Assessing the Trends of Tramadol Utilization in the Medicare Part D Population in Rhode Island

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ABSTRACT

OBJECTIVE: To assess the trends in tramadol dispensing among Medicare Part D patients in Rhode Island.

METHODS: An analysis was conducted of the Medicare Part D Provider Utilization and Payment Data Public Use File for the years 2013–2021. Chi squared tests were conducted to assess statistical significance of annual changes in proportions.

RESULTS: Following tramadol becoming a controlled substance in 2014, the number of dispensed tramadol prescriptions and patients with a tramadol prescription decreased every subsequent year through 2021 (prescriptions: 42,157 to 33,026; patients: 12,654 to 9,653). The percentage of opioid prescriptions that were tramadol increased from 16.32% in 2013 to 21.19% in 2020.

CONCLUSION: Tramadol utilization has been decreasing among the Medicare Part D population in Rhode Island while the percentage of opioid dispensings that were tramadol have been increasing. Future studies are needed to assess whether patients utilizing tramadol are at a higher risk for adverse outcomes.

KEYWORDS: Tramadol; Utilization; Geriatric; Controlled Substance; Opioids

INTRODUCTION

The opioid epidemic has hit the United States the past couple of decades, with opioid overdose deaths increasing from 21,089 in 2010 to 47,600 in 2017.[1] While fatal opioid overdoses decreased slightly in 2018, they increased to record highs of over 50,000 in 2019, 68,630 in 2020, and 80,411 in 2021.[1] The hardship from the epidemic has especially been true in Rhode Island, which has been hit particularly hard. There have been over 2,500 confirmed accidental overdose deaths in Rhode Island from 2016–2022.[2] Opioids contributed to over 85% of these deaths.[2]

Tramadol is an opioid analgesic that is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments were inadequate.[3] While it is an opioid agonist, it has a unique mechanism of action which also includes weak inhibition of norepinephrine and serotonin reuptake.[3] In 2014, the United States Drug Enforcement Administration (DEA) classified tramadol as a Schedule IV controlled substance after it was previously a noncontrolled medication.[4]

While tramadol is one of the few opioids that is not a Schedule II controlled substance, that does not necessarily mean that it is a safer opioid.[5-6] Tramadol has nine black boxed warnings listed in its package insert.[3] Additionally, tramadol also had several key drug-drug interactions with central nervous system depressants, cytochrome P450 (CYP) 2D6 inhibitors, CYP 3A4 inhibitors, CYP3A4 inducers, and serotonergic medications as well as drug-disease interactions with patients with a history of epilepsy or seizures, patients with impaired renal function, and patients under the age of 18 following adenoidectomy or tonsillectomy.[3] Additionally, tramadol is included in the American Geriatric Society's Beers Criteria for Potentially Inappropriate Medication Use in Older Adults and is recommended to be used with caution in the geriatric population due to it increasing the risk of hyponatremia or syndrome of inappropriate antidiuretic hormone secretion.[7] Although tramadol has this concerning safety and prescribing profile, it is still a commonly prescribed medication in the United States.

Considering the safety profile of tramadol mixed with the severity of the opioid epidemic, it is important to assess its utilization in real-world settings. Additionally, tramadol's safety profile poses an increased risk of adverse outcome to the geriatric population. Therefore, the objective of this study was to assess the trends in tramadol dispensing among Medicare Part D patients in Rhode Island.

METHODS

An analysis was conducted of the Medicare Part D Provider Utilization and Payment Data Public Use File (PUF) for the years 2013–2021.[8] The PUF database includes all prescription medications billed to Medicare Part D from the outpatient setting on the aggregate drug level. It includes both stand-alone Prescription Drug Plans and Medicare Advantage Prescription Drugs. While this database does include 100% of Medicare Part D patients, it represents approximately only 70% of Medicare patients since about 30% of Medicare patients do not have Part D coverage.[9] More information about this database is available at CMS's website[8] as well as in their methodology documents.[9-11]

The outcomes of interest were the annual number of tramadol prescriptions dispensed, total number of patients with a tramadol prescription dispensed annually, percent of Medicare Part D beneficiaries with a tramadol prescription, annual number of opioid prescriptions, and annual percent of opioid prescriptions that were tramadol. The number of total patients with an opioid prescription was not included. This is due to the fact that the database assessed only provides information on the aggregate drug level without any patient information. While it is possible to calculate the total number of patients with a prescription for each individual opioid, it is possible patients were on more than one opioid within the particular calendar year, and summing all of the patients on each individual opioid would provide an overinflated class estimate. Chi squared tests were conducted to assess statistical significance of annual changes in proportions of Medicare beneficiaries utilizing tramadol as well as annual change in proportion of opioid prescriptions that were tramadol. Chi squared tests were conducted using OpenEpi.[12]

