per 10,000 prescriptions dispensed (**B**), and per 100,000 dosing units dispensed (**C**) from the fourth quarter (Q) of 2011 to the second Q of 2016.

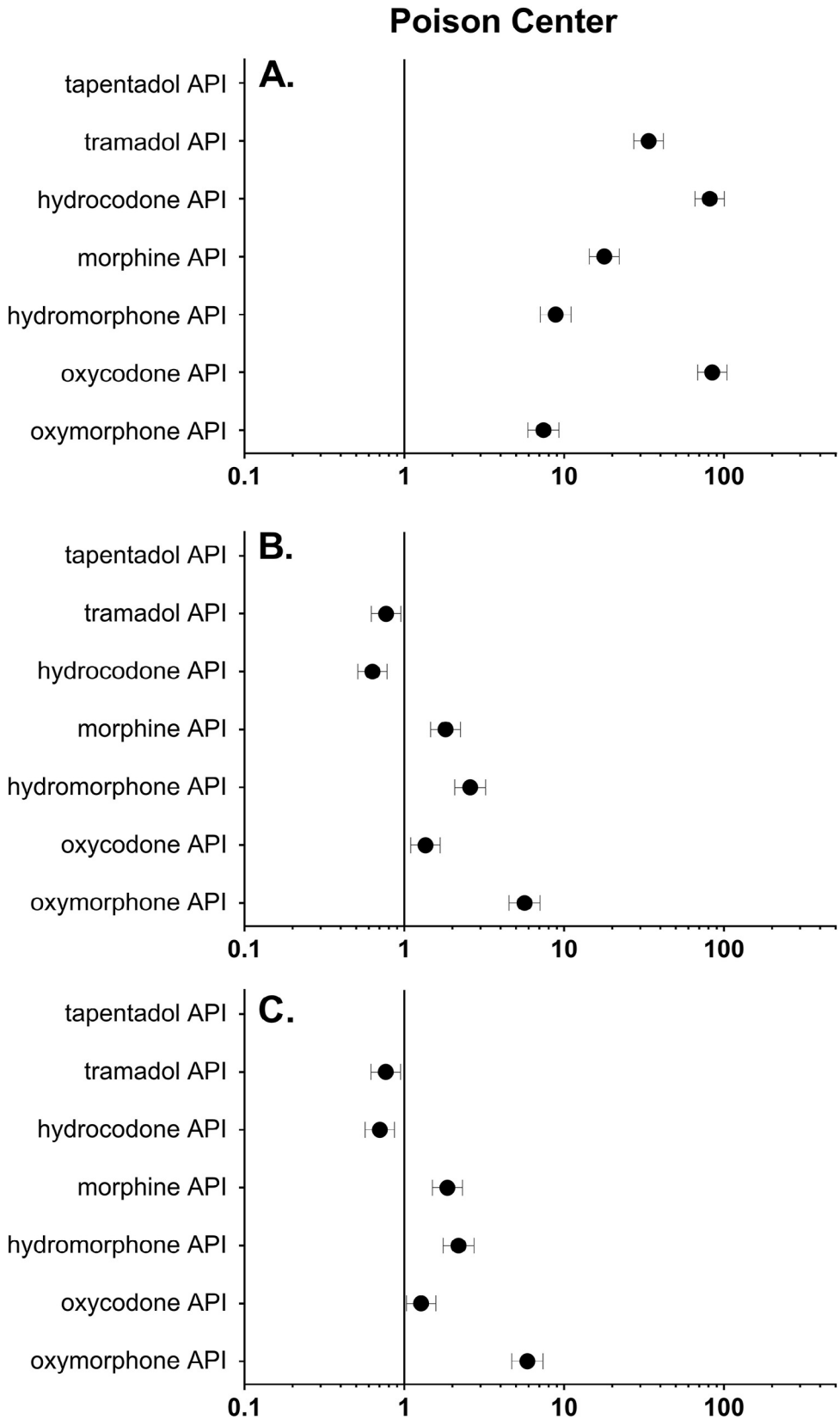

Figure 2. Poison Center: intentional abuse. Rate ratios of tapentadol and comparator opioid intentional abuse per 1,000,000 population (**A**), per 10,000 prescriptions dispensed (**B**), and per 100,000 dosing units dispensed (**C**) from fourth quarter (Q) of 2011 to the second Q of 2016. Tapentadol is the comparator and represented by the vertical line at 1.

prescriptions dispensed calculated between tapentadol and comparators revealed that hydrocodone and tramadol were intentionally abused less than tapentadol (.632 and .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 section; Fig 2B).

