Drug and Alcohol Dependence 205 (2019) 107693

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Overlapping prescriptions of opioids, benzodiazepines, and carisoprodol: "Holy Trinity" prescribing in the state of Florida

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ARTICLE INFO

Keywords:
Inappropriate prescribing
Prescription drug monitoring program
Opioid
Benzodiazepine
Carisoprodol

ABSTRACT

Background: High-risk combinations of controlled medications, such as those involving opioid analgesics, are under increased scrutiny because of their contribution to the opioid epidemic in the United States. Responsible prescribing guidelines indicate that the triple drug combination–opioids, benzodiazepines and skeletal muscle relaxants, especially carisoprodol–should not be concurrently prescribed.
Methods: This pharmacoepidemiologic study was designed to primarily examine the characteristics of patients receiving this triple combination compared to the group receiving only opioids and benzodiazepines.
Results: Results show that, while the number of exposed patients has declined since 2012, approximately 17,000 Floridians were prescribed this combination in 2017 alone. Demographically, recipients of these prescriptions were younger, more likely to be female, and geographically-localized. Furthermore, these patients were more frequently associated with a prescriber in the top 1% of opioid and/or benzodiazepine prescribing, have more multiple provider episodes ("doctor shopping"), and receive higher mean daily opioid dosages.
Conclusions: These findings raise important questions as to how frequently prescribers are checking prescription drug monitoring programs, following US Centers for Disease Control and Prevention opioid prescribing guidelines, and/or handling the clinical challenges associated with pharmaceutical management of patients with complex, painful health conditions.

1. Introduction

In the United States, the concurrent use of prescription opioids with benzodiazepines is common but concerning, as it is associated with a greater risk of overdose. The US Centers for Disease Control and Prevention (CDC), in its *Guideline for Opioid Prescribing for Chronic Pain* ("CDC Guideline"), makes specific recommendations to avoid, when possible, the co-prescribing of these two medication classes (Dowell et al., 2016; Paulozzi, 2012; Warner et al., 2011). The CDC Guideline further cautions prescribing of opioids and skeletal muscle relaxants (SMRs), given the central nervous system (CNS) depressant properties of these agents (Dowell et al., 2016; See and Ginzburg, 2008). While not addressed in the CDC Guideline, the opioid-benzodiazepine-SMR triple drug combination poses enhanced overdose risk (Munzing, 2017).

Carisoprodol (Soma®, Meda Pharmaceuticals Inc.) is a Schedule IV SMR in the United States. It is structurally similar to its primary active metabolite meprobamate, another schedule IV sedative with known risk for respiratory depression (Lewandowski, 2017). According to the 2017 National Survey on Drug Use and Health, an estimated 270,000 people aged 18 or older misused carisoprodol in the past year (Center for Behavioral Health Statistics and Quality, 2018). Abuse *potential* concerns led to market withdrawals in several European Union countries in 2008 (Bramness et al., 2012). When carisoprodol is the SMR constituting the triple drug combination described above, the mixture is known colloquially as the "Holy Trinity" for its intensely euphorigenic effects (Munzing, 2017).

Pharmacological studies suggest carisoprodol can activate the $GABA_A$ receptor, producing a central nervous system depressant effect

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https://doi.org/10.1016/j.drugalcdep.2019.107693
Received 27 April 2019; Received in revised form 18 September 2019; Accepted 21 September 2019
Available online 28 October 2019
0376-8716/

(Gonzalez et al., 2009b, 2009a). When co-ingested with an opioid, carisoprodol amplifies the effect of co-administered benzodiazepines or other sedatives present, increasing the risk of overdose and/or enhancing the euphorigenic effects (Bramness et al., 2012). Geissert et al. (2018) found that even when a carisoprodol prescription did not immediately overlap the opioid-benzodiazepine prescriptions, but was in the patient's recent prescribing history, the triple combination was associated with an increased odds (OR: 1.59 CI: 1.08, 2.32) of a fatal or nonfatal overdose event. In a study of decedents with prescription opioids or fentanyl-heroin present, 5.7 % and 1.7 %, respectively, had evidence of the triple combination in the six month period preceding death (Lawrence Scholl (Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC), 2017).

This type of high-risk co-prescribing is frequently monitored by state prescription drug monitoring programs (PDMP) and healthcare organizations as signals for further medical or legal follow-up (Florida Department of Health, 2016; Forrester, 2011; Freeman et al., 2015; Losby et al., 2017). In the state of Florida, the count of unique recipients of this combination was reported to be 3,111 in June 2017 (Florida Department of Health, 2017). Despite overdose risks and increased prescribing scrutiny, this co-prescribing persists. The literature is limited regarding the prevalence and characteristics of such prescribing episodes from either prescriber or recipient perspectives.

Thus, we aim to characterize this type of prescribing using Florida's PDMP controlled substance (CS) data and measures developed by the CDC's Prescription Behavioral Surveillance System (PBSS) (Paulozzi et al., 2015). When examined against a comparator group (i.e., those receiving overlapping prescriptions of opioids and benzodiazepines (OPI-BZO only), we expected to find a set of unique and shared factors associated with the "Holy Trinity" prescribing behavior.

