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HOT TOPICS IN PAIN AND HEADACHE (N ROSEN, SECTION EDITOR)

Tramadol Prescription over a 4-Year Period in the USA

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Abstract

Purpose of Review Deaths associated to tramadol, a synthetic opioid, are rising globally. Herein, we characterize prescription patterns of tramadol relative to other opioids in the USA from 2012 to 2015, by geographic region and physician specialty.

Recent Findings Data on opioid was obtained using Truven Health Analytics MarketScan for the years 2012–2015. Inclusion criteria included subjects living in the USA with ages from 12 to 64 years. Patterns of prescription of tramadol were contrasted with other prescription opioids including hydrocodone, codeine, oxycodone, oxymorphone, methadone, and fentanyl. Between 2012 and 2015, prescriptions for tramadol increased by 22.8%. The absolute rate of prescription varies considerably per region, with tramadol representing nearly 20% of opioid prescriptions in the South, which, in turn, represents nearly 50% of all prescriptions in the USA. Significant differences were seen when comparing prescribers of tramadol with other opioids ($p < 0.0001$). Tramadol was more frequently prescribed by family practice (40% vs. 32%) and internal medicine physicians (19% vs. 16%). Family medicine, internal medicine, and non-physician prescribers responded by 67.2% of all tramadol prescriptions in 2015. The proportion of patients receiving tramadol from non-physician prescribers increased by 56% between 2012 and 2015 ($p < 0.001$) IOM.

Summary Tramadol prescriptions rates have continuously increased both nationally and throughout all US regions. Important differences exist among regions and physician specialties. These results may be helpful in the creation of regional policies to monitor reasons for this increase and to avoid excessive use of tramadol.

Keywords Tramadol · Opioids · Prescription rates · Prescription patterns

Introduction

Opioid analgesics are recommended for the treatment of certain moderate to severe pain syndromes that persist after non-pharmacological therapies and non-opioid medications have been used [1, 2]. Opioids are widely prescribed in the USA [3, 4], and around 20% of adult patients presenting with non-cancer pain are prescribed opioids [5], with 4% of them receiving long-term opioid therapy [6].

The increased availability and rates of prescription of opioids observed until recent years have been paralleled by a robust increase in the rate of diversion, misuse, and deaths, resulting in significant personal, familial, and public health burdens [7, 8]. The causes of this opioid crisis are multifactorial and complex and should not be conceptualized in terms of simple cause/effect models [9]. Even the risk factor per se (opioid exposure) needs to be nuanced. Opioids may be natural, semi-synthetic, and synthetic. They are formulated differentially and have different potencies and duration of effects [10]; therefore, they may be differently associated with rates of abuse and misuse.

Tramadol is a synthetic opioid often used for acute pain after surgery [11] or for chronic pain from conditions like fibromyalgia [12, 13], chronic back pain [14], and diabetic neuropathy [15]. Tramadol is considered less addictive than other opioids, which are schedule II substances under the

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Controlled Substances Act, tramadol being a schedule IV substance [16]. Nonetheless, concerns exist. Analysis of drug poisoning databases in England and Wales revealed that the number of tramadol mentions on death certificates increased twofold in only 2 years [17], and real concerns exist in certain areas of the world such as Africa, where a "tramadol epidemic" has been described [18]. Accordingly, obtaining descriptive data on patterns of tramadol prescription in the USA is informative in the context of the opioid epidemic.

Herein, we take advantage of the Truven database, which maps data from 230 million lives since 1995, in order to characterize prescription patterns of tramadol, relative to other opioids, in the USA. We contrast prescription patterns by region and prescribing physician in the period of 2012 to 2015.

Methods

Database Specifications

Data on opioid prescription rates per region and physician specialty was obtained from Truven Health Analytics MarketScan Databases [19], which include data on nearly 230 million patients beginning in 1995. Patient-level data is fully adjudicated and linked with other relevant datasets. The Health Analytics MarketScan Databases are often used in general research [20] and in studies focusing on opioids [21, 22]. Herein, we used the datasets to ascertain tramadol usage during the years 2012–2015.