Rate Per 100,000 Dosage Units Dispensed

Fig 1C presents the Poison Center rate of intentional abuse per 100,000 dosing units dispensed according to quarter. Rates of tapentadol intentional abuse ranged from .012 to .066 during this period. Average quarterly rate (event rate) of intentional abuse of tapentadol per 100,000 dosing units dispensed was .028 (95% CI, .023–.035) which was neither the largest nor smallest event rate of intentional abuse (Table 1, bottom section). Event rates were greatest for oxymorphone (.166, 95% CI, .153–.179), and lowest for hydrocodone (.020, 95% CI, .019–.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 (.703 and .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, bottom section; Fig 2C).

Drug Diversion

Rate Per 1,000,000 Population

From October 2011 through June 2016 there were 58 reports of tapentadol diversion. Fig 3A presents the rates of drug diversion per 1,000,000 population according to quarter. Rates of tapentadol diversion were the lowest among all products and ranged from .000 to .070 during this period.

Average quarterly rate (event rate) of diversion was .029 (95% CI = 022–.038) for tapentadol (Table 2, top section). Drug diversion rates were greatest for oxycodone (9.234, 95% CI = 9.101–9.368) and hydrocodone (7.656, 95% CI = 7.535–7.779). 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, top section; Fig 4A).

Rate Per 10,000 Prescriptions Dispensed

Fig 3B presents the rates of drug diversion per 10,000 prescriptions dispensed according to quarter. Rates of tapentadol diversion were similar to tramadol and ranged from .000 to .794 during this period. Average quarterly rates (event rates) of diversion per 10,000 prescriptions dispensed were lowest for tapentadol and tramadol (.334 and .335, 95% event rate CIs overlap; Table 2, middle section). Drug diversion rates were greatest for oxymorphone (6.183, 95% CI = 5.856–6.522) and hydromorphone (5.427, 95% CI = 5.221–5.638). 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 section; Fig 4B).

Rate Per 100,000 Dosage Units Dispensed

Fig 3C presents the rates of drug diversion per 100,000 dosing units dispensed according to quarter. Rates of tapentadol diversion were similar to tramadol and ranged from .000 to .1027 during this period. Average quarterly rates (event rates) of diversion per 100,000 dosage units dispensed were lowest for tapentadol and tramadol (.045 and .047, respectively; 95% event rate CIs overlap; Table 2, bottom section). Drug diversion rates were greatest for oxymorphone (.860, 95% CI = .814–.907) and hydromorphone (.620, 95% CI = .596–.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, bottom section; Fig 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. Fig 5A presents the Treatment Center Programs Combined rates of past-month use to get high per 1,000,000 population according to quarter. Rates of past month use of tapentadol to get high were the lowest among all products and ranged from .115 to .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 (.245, 95% CI = .228–.263; Table 3, top section). Rate of reported use for getting high in the past month was greatest for oxycodone (12.969; 95% CI = 12.841–13.097) and hydrocodone (10.102, 95% CI = 9.989–10.216). 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, top section; Fig 6A).

Rate Per 10,000 Prescriptions Dispensed

Fig 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 = 2.939–3.398), which was neither the largest nor smallest event rate (Table 3, middle section). Rate of reported use for getting high in the past month was greatest for oxymorphone (29.450, 95% CI = 28.881–30.027) and hydromorphone (21.240, 95% CI = 20.924–21.559) and