2. Methods

2.1. Study design and data source

The analysis used Schedule II to IV CS dispensing records for state of Florida residents aged 18 and over from January 1, 2012 to December 31, 2017. Recipients were excluded if their dispensing record was missing, did not include prescriptions, or had a supply greater than 90 days. We used National Drug Codes to identify prescriptions and excluded buprenorphine and tramadol from the study as both opioids were inconsistently reported to the Florida PDMP during the study period. Recipients who had at least one overlapping opioid-benzodiazepine episode ("OPI-BZO episode") were included in the study ("OPI-BZO recipient"). An OPI-BZO episode is defined as when the supply of opioid and benzodiazepine prescriptions overlap by seven or more consecutive days.

We further categorized OPI-BZO recipients into "OPI-BZO-CAR recipients" and "OPI-BZO{CAR} recipients". OPI-BZO-CAR recipients had at least one *concurrent* opioid, benzodiazepine, and carisoprodol episode ("OPI-BZO-CAR episode") in a given calendar year, defined as OPI-BZO episode with at least one day's supply overlapping a carisoprodol prescription. On the contrary, OPI-BZO{CAR} recipients experienced at least one OPI-BZO episode in a given calendar year and {CAR} signifies that a patient did not have exposure to carisoprodol during the OPI-BZO episode. The OPI-BZO{CAR} group includes receipts who did not fill carisoprodol in the given year and who filled carisoprodol but not during the OPI-BZO episode ([< 1 %] since 2015, see Supplementary Table 1). Fig. 1 illustrates each of these prescribing scenarios for a hypothetical recipient.

2.2. Measures

2.2.1. Episode-level measures

First, we calculated the proportion of OPI-BZO episodes with at least one day's supply overlapping a carisoprodol prescription (i.e., # of OPI-BZO-CAR divided by # of OPI-BZO). We then reported: the proportion of OPI-BZO-CAR episodes in which all prescriptions were written by the single prescriber (co-prescribing), the proportion of OPI-BZO-CAR episodes in which all prescriptions were dispensed by the single pharmacy (co-dispensing), the proportion of OPI-BZO-CAR episodes in which prescriptions were paid by more than one payer, and the proportion of OPI-BZO-CAR episodes in which at least one prescription was written by an out-of-state prescriber. These measures, or variations thereof, examine potentially inappropriate prescribing behaviors.

2.2.2. Recipient-level measures

We compared the sociodemographic characteristics (age groups, sex, and residential county), and three high-risk prescribing indicators between OPI-BZO-CAR and OPI-BZO{CAR} recipients. County of residence was categorized according to the US Drug Enforcement Administration's High Intensity Drug Trafficking Areas (HIDTA; https://www.dea.gov/hidta). We examined the proportion of recipients involved in a Multiple Provider Episode (MPE), which is defined by the state as having ≥ 5 distinct prescribers and ≥ 5 distinct pharmacies within a calendar quarter for any CS in Schedules II to IV (Florida Department of Health, 2016). An MPE is a data-driven signal of potentially inappropriate drug-seeking behavior, sometimes referred to as "doctor shopping." We also estimated the mean daily dosage in morphine milligram equivalents (MME/day) for the OPI-BZO episode component of the overlapping window for each group and compared the proportion of recipients with opioid dosage $\geq$ 90 MME/day (Dowell et al., 2016). Any active opioid prescription dispensed within the OPI-BZO episode overlapping window was used for the MME calculation. The MME/day for each recipient was calculated as the cumulative daily MME for each opioid prescription divided by the total number of days in the OPI-BZO episode overlapping window, accounting for overlapping opioid prescription days (see Fig. 1). The formula for calculating daily MME for each opioid prescription is: (Drug Strength)*(Drug Quantity)*(MME Conversion Factor)/(Days Supply) (National Center for Injury Prevention and Control, 2017).

2.2.3. Prescriber-level measures

We ranked prescribers based on the total number of opioid, benzodiazepine and carisoprodol prescriptions in each year. We then compared the proportion of prescribers in the top 1% of prescribing for opioids, benzodiazepines, and carisoprodol between OPI-BZO-CAR prescribers (those who wrote prescriptions involved in at least one OPI-BZO-CAR episode) and OPI-BZO{CAR} prescribers (those who only wrote prescriptions for OPI-BZO{CAR} episodes) in terms of total prescriptions written per year during the study period in our database. We also examined differences in the top 1% of prescribing between two groups: prescribers that wrote for all OPI-BZO-CAR prescriptions involved in one or more episode (triple prescriber) and those that did not write for all three (non-triple prescriber).

2.3. Analysis

Our study evaluated the changes in measures at the episode-, recipient-, and prescriber-level from 2012 to 2017. Analyses were conducted at the episode-, recipient-, and prescriber-level by comparing 2012 to 2017. The data analysis was conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC). This study was approved by the Institutional Review Board of the University of Florida (study number IRB201700521).