Inclusion Criteria

The MarketScan database contains information on patients who are commercially insured via employer-based health insurance. We selected individuals with an age ranging from 12 to 64 years, living in the USA, and filing a prescription claim involving an opioid between 2012 and 2015. Patients covered by Medicare are underrepresented in the database [23]; thus, we excluded those over 65 from our study. We defined opioid usage as having evidence of at least one fill for opioid medications during any year between 2012 and 2015. Patients receiving multiple opioids over time were counted once for each used opioid. Similarly, prescribers were counted once for each prescribed opioid medication.

Opioids included in the study were tramadol, hydrocodone, codeine, oxycodone, oxymorphone, methadone, and fentanyl. These opioids were chosen due to their public health relevance [24]. With the exception of medications intended for cough and cold such as codeine product combinations, all doses, forms, and routes of administration of the studied opioids were included. We included all codeine products not used for cough and cold in this study.

Analysis

As per the Truven Health Analytics MarketScan data collection methods, four geographic regions were defined: the Northeast, North Central, South, and West regions. Table 1 shows the states in each region. Opioids were quantified as per the number of prescriptions and days supplied per calendar year.

Physician specialties were included in the study based on previously published studies [25]. Specialties included family practice; internal medicine; non-physician prescriber (nurse practitioners and physician's assistants); pain medicine; neurology; oncology and palliative care; geriatrics and gerontology; rheumatology; pediatrics; surgery. Prescription claims were linked to medical claims within 7 days after visiting a prescriber. By utilizing this function, we attempted to link opioid prescriptions to physician specialty.

We summarized the data using descriptive statistics and summary tables. Tramadol was compared with other opioids as a function of region, prescribers, and demographics, including age and gender. We also highlight the 75% and 95% percentiles of use of tramadol relative to all other opioids, as well as to specific opioids. In order to measure change, we compared data from 2012 to 2015. We used the two-sided chi-square test to contrast proportions for selected variables.

Results

The number of participants per year and their demographics are presented in Table 2. For each year, around 57% of the subjects included in the study were female, while around 42% were male. Median age was 45 years in 2012 and 47 years in 2015. The absolute number of opioid prescriptions decreased in all regions, but the South accounted for a larger proportion of opioid prescriptions in 2016, as compared with 2012 (49% vs. 44%).

Table 1 Description of regions in the Truven database

Northeast	North Central	South	West
Maine	Ohio	West Virginia	Alaska
New Hampshire	Michigan	Virginia	Hawaii
Vermont	Indiana	Kentucky	Washington
New York	Illinois	North Carolina	Oregon
Massachusetts	Missouri	South Carolina	California
Rhode Island	Kansas	Tennessee	Idaho
Connecticut	Wisconsin	Georgia	Nevada
Pennsylvania	Minnesota	Florida	Montana
New Jersey	Iowa	Alabama	Wyoming
Maryland	Nebraska	Mississippi	Utah
Delaware	South Dakota	Louisiana	Colorado
	North Dakota	Arkansas	Arizona
		Oklahoma	New Mexico
		Texas	

Table 2 Demographic characteristics of the study sample

Characteristics	2012		2013		2014		2015	
	N	%	*N*	%	*N*	%	*N*	%
Gender								
Male	2,502,970	42.70	2,016,248	42.30	2,016,248	42.30	1,450,274	42.20
Female	3,357,126	57.30	2,747,679	57.70	2,747,679	57.70	1,984,700	57.80
Age								
Median	45.00		46.00		46.00		47.00	
Region								
North Central	1,292,939	22.10	1,023,312	21.50	1,023,312	21.50	724,410	21.10
Northeast	870,871	14.90	650,864	13.70	650,864	13.70	476,435	13.90
South	2,559,505	43.70	1,984,266	41.70	1,984,266	41.70	1,687,463	49.10
West	1,057,757	18.10	991,843	20.80	991,843	20.80	537,929	15.70

Table 3 contrasts the number of opioid prescription per 1000 lives as a function of the opioid type and region of the country in 2012 and 2015. Prescriptions for tramadol increased by 22.8% during this time frame. Figure 1 presents the relative variation on a year-to-year basis for the most commonly prescribed opioids, demonstrating the steady increase in the prescription of tramadol. Although codeine prescriptions also increased (Table 3), the variation seems to have happened in the last year of the study, while tramadol demonstrates a steady increase over 4 years (Fig. 1).