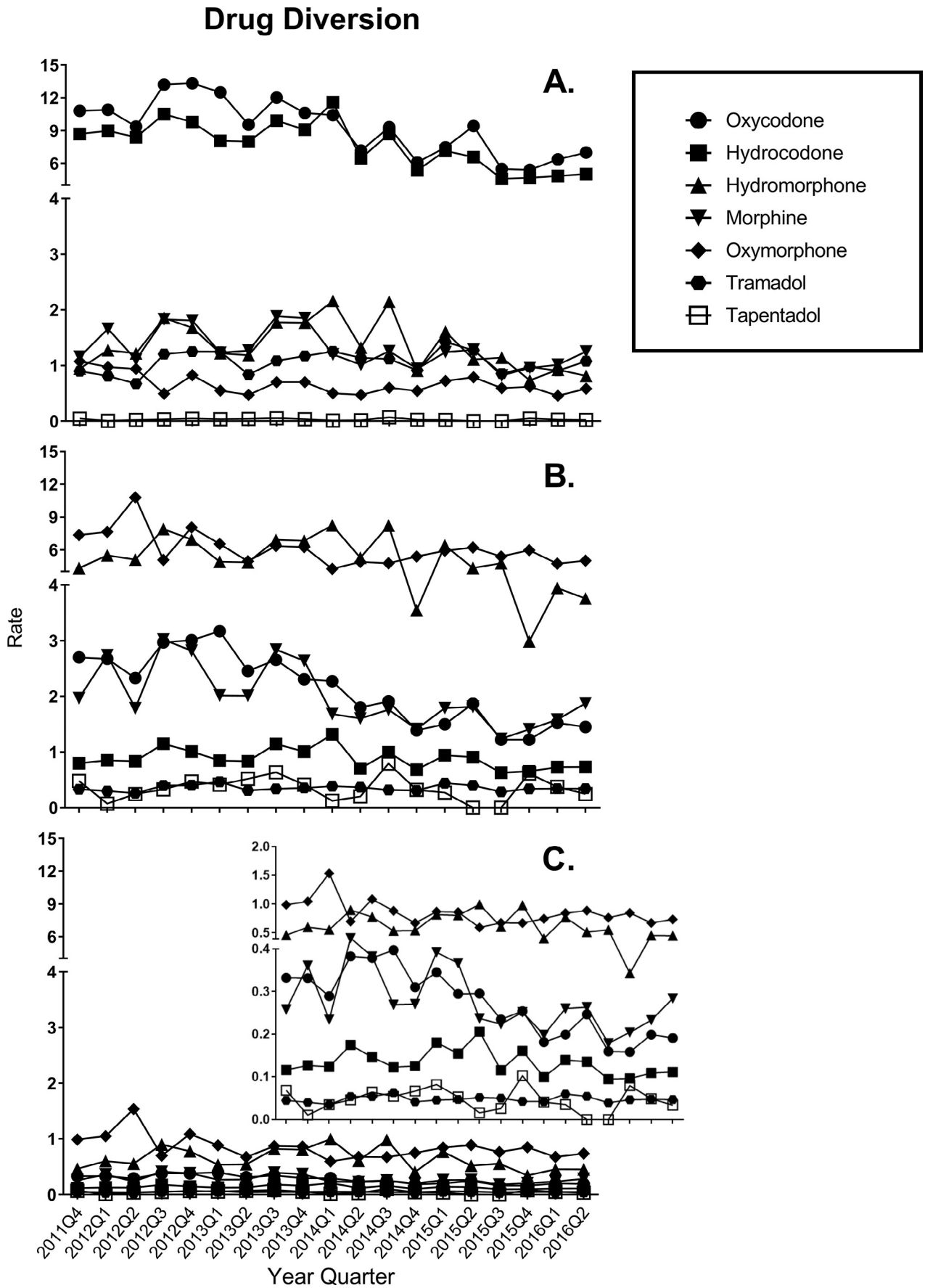

Figure 3. Drug Diversion. Quarterly rates of tapentadol and comparator opioid drug diversion per 1,000,000 population (**A**), per 10,000 prescriptions dispensed (**B**), and per 100,000 dosing units dispensed (**C**), from the fourth quarter (Q) of 2011 to the second Q of 2016.