3. Results

Table 1 shows the prescription-, recipient-, and episode-level characteristics used in this analysis in 2012 and 2017 (information for intervening years is presented in the supplemental document). In 2017, 12.8% (432,085) of individuals receiving an opioid prescription had

Table 1
Summary of the prescription-, recipient-, and episode-level characteristics, 2012 and 2017.

	2012	2017	relative change (2012 – 2017)
Prescription			
Opioid	13,052,347	11,725,545	−10.2 %
Benzodiazepine	10,424,832	10,329,846	−0.9 %
Carisoprodol	705,148	317,315	−55.0 %
Recipient			
Recipients with at least one opioid, benzodiazepine or carisoprodol prescription	4,931,098	4,718,172	−4.3 %
Recipients with opioid prescriptions	3,689,814	3,365,588	−8.8 %
Recipients with benzodiazepine prescriptions	2,227,295	2,228,997	0.1%
Recipients with carisoprodol prescriptions	172,524	73,262	−57.5 %
Recipients with at least one overlapping opioid-benzodiazepine episode (OPI-BZO recipients)[a]	530,773 (14.4 %)	432,085 (12.8 %)	−18.6 %
Recipients with concurrent opioid, benzodiazepine and carisoprodol use (OPI-BZO-CAR recipients)[b]	51,945 (9.8 %)	17,633 (4.1 %)	−66.1 %
Recipients with OPI-BZO episodes but no concurrent use of carisoprodol (OPI-BZO{CAR} recipients)[c]	478,828 (90.2 %)	414,452 (95.9 %)	−13.4 %
The proportion of OPI-BZO-CAR recipients among recipients with opioid prescriptions	1.4 %	0.5%	−62.8 %
The proportion of OPI-BZO-CAR recipients among recipients with carisoprodol prescriptions	30.1 %	24.1 %	−20.1 %
Episode			
OPI-BZO episodes per opioid recipient	1.21	1.06	−12.5 %
Overlapping opioid-benzodiazepine episodes (OPI-BZO episodes)	4,453,524	3,552,504	−20.2 %
Concurrent opioid-benzodiazepine-carisoprodol episodes (OPI-BZO-CAR episodes)[d]	553,778 (12.4 %)	192,525 (5.4 %)	−65.2 %
Co-prescribing[e]	329,794 (59.6 %)	96,447 (50.1 %)	−70.8 %
Co-dispensing[f]	365,988 (66.1 %)	147,932 (76.8 %)	−59.6 %
Multi-payer[g]	237,342 (42.9 %)	69,053 (35.9 %)	−70.9 %
Out-of-State Prescriber[h]	7,735 (1.4 %)	7,305 (3.8 %)	−5.6 %

Note: OPI-BZO-CAR recipients and OPI-BZO{CAR} recipients are mutually exclusive.
[a] The proportion of OPI-BZO recipients among recipients with opioid prescriptions.
[b] The proportion of OPI-BZO-CAR recipients among OPI-BZO recipients.
[c] The proportion of OPI-BZO{CAR} recipients among OPI-BZO recipients.
[d] The proportion of OPI-BZO-CAR episodes among OPI-BZO episodes.
[e] OPI-BZO-CAR episodes where all prescriptions were written by the single prescriber.
[f] OPI-BZO-CAR episodes where all prescriptions were dispensed by the single pharmacy.
[g] OPI-BZO-CAR episodes where prescriptions were paid by more than one payer.
[h] OPI-BZO-CAR episodes with at least one prescription was written by the out-of-state prescriber.

one or more overlapping OPI-BZO episodes. Overall, there were 3,552,504 OPI-BZO episodes, with 192,525 (5.4 %) having at least one day's supply overlapping a carisoprodol prescription. This represented a 20.2 % and 65.2 % decline, respectively, from 2012 (4,453,524 OPI-BZO episodes and 553,778 OPI-BZO-CAR episodes). The larger decrease in number of OPI-BZO-CAR episodes was driven by the decrease in carisoprodol prescribing (55 % decrease in prescription written; 58 % decrease in the number of recipients). As shown in Table 1 and Fig. 2, in 2017, approximately one-half of the OPI-BZO-CAR episodes were written by single, as opposed to multiple, prescribers. More than one-third of the OPI-BZO-CAR episodes were paid by more than one payer. The percentage of OPI-BZO-CAR episodes in which each of the medications was written by a single prescriber decreased from 2012 to 2017 (59.6 % versus 50.1%, respectively) while the percentage dispensed by the same pharmacy increased (66.1 % versus 76.8 %, respectively). While the absolute number of out-of-state prescribers involved in these