Table 1. Tramadol Utilization among Medicare Part D Beneficiaries in Rhode Island from 2013–2021

Year	Total Tramadol Prescriptions	Total Patients with Tramadol Prescription	Rhode Island Medicare Beneficiaries	Percent of Rhode Island Medicare Patients with a Tramadol Prescription	Percent Change from Prior Year	P value
2021	33,026	9,653	180,885	5.34%	-0.14%	0.0581
2020	34,955	9,657	176,223	5.48%	**-0.37%**	<0.0001
2019	35,368	9,916	169,415	5.85%	**-0.49%**	<0.0001
2018	37,046	10,476	165,199	6.34%	**-0.90%**	<0.0001
2017	39,917	11,578	159,968	7.24%	**-0.84%**	<0.0001
2016	41,792	12,619	156,284	8.07%	**-0.28%**	0.0054
2015	42,157	12,654	151,551	8.35%	**-0.41%**	<0.0001
2014	44,702	12,863	146,834	8.76%	0.12%	0.2692
2013	42,514	12,271	141,959	8.64%		

Table 2. Prescription Opioid Utilization among Medicare Part D Beneficiaries in Rhode Island from 2013–2021

Year	Total Tramadol Prescriptions	Total Non-Tramadol Opioid Prescriptions	Total Opioids Opioid Prescriptions	Percent of Opioids Prescriptions that were Tramadol	Percent Change from Prior Year	P value
2021	33,026	131,098	164,124	20.12%	**-1.07%**	<0.0001
2020	34,955	130,009	164,964	21.19%	**0.62%**	<0.0001
2019	35,368	136,547	171,915	20.57%	**0.55%**	<0.0001
2018	37,046	147,932	184,978	20.03%	**0.68%**	<0.0001
2017	39,917	166,395	206,312	19.35%	**0.71%**	<0.0001
2016	41,792	182,388	224,180	18.64%	**0.62%**	<0.0001
2015	42,157	191,803	233,960	18.02%	0.06%	0.5803
2014	44,702	204,227	248,929	17.96%	**1.64%**	<0.0001
2013	42,514	218,009	260,523	16.32%		

RESULTS

In Rhode Island, the number of tramadol prescriptions dispensed annually increased from 42,514 in 2013 to 44,702 in 2014 for Medicare Part D patients (**Table 1**). Following 2014, the number of dispensed tramadol prescriptions decreased every subsequent year from 42,157 in 2015 to 33,026 in 2021. Following the same trend, the number of patients with a tramadol prescription increased from 12,271 in 2013 to 12,863 in 2014. Following 2014, the number of patients with a dispensed tramadol prescription decreased every subsequent year from 12,654 in 2015 to 9,653 in 2021. These decreases happened while the number of Medicare Part D beneficiaries in Rhode Island increased every year from 141,959 in 2013 to 180,885 in 2021.

When assessing the percentage of Medicare beneficiaries with a tramadol dispensing, there was a non-significant increase from 2013 to 2014 (8.76% vs 8.64%, p=0.2692). After 2014, there was a significant decrease annually with 8.35% of Medicare beneficiaries in 2015 to 5.48% in 2020. 2021 also saw a decrease in the percentage of Medicare beneficiaries with a tramadol prescription; however, this decrease was not statistically significant (5.34%, p=0.0581).

The number of non-tramadol opioids dispensed decreased every year from 218,009 in 2013 to 130,009 in 2020, with 2021 seeing a slight increase with 131,098 (**Table 2**). When assessing all opioid prescriptions, the percentage that were tramadol increased every year from 16.32% in 2013 to 21.19% in 2020 (all annual increases were statistically significant except from 17.96% in 2014 to 18.02% in 2015 p=0.5803). The percent of opioids that were tramadol then saw a significant decrease from 21.19% in 2020 to 20.12% in 2021 (p<0.0001).