Table 2. Drug Diversion. Rates of Diversion per 1,000,000 Population, Rate Ratios, and 95% CIs for Tapentadol API and Comparators

Drug (API)	Event Rate	Lower 95% CI	Upper 95% CI	Rate Ratio	Lower 95% CI	Upper 95% CI
	Rates and Rate Ratios of Drug Diversion per 1,000,000 Population, 95% CIs					
Tapentadol API	**.029**	**.022**	**.038**	**1**		
Oxymorphone API	.675	.640	.712	23.172	17.816	30.139
Tramadol API	1.034	.990	1.080	35.483	27.333	46.063
Morphine API	1.284	1.234	1.334	44.052	33.957	57.147
Hydromorphone API	1.322	1.272	1.373	45.362	34.970	58.842
Hydrocodone API	7.656	7.535	7.779	262.724	203.011	340.001
Oxycodone API	9.234	9.101	9.368	316.862	244.864	410.029
	Rates and Rate Ratios of Drug Diversion per 10,000 Prescriptions Dispensed, 95% CIs					
Tapentadol API	**.334**	**.254**	**.432**	**1**		
Tramadol API	.350	.335	.365	1.047	.806	1.359
Hydrocodone API	.873	.859	.887	2.613	2.019	3.381
Morphine API	1.974	1.898	2.052	5.908	4.554	7.664
Oxycodone API	2.119	2.089	2.150	6.343	4.902	8.208
Hydromorphone API	5.427	5.221	5.638	16.243	12.522	21.070
Oxymorphone API	6.183	5.856	6.522	18.507	14.229	24.070
	Rates and Rate Ratios of Drug Diversion per 100,000 Dosage Units Dispensed, 95% CIs					
Tapentadol API	**.045**	**.034**	**.058**	**1**		
Tramadol API	.047	.045	.050	1.064	.820	1.382
Hydrocodone API	.132	.130	.134	2.957	2.285	3.826
Oxycodone API	.272	.269	.276	6.118	4.728	7.917
Morphine API	.274	.264	.285	6.163	4.750	7.994
Hydromorphone API	.620	.596	.644	13.918	10.729	18.053
Oxymorphone API	.860	.814	.907	19.308	14.845	25.112

NOTE. Data are organized according to rate of diversion. Also see Fig 2.

lowest for tramadol (.264, 95% CI = .254–.274). Rate ratios reveal that comparator use for getting high in the past month ranged from .083 (tramadol) to 9.313 (oxymorphone) times the rate of tapentadol use (Table 3, middle section; Fig 6B).

Rate Per 100,000 Dosage Units Dispensed

Fig 5C presents the rates of past month use of tapentadol to get high per 100,000 dosing units dispensed according to quarter. Rates of tapentadol use to get high ranged from .219 to .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 .436 (95% CI = .405–.468), which was neither the largest nor smallest event rate (Table 3, bottom section). Rate of reported use for getting high in the past month was greatest for oxymorphone (4.221, 95% CI = 4.140–4.304) and hydromorphone (2.471, 95% CI = 2.434–2.508) and lowest for tramadol (.036, 95% CI = .034–.037). Rate ratios reveal that comparator use for getting high in the past month ranged from .082 (tramadol) to 9.686 (oxymorphone) times the rate of tapentadol use (Table 3, bottom section; Fig 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 <.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 (ie, per 10,000 prescriptions dispensed and per 100,000 dosage units dispensed), tapentadol abuse liability was generally low compared with other opioids, but present, nonetheless. Reports varied according to 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 Schedule IV opioid with pharmacology including μ-receptor agonism and norepinephrine and serotonin reuptake inhibition,[26] is recognized for low to modest abuse liability and relatively low levels of abuse and diversion.[9,35,37] 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[6,11,13,24] suggesting that to date, this is a stable finding.