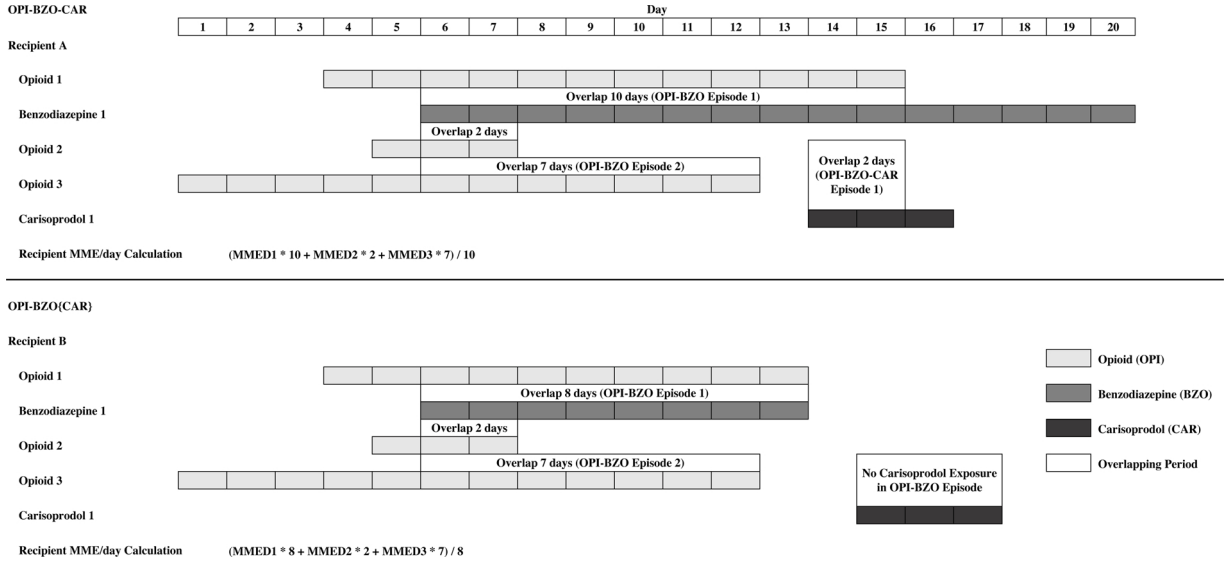

Fig. 1. Illustrated examples of prescribing scenarios for two hypothetical recipients of overlapping opioids, benzodiazepines and carisoprodol. {Carisoprodol} signifies that Recipient B received a carisoprodol prescription but not in the window of opioid and benzodiazepine overlap.

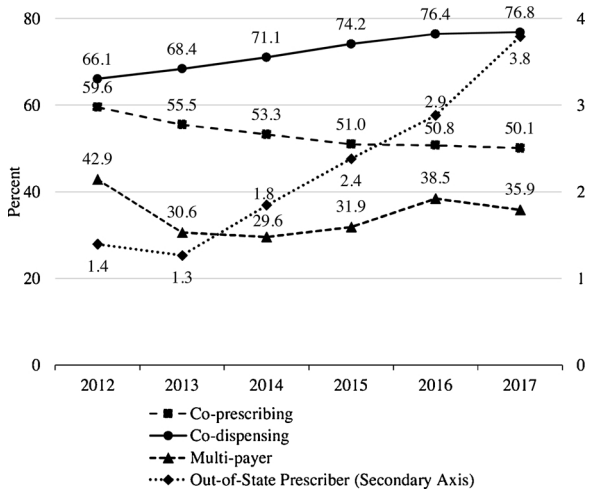

Fig. 2. Percentage of concurrent opioid, benzodiazepine and carisoprodol (OPI-BZO-CAR) episodes with selected characteristics.

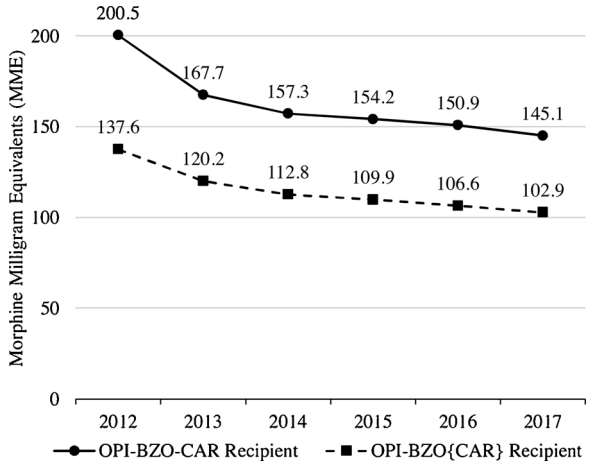

Fig. 3. Mean daily dosage in morphine milligram equivalents (MME) during the opioid and benzodiazepine (OPI-BZO) episode window, with and without carisoprodol (CAR).

episodes was small, their overall representation nearly tripled from 1.4% to 3.8% from 2012 to 2017.