Regional differences in the pattern of tramadol prescription are worth mentioning. Although an increase was seen in all regions from 2012 to 2015, the increase was highest in the South (22.5%) and West (21.3%) and lower in the Northeast (10.8%) and North Central (12.3%). Tramadol now corresponds to nearly 20% of prescriptions in the South, followed by NC (15.9%), NE (13%), and West (12%). The quantity of prescribed tramadol, as measured by days of supply per year, as well as the number of distinct prescriptions per patient, remained fairly stable from 2012 to 2015 (Table 4).

Significant differences were seen when comparing prescribers of tramadol with other opioids ($p < 0.00001$). Relative to other opioids, tramadol was more frequently prescribed by family practice (40% vs. 32%) and internal medicine physicians (19% vs. 16%) and was less frequently prescribed by gynecologists (4% vs. 9%) and surgeons (21% vs. 28%). Table 5 outlines the tramadol prescriptions by specialty in 2015, relative to other opioids, while Table 6 contrasts prescribers of tramadol in 2012 and 2015. Of interest, the proportion of patients receiving tramadol from non-physicians increased by 56%, from 4.7 to 7.3% ($p < 0.001$).

Table 3 Opioid prescription per 1000 persons in 2012 and 2015

	2012	2015	Variation (%)
Codeine	108.02	137.48	27.3
Fentanyl	7.95	7.44	− 6.4
Hydrocodone	696.84	593.75	− 14.8
Methadone	3.81	3.04	− 20.2
Oxycodone	236.65	289.67	22.4
Oxymorphone	2.63	2.39	− 9.1
Tramadol	170.09	208.85	22.8

Discussion

Misuse, abuse, and addiction to opioids are associated to a large societal and economic burden [1, 8, 26, 27]. From 1999 to 2015, opioid overdose deaths have quadrupled [28], showing that the effects of the crisis are both real and tangible. Opioids were involved in 63.1% of total drug overdose deaths in 2015 [29]. The specific opiates causing these deaths, however, have also changed. Since 2015, a decrease has been seen in overdose deaths involving prescription opioids, while overdose deaths involving heroin and non-prescribed fentanyl have increased sharply [30–32].

The opioid crisis is incredibly complex and attempts to describe it are often very simplistic [33]. Greater expectation of pain relief by an aging population, increased survivorship after injury and cancer, increased availability of prescribed opioid medications, economic disadvantage and hopelessness, medical prescription patterns, lack of integrated databases that allowed proper surveillance, and other factors may have differentially contributed to the crisis [33]. Even an established risk factor per se (opioid exposure) should be well characterized. Opioids may be natural, semi-synthetic, and synthetic and may be prescribed or obtained via diversion. They are formulated differentially and have different potencies and duration of effects [10]. Beyond opioid differences, the various patterns of prescriptions by physician specialties and regional