DISCUSSION

This analysis found that among the Medicare Part D population in Rhode Island, tramadol's utilization (both in number of prescriptions and number of beneficiaries with a prescription) increased from 2013 to 2014, before decreasing in the years following it becoming classified as a Schedule IV controlled substance through 2021. While tramadol's utilization decreased following 2014, the percentage of opioid prescriptions dispensed to the Medicare Part D population in Rhode Island that were tramadol increased every year through 2020 before slightly decreasing in 2021.

In August 2014, the DEA classified tramadol as a Schedule IV controlled substance after being noncontrolled.[4] This occurred within months of hydrocodone being reclassified as a Schedule-II controlled substance from being a Schedule III.[13] While tramadol went from being noncontrolled to being a controlled substance, several studies found that its utilization actually increased in the years following it being a controlled substance.[14-18] Several theories as to why this occurred exist. One is that while tramadol became a controlled substance, it had a lower abuse classification compared to the other opioid medications and is therefore a "safer" opioid.[5,6] Additionally, with hydrocodone becoming a Schedule-II controlled substance, more restrictions were placed on its prescribing such as limiting to maximum 30-day supplies, not allowing refills, and before electronic prescriptions became more readily available, patients had to physically pick up a hard copy prescription from their prescriber and bring it to their pharmacy. Even though tramadol had more restrictions than it did before (maximum five refills), it still could be written with refills and up to 90-day supplies, and have prescriptions called or faxed into the pharmacy. While several studies saw these trends, it was not found in this study of Medicare Part D patients in Rhode Island which found a nonsignificant increase in percentage of Medicare Part D beneficiaries utilizing tramadol from 2013–2014 followed by a statistically significant decrease every subsequent year through 2020. However, the percentage of prescription opioids that were tramadol increased annually, indicating that of the opioids being prescribed, tramadol's use was increasing versus its comparators. The existence and increased utilization of state Prescription Drug Monitoring Programs (PDMPs) has helped assist prescribers and pharmacists in the process of prescribing and dispensing controlled substances, like tramadol, in Rhode Island.[19-22] The Rhode Island PDMP allows prescribers and dispensing pharmacists the opportunity to see all controlled substances a patient is getting, regardless of prescriber or pharmacy, allowing an assessment of potentially concurrent utilization in instances of drug-drug interactions with controlled substances.[22,23]

Tramadol is one of the few non-Schedule II opioids, indicating it has a lower abuse potential compared to other agents in its class. However, several studies have come out in the past decade detailing tramadol having a higher risk of chronic opioid utilization compared to other opioid options.[24-27] Most of these studies assessed initial opioid therapy for opioid naive patients, with consistent results found both in the commercially insured population as well as the Medicare population. While it was outside the scope of this study to assess and outside the capabilities of the database of this analysis, future studies are needed to assess whether patients initiating opioid therapy on tramadol have a higher risk of chronic opioid utilization compared to other short-acting opioid medications.

The findings that the number of Medicare Part D patients with a tramadol prescription as well as total annual number of tramadol prescriptions decreasing annually from 2014 in Rhode Island is similar to findings on the state level for all patients in Rhode Island. An analysis of the Rhode Island PDMP was conducted of the years 2017-2021 assessing the dispensings of opioids, benzodiazepines, and stimulants among Rhode Island residents.[28] They found that for all residents in Rhode Island, the number of tramadol prescriptions decreased annually from 90,361 in 2017 to 67,593 in 2021.[28] However, contrary to our findings in the Medicare population specifically, the percentage of opioid prescriptions that were tramadol did not vary much during this time period, ranging from a low of 15.7% in 2017 to a high of 16.6% in 2020.[28] Additionally, while the number of patients with a tramadol prescription increased from 39,145 to 41,626 from 2017 to 2018, the number of patients decreased the following three years from 38,501 in 2019 to 35,303 in 2021.[28]

Another finding from this analysis shows that while tramadol utilization, both number of patients and number of prescriptions, has been decreasing annually since 2014 when tramadol became a controlled substance, the percentage of opioids that were tramadol prescriptions has been increasing annually with the exception of 2021. The implications of these findings are difficult to decipher without having further clinical information, which is not provided in this database. Without having clinical diagnoses, it is impossible to know whether tramadol was a more appropriate therapy option than other opioid therapies (i.e., treating diabetic peripheral neuropathy)[29] or less appropriate option (patients with seizure disorders).[3]