Table 2 shows the available demographic characteristics and select risk profiles of Florida recipients in the study. In 2017, 19.0% of OPI-BZO-CAR recipients were 65 or older compared to 41.0% of OPI-BZO{CAR} recipients who were 65 or older. Two-thirds of these recipients were female and they were more likely to reside in the Central Florida HIDTA counties. The percentage of recipients with one or more MPE decreased from 2012 to 2017 for both groups. A larger percentage of recipients with carisoprodol concurrency had a daily MME ≥ 90 during the overlapping window (37.1% vs. 23.4% in 2017) with an overall higher mean daily MME (145.1 vs. 102.9 in 2017). As expected and previously reported, mean MME per day declined in Florida over this time period (Florida Department of Health, 2016). The decline occurred at a similar rate, 27.6% and 25.3%, respectively (Fig. 3). However, in 2017, the average daily opioid MMEs were 41.1% higher in the OPI-BZO-CAR group than the OPI-BZO{CAR} group (Fig. 4).

Table 3 shows select ranking characteristics of prescribers by drug class and combination. Prescribers who wrote a prescription involved in an OPI-BZO-CAR episode were more likely to be ranked in the top 1% of opioid (11.5% vs.0.2 % in 2017) and benzodiazepine (10.9 % vs. 0.5 % in 2017) prescribers. The involvement of the top 1% in prescribing for each drug class increased through time. For the group writing all three prescriptions in the episode (triple prescriber), during 2012–2017,

Table 2
Overlapping opioid and benzodiazepine prescriptions with/without a concurrent carisoprodol prescription in state of Florida residents, 2012 and 2017.

	2012		2017	
	OPI-BZO-CAR N = 51,945	OPI-BZO{CAR} N = 478,828	OPI-BZO-CAR N = 17,633	OPI-BZO{CAR} N = 414,452
Demographics				
Age Group				
18-24	447 (0.9 %)	5,277 (1.1 %)	40 (0.2 %)	2055 (0.5 %)
25-34	5,924 (11.4 %)	39,537 (8.3 %)	664 (3.8 %)	16,800 (4.1 %)
35-44	10,000 (19.3 %)	59,944 (12.5 %)	2,196 (12.5 %)	38,789 (9.4 %)
45-54	16,701 (32.2 %)	102,837 (21.5 %)	4,716 (26.8 %)	73,480 (17.7 %)
55-64	13,303 (25.6 %)	107,912 (22.5 %)	6,664 (37.8 %)	113,502 (27.4 %)
65 +	5,570 (10.7 %)	163,321 (34.1 %)	3,353 (19.0 %)	169,826 (41.0 %)
Sex				
Missing	11 (0.0 %)	153 (0.0 %)	4 (0.0 %)	56 (0.0 %)
Male	19,304 (37.2 %)	183,370 (38.3 %)	5,755 (32.6 %)	152,832 (36.9 %)
Female	32,630 (62.8 %)	295,305 (61.7 %)	11,874 (67.3 %)	261,564 (63.1 %)
High Intensity Drug Trafficking Area (HIDTA)				
Missing	94 (0.2 %)	817 (0.2 %)	17 (0.1 %)	307 (0.1 %)
North Florida	6,980 (13.4 %)	71,064 (14.8 %)	1,770 (10.0 %)	58,463 (14.1 %)
Non-HIDTA	16,838 (32.4 %)	159,225 (33.3 %)	5,134 (29.1 %)	115,432 (27.9 %)
Central Florida	19,593 (37.7 %)	144,322 (30.1 %)	6,845 (38.8 %)	144,492 (34.9 %)
South Florida	8,440 (16.3 %)	103,400 (21.6 %)	3,599 (20.4 %)	83,705 (20.2 %)
Gulf Coast[a]			268 (1.5 %)	12,053 (2.9 %)
High-risk prescribing indicator				
Multiple Provider Episodes (MPE)	738 (1.4 %)	2,871 (0.6 %)	97 (0.6 %)	1,342 (0.3 %)
Mean daily dosage in morphine milligram equivalents (MME/day) during the OPI-BZO episode window	200.5	137.6	145.1	102.9
Recipients with opioid dosage ≥90 during the OPI-BZO episode window	27,051 (52.1%)	150,121 (31.4%)	6,536 (37.1%)	97,079 (23.4%)

[a] Counties in the panhandle of Florida were designated to Gulf Coast HIDTA in January 2016, therefore no prior data is available.

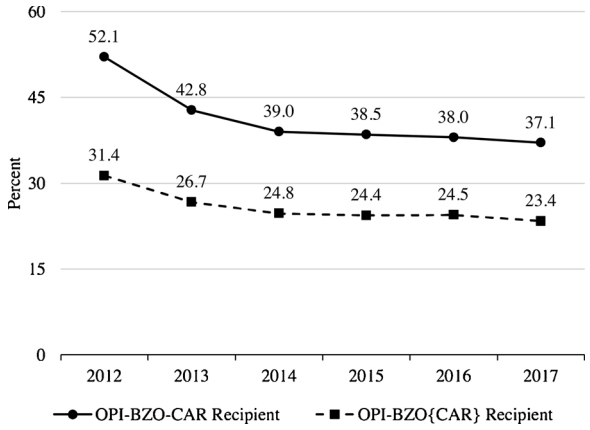

Fig. 4. Percentage of recipients with morphine milligram equivalents (MME)/day > = 90 during the opioid and benzodiazepine (OPI-BZO) episode window, with and without carisoprodol (CAR).

about 13.5 % were in the top 1 % of opioid prescribers and 3.4 % were in the top 1% carisoprodol prescribers (Fig. 5). The range of top 1% benzodiazepine prescribers showed the most variation over the study period (9.4 %–12.2 %). This compares to only 2.3 %, 6.1 % and 0.2 % of the non-triple prescribers, respectively, in 2012. For this group, however, we found that these proportions increased sharply to 8.8%, 9.8 % and 0.5 % in 2017.