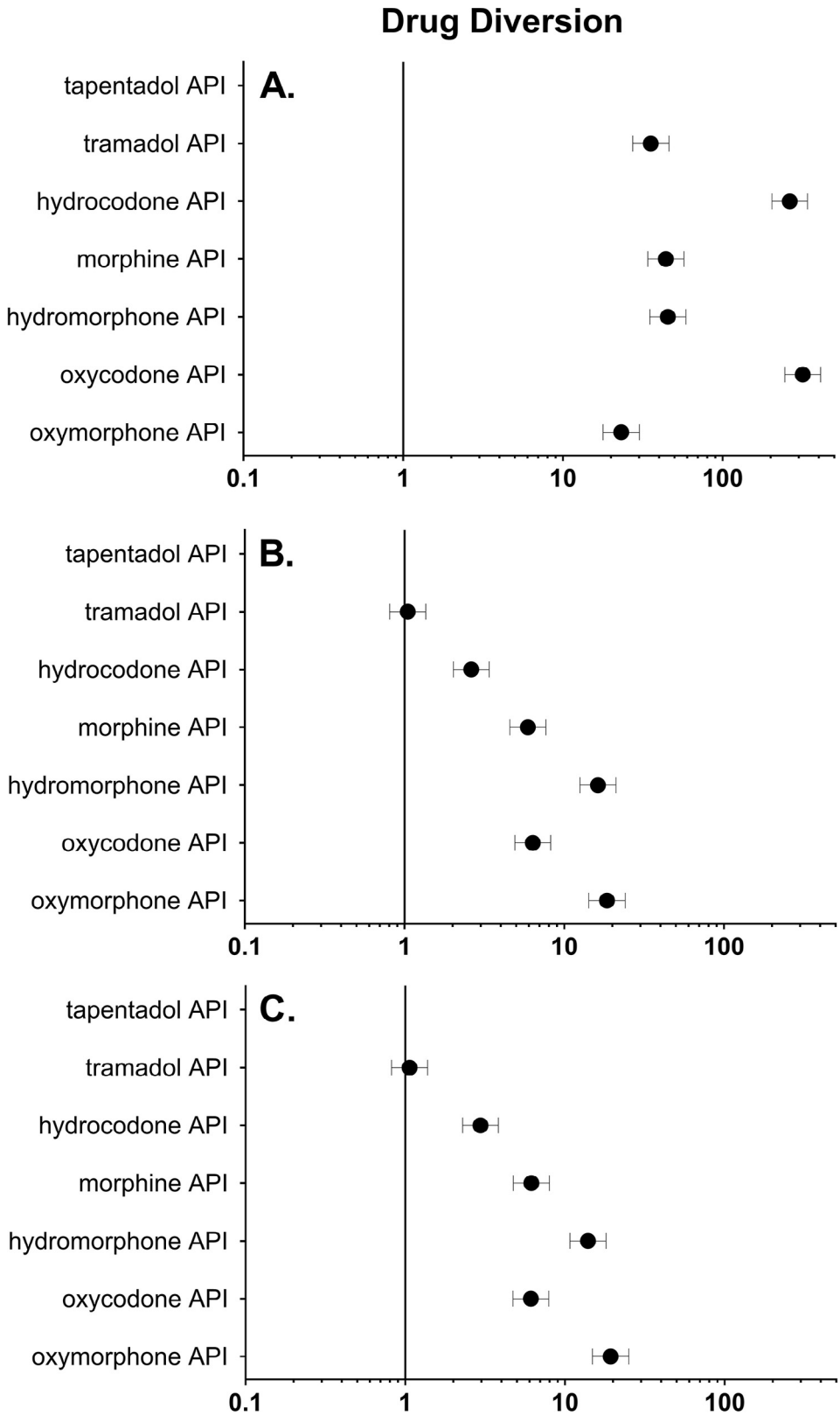

Figure 4. Drug Diversion. Rate ratios of tapentadol and comparator opioid drug diversion per 1,000,000 population (**A**), per 10,000 prescriptions dispensed (**B**), and per 100,000 dosing units dispensed (**C**) from the fourth quarter (Q) of 2011 to the second Q of 2016. Tapentadol is the comparator and represented by the vertical line at 1.

Evaluation of Treatment Center Programs Combined and Poison Center data when adjusted for drug utilization revealed similar patterns between the 2 data streams. Tapentadol had neither the highest nor lowest reported rates of use to get high in the past month (Treatment Center Programs Combined) or intentional abuse (Poison Center). Across both data sets, rates of tapentadol abuse were greater than tramadol and