Additionally, without having additional clinical information in the database such as medication utilization by patient, it is not possible to know if tramadol was being prescribed safely. Tramadol has a host of drug-drug interactions that increase the risk of adverse outcomes for patients when taken concurrently. These drug-drug interactions include interactions with central nervous system depressants, CYP 2D6 inhibitors, CYP 3A4 inhibitors, CYP3A4 inducers, and serotonergic medications.[3] Additionally, tramadol has been shown to increase the risk of QT prolongation or torsade de pointes, with the risk being heightened among patients with concurrent utilization of other QT prolonging medications.[3]

A study assessing tramadol utilization in a large population of commercially insured and Medicare Advantage patients found that almost one in three patients with a tramadol prescription had a clinically significant concurrent drug-drug or drug-disease interaction.[30] They also found that compared to commercially insured patients, Medicare patients 65 years and older had significantly higher odds of concurrent tramadol utilization with every interacting drug class assessed except for nonbenzodiazepine sedative hypnotics as well as for every drug-disease interaction after adjusting for clinical and demographic covariables.[30] Medicare patients younger than 65 years had significantly higher adjusted odds of tramadol utilization for every drug-drug and drug-disease category assessed than both commercially insured patients as well as Medicare patients 65 years and older.[30] They also found that generalists compared to other specialties were more likely to prescribe to patients with concurrent utilization of interacting medications but less likely among patients with drug-disease and condition interactions.[30] Several analyses of emergency department prescribing in the United States found tramadol prescribing increasing annually with a dramatic increase following it becoming a controlled substance in 2014 through 2017 and 2018.[16,18] While the trends of tramadol utilization are decreasing in Rhode Island in the Medicare Part D population, it would be important to assess whether patients utilizing tramadol are under higher risk of adverse outcomes due to drug-drug or drug-disease interactions.

Several studies have shown adverse outcomes of patients utilizing tramadol. A propensity-score matched cohort study conducted in Spain found that compared to codeine, new utilizers of tramadol had significantly higher risk of all-cause mortality (hazard ratio (HR): 2.31, 95% CI: 2.08–2.56), cardiovascular events (HR: 1.15, 95% CI: 1.05–1.27), and fractures (HR: 1.50, 95% CI: 1.37–1.65).[31] A propensity-score matched cohort study in the United Kingdom of individuals at least 50 years of age with osteoarthritis found that patients utilizing tramadol had significantly higher rates of all-cause mortality compared to patients utilizing naproxen (HR: 1.71, 95% CI: 1.41–2.07), diclofenac (HR: 1.88, 95% CI: 1.51–2.35), celecoxib (HR: 1.70, 95% CI: 1.33–2.17), and etoricoxib (HR: 2.04, 95% CI: 1.37–3.03) while having no significant difference compared to codeine (HR: 0.94, 95% CI: 0.83–1.05).[32] Similar findings were observed in an propensity-score matched cohort study in Canada which found tramadol having a significantly higher risk of all-cause mortality compared to naproxen (HR: 1.2, 95% CI: 1.0–1.4), diclofenac (HR: 1.3, 95% CI: 1.1–1.5), Cox-2 inhibitors (HR: 1.5, 95% CI: 1.3–1.8), but no significant difference compared to codeine (HR: 0.9, 95% CI: 0.7–1.1).[33] In addition to its potential increased risk in all-cause mortality, a systematic literature review of case studies and case series conducted in 2020 found 127 cases of unintentional overdose deaths involving tramadol.[34] While 70% involved concomitant utilization of central nervous system depressants, there were eight reports of tramadol utilization being the sole cause of death.[34]

Several limitations exist in addition to what has already been stated. One limitation is that while this analysis does include every Medicare Part D patient who had a prescription dispensed that was billed to Medicare, it does not include all Medicare patients as only 70% of Medicare patients have prescription coverage through Medicare Part D.[9] Additionally, this only includes prescriptions that were billed to Medicare, and does not include prescriptions that were paid for out of pocket (either because insurance did not cover the prescription and the patient still proceeded to fill the medication, or if the patient opted not to have the prescription filled through their insurance), workers compensation, or other means. Additionally, it only represents prescriptions filled in the outpatient pharmacy setting, and not prescriptions that were dispensed in inpatient settings.

CONCLUSION

Trends in tramadol utilization have been decreasing among the Medicare Part D population in Rhode Island following tramadol's classification as a controlled substance. While tramadol's utilization has been decreasing, the percentage of opioids that were tramadol have been increasing. Considering tramadol's concerning safety profile, future studies are needed to assess whether patients utilizing tramadol are at a higher risk for adverse outcomes.

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Disclosures

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