4. Discussion

Despite the reported risks associated with the co-administration of opioids, benzodiazepines, and carisoprodol, more than 17,000 Floridians were prescribed this triple drug combination in 2017. The impact of federal scheduling of carisoprodol on dispensing proved modest so the persistence of high-risk prescribing involving carisoprodol is unsurprising (Hernandez et al., 2018). Li et al. (2019) found that the prevalence of concurrent OPI-BZO prescribing, which increased the risk of overdose by 5 times in the first 90 days, remained prevalent in national Medicare Part D claims.

Several unique and shared characteristics associated with concurrent carisoprodol prescribing were discovered. Recipients of OPI-BZO-CAR were younger, more likely to be female and residing in the Central Florida area compared to individuals who received prescriptions for OPI-BZO{CAR} only. Furthermore, OPI-BZO-CAR recipients were exposed to a larger number of top 1 % prescribers for *both* opioids and benzodiazepines by an order of magnitude. Kreiner et al. (2017) found an association between top 1 % opioid prescribing and an increased likelihood of medical board disciplinary actions citing inappropriate prescribing. Guy and Zhang (2018) reported that primary care physicians (i.e., family medicine, internal medicine, general practice) accounted for 37.1 % of all opioid prescriptions written in FY 2017, but it is unclear if the OPI-BZO-CAR combination was associated with a particular specialty. At the time of this analysis, we were unable to examine specialty information from the Florida PDMP, but system changes should make this type of analysis possible in the future.

Exposure to high-risk levels of daily MME declined at a similar rate for both groups. As of 2017, the average opioid dosage for OPI-BZO {CAR} recipients still exceeded CDC Guideline recommendations that dosages not exceed 90 MME per day (Dowell et al., 2016). Dosages ≥100 MME per day reportedly increase risk of overdose 2.0–8.9 times compared to dosages of 1 to < 20 MME per day (Dowell et al., 2016). The PDMP does not contain information on medical diagnoses, nor whether medications were taken as prescribed. The findings do indicate that, while the absolute number was low, the relative risk of a recipient being involved in multiple provider episodes was twice as high for the carisoprodol concurrent group as for the OPI-BZO{CAR} group.

When concurrent OPI-BZO-CAR prescriptions were written by multiple prescribers, it is unknown if the prescribers were aware of the risks associated with this drug combination. Furthermore, it is not clear from PDMP data if these prescribers were in the same practice or if they utilized the PDMP prior to prescribing. During the period of this study, PDMP utilization was voluntary in Florida, and interpreting PDMP reports remains a challenge for prescribers. Efforts are underway to improve prescription-level data visualization so that overlapping OPI-BZO prescriptions are quickly and easily identifiable on reports during clinical encounters. Geissert et al. (2018) found that when predicting opioid overdose, the predictive power of the model with any prescriptions for long-acting opioids, carisoprodol, benzodiazepine, or other sedatives is similar to the model including prescription overlap variables. Simply highlighting that a patient has a carisoprodol prescription on a PDMP report may be just as effective as displaying complex overlapping windows. In 2017, about half of the OPI-BZO-CAR episodes were written by the single prescriber. One study using Oregon's PDMP data found that patients with long-term opioid use and lower opioid-prescribing continuity (i.e., multiple prescribers) were more likely to receive risky prescriptions and be hospitalized for opioid-related causes (Hallvik et al., 2018). Future studies could further examine prescribing patterns to differentiate co-prescribing scenarios (e.g., prescriptions from 3 drug categories written at the same time, the duration of the OPI-BZO-CAR episode, etc.). Even when high-risk prescribing episodes are created by a single prescriber unintentionally, such as when refills

Table 3
High-volume prescribers of overlapping opioid and benzodiazepine prescriptions with/without a concurrent carisoprodol prescription, 2012 and 2017.