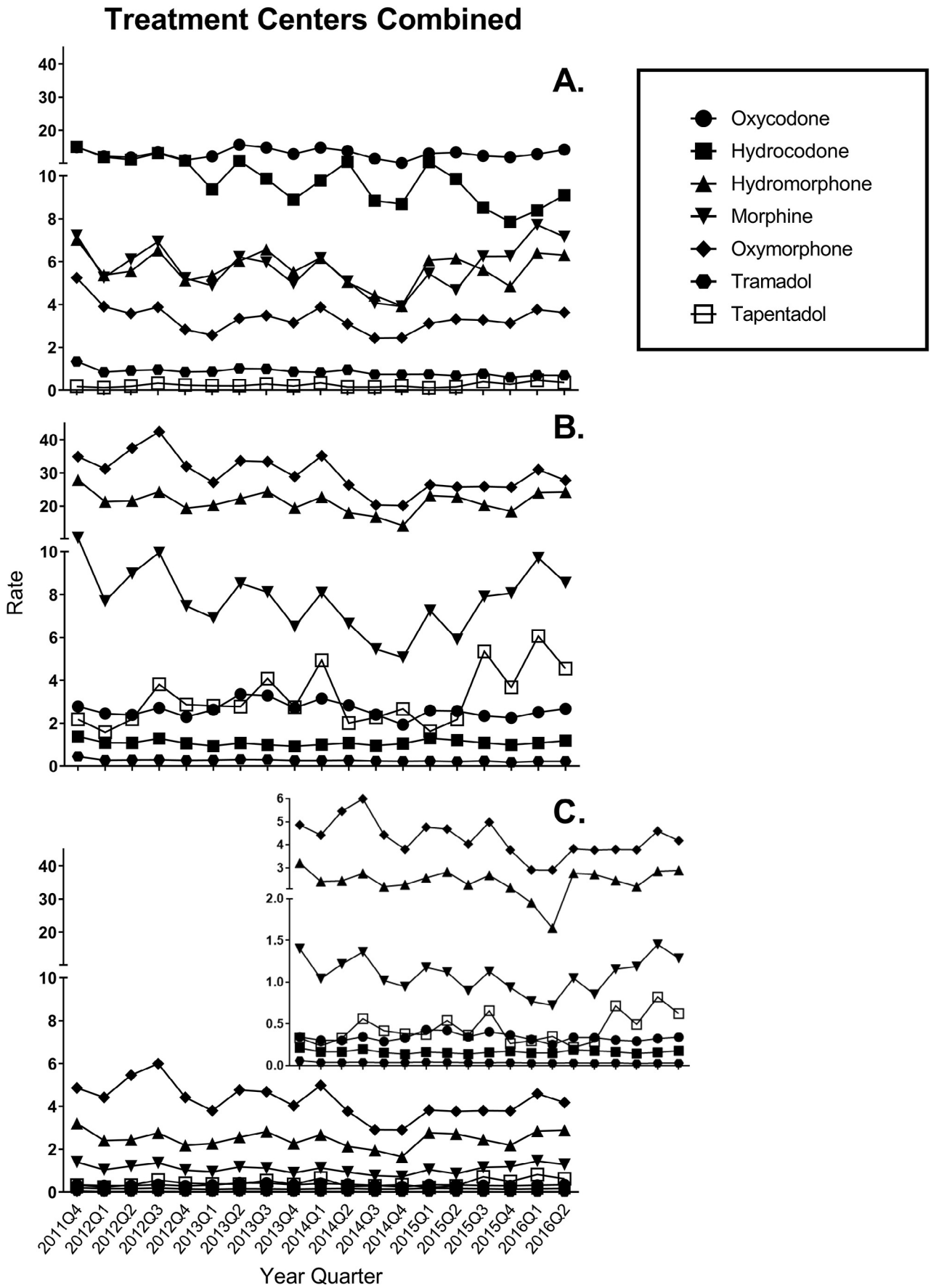

Figure 5. Treatment Center Programs Combined: past month use to get high. Quarterly rates of tapentadol and comparator opioid past month use to get high per 1,000,000 population (**A**), per 10,000 prescriptions dispensed (**B**), and per 100,000 dosing units dispensed (**C**) from the fourth quarter (Q) of 2011 to the second Q of 2016.