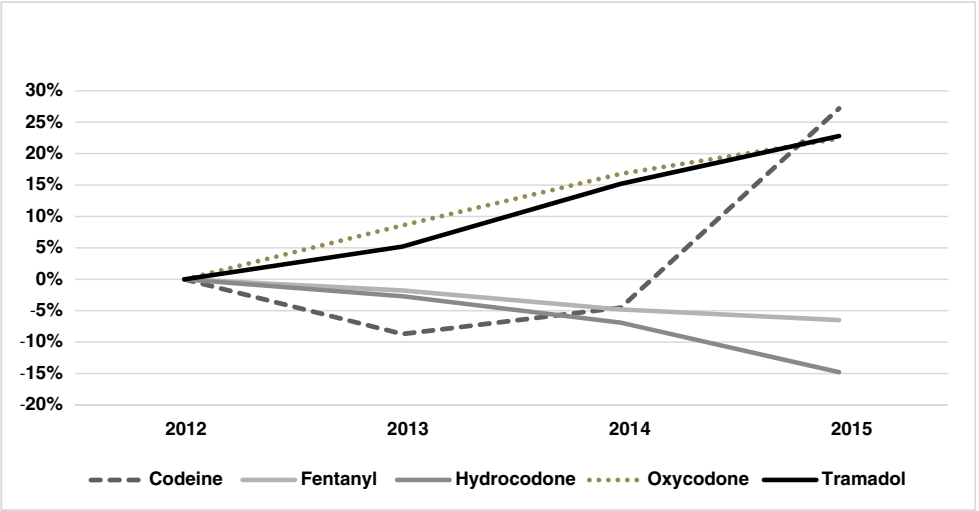

Fig. 1 Year-to-year variation relative to the prescription share in 2012

patterns of prescription are also of importance, especially at times where abuse is shifting to synthetic opioids [34, 35].

Tramadol is a centrally acting analgesic with a multimode of action. Its analgesic potency is claimed to be about one-tenth that of morphine. While its metabolite O-desmethyltramadol acts on the μ-opioid receptor, the (+) and (−) enantiomers act on the serotonin and noradrenaline reuptake. This implies that the analgesic mechanism of action of tramadol includes both non-opioid components, i.e., noradrenergic and serotonergic components and opioid components [11, 13]. The mechanism of receptor occupancy is virtually identical to tapentadol, which is a schedule II substance. Tramadol and tapentadol both inhibit reuptake of norepinephrine to roughly the same degree, but tramadol inhibits serotonin reuptake three times more than tapentadol [47], which translates into a higher incidence of serotonin-related toxicities for tramadol [46]. Tramadol is available not only as an immediate-release formulation but also as an extended-release formulation, approved by the FDA in 2005 for around-the-clock, once-daily dosing. The immediate-release formulation is often associated with non-opioid analgesics such as acetaminophen, which might also increase the perception of the drug as being mild and safe. As mentioned in the limitation section of this paper, our database algorithm did not allow for discrimination of immediate- vs. extended-release formulations and of combination of medications.

We found that tramadol was being substantially more frequently prescribed in 2015 than in 2012 in the USA. During

Table 4 Description of tramadol prescription per region, as well as days of supply and prescriptions per year in 2012 and 2015

Share of tramadol prescriptions among all opioids			
	2012 (%)	2015 (%)	Increase from 2012 (%)
NC	14.2	15.9	12.3
NE	11.7	13	10.8
S	16.1	19.8	22.5
W	9.6	11.7	21.3
Total	13.8	16.8	21.2
Days of supply/year			
	2012		2015
Mean	52.32		49.56
Median	15.00		12.00
SD	91.20		87.85
Range	0–2160		0–1150
Number of prescriptions/year			
	2012		2015
Mean	2.57		2.50
Median	1.00		1.00
SD	3.24		3.08
Range	1–82		1–110

Table 5 Tramadol and other opioid prescriptions in 2015 as a function of prescribers

Specialty	Other opioids (%)	Tramadol (%)
Family practice	32.30	40.10
Surgery	28.13	20.61
Internal medicine	16.04	19.84
Non-physician prescriber	9.04	7.27
Gynecology	6.92	4.09
Rheumatology	2.55	2.45
Pain medicine	1.63	1.84
Neurology	1.37	1.83
Pediatrics	1.05	1.11
Oncology	0.92	0.81
Geriatrics	0.05	0.06

All prescriptions were included, and prescribers were counted multiple times if they prescribed multiple medications

Table 6 Patterns of tramadol prescription in 2012 and 2015

	2012 (%)	2015 (%)
Family practice	43.8	40.1
Internal medicine	20.2	19.8
Surgery	19.2	20.6
Non-physician	4.7	7.3
Other specialties	12.1	12.2

the same period of time, prescription of fentanyl had remained stable, while oxycodone has increased its share while hydrocodone share has significantly decreased, and the share of codeine was kept consistent (Bigal et al., in press). An increase of tramadol was seen in all regions but more frequently in the South and West regions. Characterizing regional differences is important to better understand the crisis. The Appalachian region is, by many, considered to be "ground zero" in the opioid epidemic [36, 37]. Furthermore, in 2012, Alabama, Tennessee, and West Virginia had the three highest national prescribing rates for opioids per 100 persons [38].