	2012		2017	
	OPI-BZO-CAR[a] N = 14,798	OPI-BZO{CAR}[b] N = 29,256	OPI-BZO-CAR[a] N = 9,784	OPI-BZO{CAR}[b] N = 32,334
Prescribers in the top 1% prescribing[c]				
Opioid	831 (8.2 %)	7 (0.0 %)	696 (11.5 %)	48 (0.2 %)
Benzodiazepine	835 (7.7 %)	65 (0.3 %)	767 (10.9 %)	128 (0.5 %)
Carisoprodol	180 (2.0 %)	N/A	131 (2.3 %)	N/A
	Triple[d] N = 5,379	**Non-Triple[e] N = 9,419**	**Triple[d] N = 3,148**	**Non-Triple[e] N = 6,636**
Prescribers in the top 1% prescribing[c]				
Opioid	723 (13.4 %)	108 (2.3 %)	439 (14.0 %)	257 (8.8 %)
Benzodiazepine	504 (9.4 %)	331 (6.1 %)	383 (12.2 %)	384 (9.8 %)
Carisoprodol	173 (3.2 %)	7 (0.2 %)	120 (3.8 %)	11 (0.5 %)

[a] Prescribers who wrote prescriptions involved in at least one OPI-BZO-CAR episode.
[b] Prescribers who only wrote prescriptions for OPI-BZO{CAR} episode.
[c] The denominators for prescribers in the top 1% prescribing opioid/benzodiazepine/carisoprodol are in the Appendix.
[d] Prescribers who wrote for all OPI-BZO-CAR prescriptions involved in at least one OPI-BZO-CAR episode.
[e] Prescribers who did not wrote for all OPI-BZO-CAR prescriptions involved in OPI-BZO-CAR episodes.

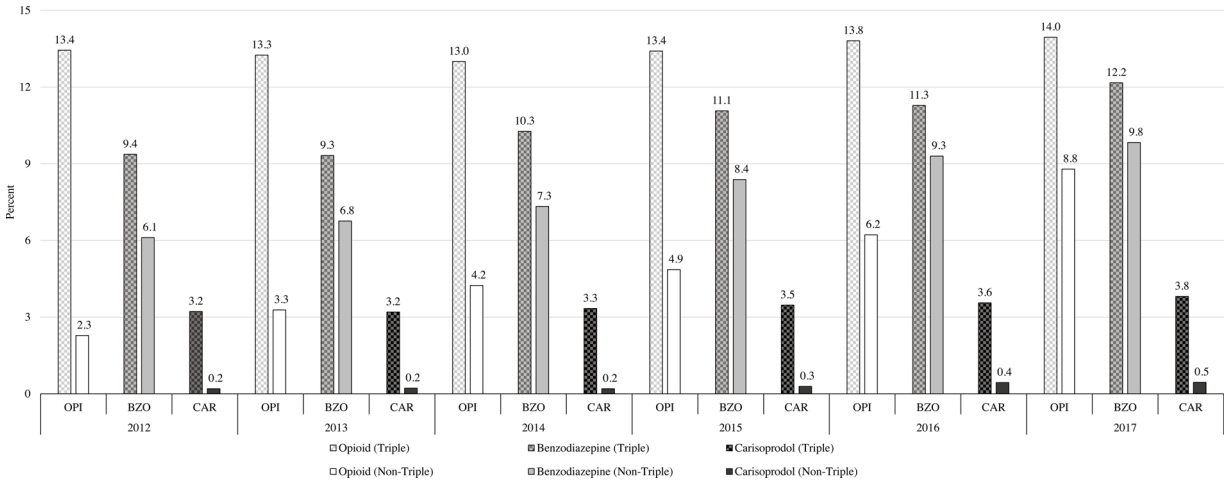

Fig. 5. High-volume Prescribers for the opioid, benzodiazepine and carisoprodol (OPI-BZO-CAR) episodes.

are made unbeknownst to the prescriber, screening by dispensers and use of the prescription drug monitoring program may help mitigate the risk of concurrent use. Shonesy et al. (2019) demonstrated the feasibility of performing screenings in a retail pharmacy setting.

One of the limitations of this study is a lack of individual-level outcomes associated with these prescribing behaviors. However, epidemiologic data on fatal poisonings from the state of Florida indicates that the number of deaths involving opioid, benzodiazepine, and carisoprodol declined at a slightly higher rate than the decline in individuals receiving OPI-BZO-CAR prescriptions (unpublished). Linking cause of death and PDMP data would provide new insights into these poisonings, but remains a challenge in the state of Florida due to data sharing and confidentiality restrictions.

To our knowledge, this is one of the only examinations of controlled substance prescribing associated with the “Holy Trinity” including the sociodemographic characteristics of recipients and the high-risk profiles of their prescribers. This information can be used to improve and enhance PDMP reporting features including risk-based scoring, predictive algorithms, and/or point-of-care alerts to healthcare providers.

Role of funding source

This work was supported by Grant No. 2016-PM-BX-K005 and 2017-PM-BX-K038 awarded by the Bureau of Justice Assistance. The Bureau of Justice Assistance is a component of the Department of Justice's Office of Justice Programs, which also includes the Bureau of Justice Statistics, the National Institute of Justice, the Office of Juvenile Justice and Delinquency Prevention, the Office for Victims of Crime, and the SMART Office. Points of view or opinions in this document are those of the author and do not necessarily represent the official position or policies of the U.S. Department of Justice.