Table 3. Treatment Center Programs Combined. Rates of Past-month Use to Get High per 1,000,000 Population, Rate Ratios and 95% CIs for Tapentadol API and Comparators

Drug (API)	Event Rate	Lower 95% CI	Upper 95% CI	Rate Ratio	Lower 95% CI	Upper 95% CI
	Rates and Rate Ratios of Past-Month Use to Get High per 1,000,000 Population, 95% CIs					
Tapentadol API	**.245**	**.228**	**.263**	**1**		
Tramadol API	.851	.818	.884	3.475	3.202	3.770
Oxymorphone API	3.355	3.290	3.420	13.702	12.719	14.760
Hydromorphone API	5.675	5.590	5.760	23.179	21.539	24.944
Morphine API	5.743	5.658	5.829	23.458	21.799	25.244
Hydrocodone API	10.102	9.989	10.216	41.262	38.368	44.375
Oxycodone API	12.969	12.841	13.097	52.972	49.266	56.957
	Rates and Rate Ratios of Past-Month Use to Get High per 10,000 Prescriptions Dispensed, 95% CIs					
Tramadol API	.264	.254	.274	.083	.077	.091
Hydrocodone API	1.086	1.074	1.099	.344	.319	.369
Oxycodone API	2.621	2.596	2.647	.829	.771	.891
Tapentadol API	**3.162**	**2.939**	**3.398**	**1**		
Morphine API	7.700	7.586	7.815	2.435	2.263	2.620
Hydromorphone API	21.240	20.924	21.559	6.716	6.241	7.228
Oxymorphone API	29.450	28.881	30.027	9.313	8.645	10.032
	Rates and Rate Ratios of Past-Month Use to Get High per 100,000 Dosage Units Dispensed, 95% CIs					
Tramadol API	.036	.034	.037	.082	.076	.089
Hydrocodone API	.166	.164	.168	.380	.354	.409
Oxycodone API	.337	.334	.340	.773	.719	.831
Tapentadol API	**.436**	**.405**	**.468**	**1**		
Morphine API	1.085	1.069	1.101	2.489	2.313	2.679
Hydromorphone API	2.471	2.434	2.508	5.669	5.268	6.101
Oxymorphone API	4.221	4.140	4.304	9.686	8.991	10.434

NOTE. Data are organized according to past month rate of use. Also see Fig 3.

hydrocodone, with a more pronounced difference in the Treatment Center Programs Combined. In particular, when adjusting for drug utilization and interpreting the longitudinal data presentation, recent Treatment Center Programs 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 reported to have a relatively low abuse liability.[1,11,27] 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 most of the time period studied were Schedule III substances; hydrocodone products without acetaminophen including Zohydro (Zogenix Inc., Emeryville, CA) and Hysingla (Purdue Pharma, Stamford, CT) were approved by the FDA in 2013 and 2014, respectively.[18] Acetaminophen-containing products have resulted in adverse health outcomes that are thought to deter illicit use,[18,36] although the effectiveness of this strategy can be debated.[22] 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 ER OxyContin (Purdue Pharma) which occurred in 2010.[2,27] In addition to early studies that revealed drug abusers generally characterized the product as less desirable than the original OxyContin (Purdue Pharma),[34] postmarketing studies have identified general decreases in the use as well as prescription of OxyContin (Purdue Pharma).[8,19]

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 Center Programs 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/second quarter of 2015 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 ER formulation) before levels of past month use to get high decreased to low levels similar to tramadol. Thus, these data warrant continued observation.

Although 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 United States have prescription drug