Our findings agree with a study conducted in British Columbia, Canada, where population-level data on out-of-hospital opioid dispensing are recorded in a drug information system that captures all retail pharmacy dispensations in the province. Tramadol prescription increased steadily during the time of the study. But since tramadol was launched in Canada in 2013, the authors suggest that the findings for this particular opioid reflect the natural uptake of a recently launched drug rather than a true change in prescription patterns [39].

A study conducted in the USA examined the effects of the 2014 Drug Enforcement Administration's reclassification of opioids containing hydrocodone from schedule III to the more restrictive schedule II. The study found that prescription rates of tramadol remained fairly stable from 2013 to 2015 [40]. However, as the authors state, several other studies reported an increase in tramadol prescription after the rescheduling of hydrocodone [41–43]. They argue that most studies that documented the increase in tramadol were based on predominantly indigent, pediatric, or veteran populations or from single health systems, hospitals, or poison centers and were not nationally representative. Our study is nationally representative; therefore, reasons for the discrepancy should be further explored.

Our findings also demonstrate an important difference in the drivers of prescriptions per physician specialty. Family medicine, internal medicine, and non-physician prescribers responded by 67.2% of all tramadol prescriptions in 2015, a substantial increase relative to 2012. Of interest, non-prescribing physicians accounted for a substantially higher share of tramadol prescriptions in 2015, relative to 2012 (56% increase). This increase was also documented in studies where data was collected up to 2012 [25], suggesting that "closer patient-prescriber communication or opioid oversight may be needed in some cases" [44]. Therefore, our study shows that a tendency for non-medical prescription of tramadol that was documented until 2012 remained in effect until 2015 as well.

This study is descriptive; therefore, future studies should confirm the reasons for our findings. As discussed above, rescheduling of compounds containing hydrocodone might have contributed to the trend. Since several states impose regulations restricting family physicians to provide schedule II drugs for chronic pain management [45], tramadol, being schedule IV, certainly became a viable option for primary care, and our data offers support to this statement. However, we found that the increase predates 2014, when reclassification happened. It might be speculated that since tramadol is considered to be less addictive, providers feel more comfortable prescribing it relative to other opioids. Vilification of prescription of other opioids, such as oxycodone and hydrocodone, may also be driving prescriptions to the more socially acceptable tramadol.

Tramadol is however addictive, and it also carries potential for several other adverse events, including increasing the risk of seizures, even at lower doses [46, 47]. The increased rate of seizures in the USA has been documented and largely considered to be a cause of fentanyl and its more potent analog, carfentanyl [48, 49], although the relative contribution of tramadol to this phenomenon is possible. Finally, the effects of the increased tramadol prescription on pain outcomes per se should be documented.

This study has limitations. We did not collect information on reasons for tramadol prescriptions; therefore, we were unable to assess appropriateness of care as per guidelines. We also failed to discriminate if tramadol was being prescribed alone or in combination with other medications such as acetaminophen. Furthermore, multiple prescriptions by single or multiple physicians were counted independently and this is of importance. Concomitant prescription of opioids [50] and of opioids and other classes of medications, such as benzodiazepines [51], has increased substantially over the last decade, with important impact on outcomes but also potential impact on prescription patterns. Additionally, we did not analyze data at state level; therefore, we cannot make inferences on the influence of state and regional laws and policies aiming to deter opioid misuse. Strengths of this study include robust sample size, use of methods that are similar to previous reports in different time points, allowing for comparability, and description of trends for opioid type.

Conclusion

We conclude that tramadol prescriptions rates have continuously increased both nationally and throughout all US

regions. Important differences exist among regions and physician specialties. Our findings suggest the need to further understand reasons for this increase in order to avoid excessive use of tramadol.

Compliance with Ethical Standards

Conflict of Interest Luisa M. Bigal conducted this study as part of a paid internship at Teva Pharmaceuticals. Kristen Bibeau is a full-time employee at Incyte Corporation and was a full-time employee at Teva at the time of data collection. Stephanie Dunbar is a full-time employee at Teva.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Dowell D, Haegerich TM, Chou RCDC. Guideline for prescribing opioids for chronic pain - United States. 2016 MMWR Recomm Rep. 2016;65(1):1–49. https://doi.org/10.15585/mmwr.rr6501e1.
2. Kahan M, Mailis-Gagnon A, Tunks E. Canadian guideline for safe and effective use of opioids for chronic non-cancer pain: implications for pain physicians. Pain Res Manag. 2011;16(3):157–8.
3. Groenewald CB, Rabbitts JA, Gebert JT, Palermo TM. Trends in opioid prescriptions among children and adolescents in the United States: a nationally representative study from 1996 to 2012. Pain. 2016;157(5):1021–7. https://doi.org/10.1097/j.pain.0000000000000475.
4. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med. 2015;372(3):241–8. https://doi.org/10.1056/NEJMsa1406143.
5. Daubresse M, Chang HY, Yu Y, Viswanathan S, Shah ND, Stafford RS, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. Med Care. 2013;51(10):870–8. https://doi.org/10.1097/MLR.0b013e3182a95d86.
6. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf. 2009 Dec;18(12):1166–75. https://doi.org/10.1002/pds.1833.
7. Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med. 2010;363(21):1981–5. https://doi.org/10.1056/NEJMp1011512.
8. Reinhart M, Scarpati LM, Kirson NY, et al. The economic burden of abuse of prescription opioids: a systematic literature review from 2012 to 2017. Appl Health Econ Health Policy. 2018. https://doi.org/10.1007/s40258-018-0402-x.
9. Herzberg D, Guarino H, Mateu-Gelabert P, Bennett AS. Recurring epidemics of pharmaceutical drug abuse in America: time for an all-drug strategy. Am J Public Health. 2016;106(3):408–10. https://doi.org/10.2105/AJPH.2015.302982.
10. Passik SD, Webster L. Opioid analgesics: does potency matter? J Opioid Manag. 2014;10(4):263–75. https://doi.org/10.5055/jom.2014.0214.
11. Chandanwale AS, Sundar S, Latchoumibady K, et al. Efficacy and safety profile of combination of tramadol-diclofenac versus tramadol-paracetamol in patients with acute musculoskeletal conditions, postoperative pain, and acute flare of osteoarthritis and rheumatoid arthritis: a phase III, 5-day open-label study. J Pain Res. 2014;7:455–63. https://doi.org/10.2147/JPR.S67817.
12. Cepeda MS, Camargo F, Zea C, et al. Tramadol for osteoarthritis: a systematic review and metaanalysis. J Rheumatol. 2007;34(3):543–55.
13. Sonis J. Tramadol for acute pain: a review of the evidence. Am Fam Physician. 2005;72(10):1964 author reply 1964, 1966.
14. Imamura T. Significant efficacy of tramadol/acetaminophen in elderly patients with chronic low back pain uncontrolled by NSAIDs: an observational study. Open Orthop J. 2015;9:120–5. https://doi.org/10.2174/1874325001509010120.