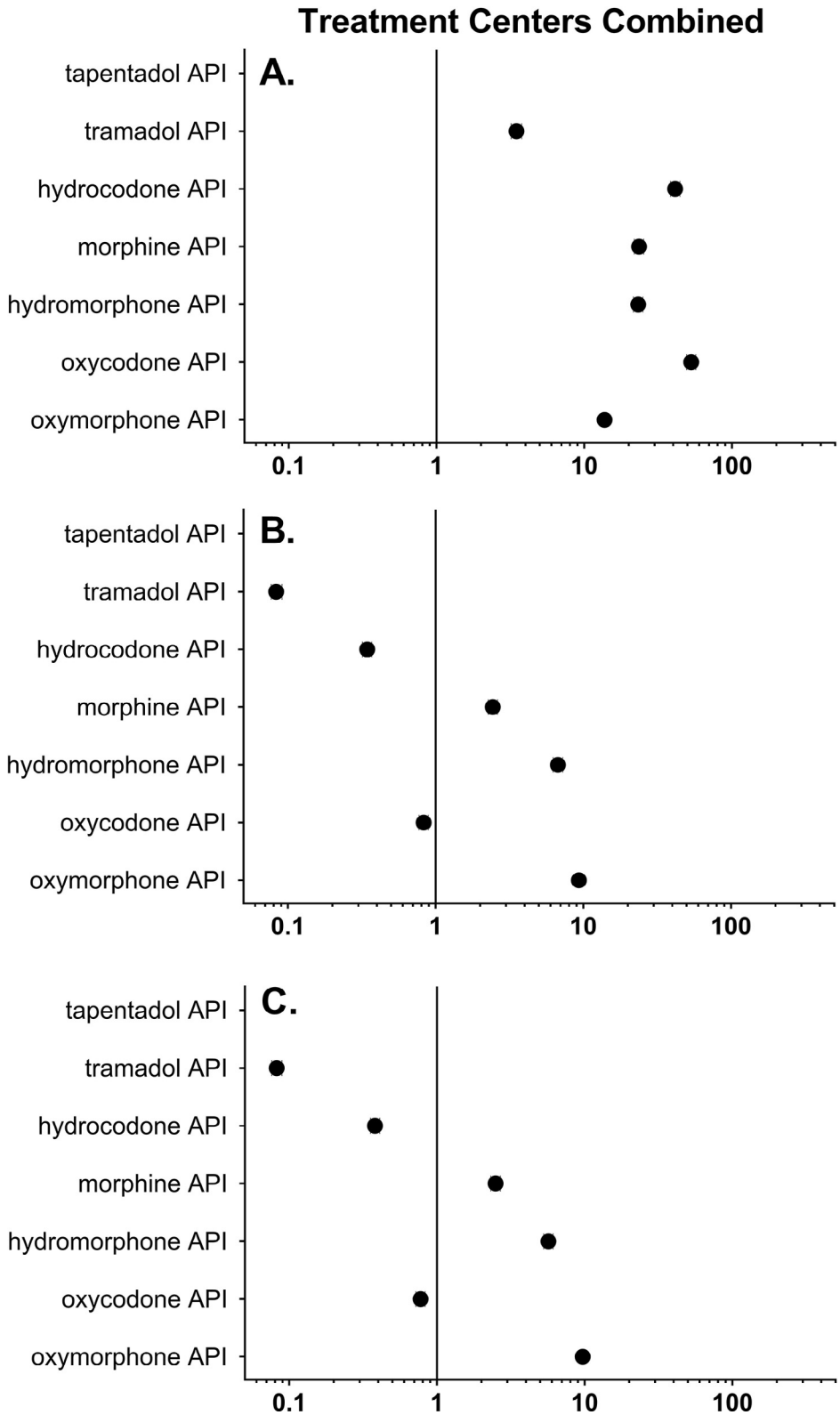

Figure 6. Treatment Center Programs Combined: past month use to get high. Rate ratios of tapentadol and comparator opioid past month use to get high per 1,000,000 population (**A**), per 10,000 prescriptions dispensed (**B**), and per 100,000 dosing units dispensed (**C**) from the fourth quarter (Q) of 2011 to the second Q of 2016. Tapentadol is the comparator and represented by the vertical line at 1.

diversion agencies, and thus data may also be subject to under-reporting. Last, Treatment Center Programs Combined data are also self-reported, and thus subject to limitations associated therewith.[12]

Analyzing the abuse liability of an API has strengths and weaknesses. It is a broad concept that serves as an estimate of the effect 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.

Conclusions

Event rates of abuse per the population-level denominator across the 3 data streams were significantly lower than all other opioids examined in this study, including Schedule II 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 Schedule II opioids studied, but were not the lowest. Disentangling these 2 sets of findings further by examination of various opioid formulations, such as ER and the role of abuse-deterrent formulations, is warranted.

Acknowledgments

The authors acknowledge the biostatistical contributions of Scott Kreider, MS and the manuscript coordination and editorial contributions of Elise Bailey, MSPH to this project.

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