15. Harati Y, Gooch C, Swenson M, Edelman SV, Greene D, Raskin P, et al. Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. J Diabetes Complicat. 2000;14(2):65–70.
16. Administration US-DE. Drug scheduling [cited 2018 08/07/2018]. Available from: https://www.dea.gov/druginfo/ds.shtml
17. Handley SA, Flanagan RJ. Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000 - 2011. Clin Toxicol (Phila). 2014 Jan;52(1):1–12. https://doi.org/10.3109/15563650.2013.872791.
18. Board INC. Report of the international narcotics control board for 2012. New York: United Nations; 2013. [cited 2018 08/07/2018]. Available from: http://incb.org/documents/Publications/AnnualReports/AR2012/AR_2012_E.pdf.
19. Analytics TH. Market scan studies - abbreviated bibliography 2018 [cited 2018 09/14/2018]. Available from: http://truvenhealth.com/Portals/0/Assets/2017_Truven_Health_MarketScan_Bibliography.pdf.
20. DeGrauw X, Thurman D, Xu L, Kancherla V, DeGrauw T. Epidemiology of traumatic brain injury-associated epilepsy and early use of anti-epilepsy drugs: an analysis of insurance claims data, 2004-2014. Epilepsy Res. 2018 Jul 23;146:41–9. https://doi.org/10.1016/j.eplepsyres.2018.07.012.
21. Young JC, Lund JL, Dasgupta N, et al. Opioid tolerance and clinically recognized opioid poisoning among patients prescribed extended-release long-acting opioids. Pharmacoepidemiol Drug Saf. 2018. https://doi.org/10.1002/pds.4572.
22. Puenpatom RA, Szeinbach SL, Ma L, et al. Daily average consumption of 2 long-acting opioids: an interrupted time series analysis. Am Health Drug Benefits. 2012;5(1):52–60.
23. Analytics TH. The Truven Health MarketScan Databases for health services researchers 2018. Available from: https://truvenhealth.com/portals/0/assets/2017_MarketScan_Databases_Health_Services_Researchers.pdf.
24. Dowell D, Haegerich TM, Chou RCDC. Guideline for prescribing opioids for chronic pain–United States, 2016. JAMA. 2016;315(15):1624–45. https://doi.org/10.1001/jama.2016.1464.
25. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. Am J Prev Med. 2015;49(3):409–13. https://doi.org/10.1016/j.amepre.2015.02.020.
26. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The opioid crisis: a comprehensive overview. Curr Pain Headache Rep. 2018 Feb 23;22(3):16. https://doi.org/10.1007/s11916-018-0670-z.
27. Pezalla EJ, Rosen D, Erensen JG, Haddox D, Mayne TJ. Secular trends in opioid prescribing in the USA. J Pain Res. 2017;10:383–7. https://doi.org/10.2147/JPR.S129553.
28. O'Donnell JK, Gladden RM, Seth P. Trends in deaths involving heroin and synthetic opioids excluding methadone, and law enforcement drug product reports, by census region - United States, 2006-2015. MMWR Morb Mortal Wkly Rep. 2017;66(34):897–903. https://doi.org/10.15585/mmwr.mm6634a2.
29. Liang Y, Turner BJ. National cohort study of opioid analgesic dose and risk of future hospitalization. J Hosp Med. 2015;10(7):425–31. https://doi.org/10.1002/jhm.2350.
30. Rowe C, Wheeler E, Stephen Jones T, Yeh C, Coffin PO. Community-based response to fentanyl overdose outbreak, San Francisco, 2015. J Urban Health. 2018;96:6–11. https://doi.org/10.1007/s11524-018-0250-x.

31. Phalen P, Ray B, Watson DP, Huynh P, Greene MS. Fentanyl related overdose in Indianapolis: estimating trends using multilevel Bayesian models. Addict Behav. 2018;86:4–10. https://doi.org/10.1016/j.addbeh.2018.03.010.
32. Mercado MC, Sumner SA, Spelke MB, Bohm MK, Sugerman DE, Stanley C. Increase in drug overdose deaths involving fentanyl-Rhode Island, January 2012-March 2014. Pain Med. 2018;19(3):511–23. https://doi.org/10.1093/pm/pnx015.
33. Dasgupta N, Beletsky L, Ciccarone D. Opioid crisis: no easy fix to its social and economic determinants. Am J Public Health. 2018;108(2):182–6. https://doi.org/10.2105/AJPH.2017.304187.
34. Minegishi T, Garrido MM, Pizer SD, et al. Effectiveness of policy and risk targeting for opioid-related risk mitigation: a randomised programme evaluation with stepped-wedge design. BMJ Open. 2018;8(6):e020097. https://doi.org/10.1136/bmjopen-2017-020097.
35. Morin KA, Eibl JK, Franklyn AM, Marsh DC. The opioid crisis: past, present and future policy climate in Ontario, Canada. Subst Abuse Treat Prev Policy. 2017;12(1):45. https://doi.org/10.1186/s13011-017-0130-5.
36. Voelker R. A day in the life: facing the opioid epidemic in Huntington, West Virginia. JAMA. 2018;319(14):1423–4. https://doi.org/10.1001/jama.2018.1353.
37. Beheshti A, Lucas L, Dunz T, et al. An evaluation of naloxone use for opioid overdoses in West Virginia: a literature review. Am Med J. 2015;6(1):9–13. https://doi.org/10.3844/amjsp.2015.9.13.
38. Bolash RB. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med. 2015;372(16):1573–4. https://doi.org/10.1056/NEJMc1501822.
39. Smolina K, Gladstone E, Morgan SG. Determinants of trends in prescription opioid use in British Columbia, Canada, 2005-2013. Pharmacoepidemiol Drug Saf. 2016 May;25(5):553–9. https://doi.org/10.1002/pds.3989.
40. Raji MA, Kuo YF, Adhikari D, Baillargeon J, Goodwin JS. Decline in opioid prescribing after federal rescheduling of hydrocodone products. Pharmacoepidemiol Drug Saf. 2018;27(5):513–9. https://doi.org/10.1002/pds.4376.
41. Jones CM, Lurie PG, Throckmorton DC. Effect of US Drug Enforcement Administration's rescheduling of hydrocodone combination analgesic products on opioid analgesic prescribing. JAMA Intern Med. 2016;176(3):399–402. https://doi.org/10.1001/jamainternmed.2015.7799.
42. Oehler EC, Day RL, Robinson DB, Brown LH. Has the rescheduling of hydrocodone changed ED prescribing practices? Am J Emerg Med. 2016;34(12):2388–91. https://doi.org/10.1016/j.ajem.2016.09.002.
43. Schultz S, Chamberlain C, Vulcan M, et al. Analgesic utilization before and after rescheduling of hydrocodone in a large academic level 1 trauma center. J Opioid Manag. 2016;12(2):119–22. https://doi.org/10.5055/jom.2016.0323.
44. Health MDo. Patterns of opioid prescribing in Minnesota: 2012 and 2015 [cited 2018 08/17/2018]. Available from: http://www.health.state.mn.us/divs/hpsc/hep/publications/opioidbrief20185.pdf.
45. Control CfD. Prescription drug time and dosage limit Laws. 2017 [cited 2018 11/04/2018]. Available from: https://www.cdc.gov/phlp/docs/menu_prescriptionlimits.pdf
46. Hassamal S, Miotto K, Dale W, et al. Tramadol: understanding the risk of serotonin syndrome and seizures. Am J Med. 2018. https://doi.org/10.1016/j.amjmed.2018.04.025.
47. Beyaz SG, Sonbahar T, Bayar F, Erdem AF. Seizures associated with low-dose tramadol for chronic pain treatment. Anesth Essays Res. 2016;10(2):376–8. https://doi.org/10.4103/0259-1162.177181.
48. Somerville NJ, O'Donnell J, Gladden RM, et al. Characteristics of fentanyl overdose - Massachusetts, 2014-2016. MMWR Morb Mortal Wkly Rep. 2017;66(14):382–6. https://doi.org/10.15585/mmwr.mm6614a2.
49. Tiscione NB, Alford I. Carfentanil in impaired driving cases and the importance of drug seizure data. J Anal Toxicol. 2018;42(7):476–84. https://doi.org/10.1093/jat/bky026.
50. Reinhart M, Scarpati LM, Kirson NY, Patton C, Shak N, Erensen JG. The economic burden of abuse of prescription opioids: a systematic literature review from 2012 to 2017. Appl Health Econ Health Policy. 2018;16(5):609–32. https://doi.org/10.1007/s40258-018-0402-x.
51. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. Am J Prev Med. 2016;51(2):151–60. https://doi.org/10.1016/j.amepre.2016.02.014.