Contributors

Ms. Wang and Dr. Delcher were lead investigators for study design, analysis, interpretation of results, and manuscript development. Mr. Li, and Drs. Goldberger and Reisfield assisted with the study design and interpretation of results, and manuscript development. All authors have contributed to and approved the final manuscript as submitted.

Declaration of Competing Interest

No conflict declared

Acknowledgements

The authors would like to thank Florida Prescription Drug Monitoring Program for providing the data, and Mr. Jungjun Bae for editing the tables and figures.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107693.

References

Bramness, J.G., Furu, K., Skurtveit, S., Engeland, A., 2012. Effect of the market withdrawal of carisoprodol on use of other prescribed drugs with abuse potential. Clin. Pharmacol. Ther. 91, 438–441. https://doi.org/10.1038/clpt.2011.250.

Center for Behavioral Health Statistics and Quality, 2018. 2017 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD.

Dowell, D., Haegerich, T.M., Chou, R., 2016. CDC guideline for prescribing opioids for chronic pain–United States, 2016. MMWR Recomm. Rep. 65, 1–49. https://doi.org/10.15585/mmwr.rr6501e1.

Florida Department of Health, 2017. 2016–2017 Prescription Drug Monitoring Program Annual Report (E-FORCSE).

Florida Department of Health, 2016. 2015–2016 Prescription Drug Monitoring Program Annual Report (E-FORCSE).

Forrester, M.B., 2011. Ingestions of hydrocodone, carisoprodol, and alprazolam in combination reported to Texas poison centers. J. Addict. Dis. 30, 110–115. https://doi.org/10.1080/10550887.2011.554778.

Freeman, P.R., Goodin, A., Troske, S., Talbert, J., 2015. Kentucky House Bill 1 Impact Evaluation (Evaluation). University of Kentucky, Institute for Pharmaceutical Outcomes and Policy.

Geissert, P., Hallvik, S., Van Otterloo, J., O'Kane, N., Alley, L., Carson, J., Leichtling, G., Hildebran, C., Wakeland, W., Deyo, R.A., 2018. High-risk prescribing and opioid overdose: prospects for prescription drug monitoring program–based proactive alerts. PAIN 159, 150–156. https://doi.org/10.1097/j.pain.0000000000001078.

Gonzalez, L.A., Gatch, M.B., Forster, M.J., Dillon, G.H., 2009a. Abuse potential of soma: the GABA(A) receptor as a target. Mol. Cell. Pharmacol. 1, 180–186.

Gonzalez, L.A., Gatch, M.B., Taylor, C.M., Bell-Horner, C.L., Forster, M.J., Dillon, G.H., 2009b. Carisoprodol-mediated modulation of GABAA receptors: in vitro and in vivo studies. J. Pharmacol. Exp. Ther. 329, 827–837. https://doi.org/10.1124/jpet.109.151142.

Guy, G.P., Zhang, K., 2018. Opioid prescribing by specialty and volume in the U.S. Am. J. Prev. Med. 55, e153–e155. https://doi.org/10.1016/j.amepre.2018.06.008.

Hallvik, S.E., Geissert, P., Wakeland, W., Hildebran, C., Carson, J., O'Kane, N., Deyo, R.A., 2018. Opioid-prescribing continuity and risky opioid prescriptions. Ann. Fam. Med. 16, 440–442. https://doi.org/10.1370/afm.2285.

Hernandez, I., He, M., Brooks, M.M., Zhang, Y., 2018. Exposure-response association between concurrent opioid and benzodiazepine use and risk of opioid-related overdose in medicare part d beneficiaries. JAMA Netw. Open 1, e180919. https://doi.org/10.1001/jamanetworkopen.2018.0919.

Kreiner, P.W., Strickler, G.K., Undurraga, E.A., Torres, M.E., Nikitin, R.V., Rogers, A., 2017. Validation of prescriber risk indicators obtained from prescription drug monitoring program data. Drug Alcohol Depend. 173, S31–S38. https://doi.org/10.1016/j.drugalcdep.2016.11.020.

Lawrence Scholl (Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC), 2017. Personal Communication.
Lewandowski, T., 2017. Pharmacokinetic modeling of carisoprodol and meprobamate disposition in adults. Hum. Exp. Toxicol. 36, 846–853. https://doi.org/10.1177/0960327116672912.
Li, Y., Delcher, Brown, C.J.D., Wei, Y.-J., Reisfield, G.M., Winterstein, A.G., 2019. Impact of Schedule IV controlled substance classification on carisoprodol utilization in the United States: An interrupted time series analysis. Drug Alcohol Depend. 202, 172–177. https://doi.org/10.1016/j.drugalcdep.2019.05.025.
Losby, J.L., Hyatt, J.D., Kanter, M.H., Baldwin, G., Matsuoka, D., 2017. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. J. Eval. Clin. Pract. https://doi.org/10.1111/jep.12756.
Munzing, T., 2017. Physician guide to appropriate opioid prescribing for noncancer pain. Perm. J. 21, 16–169. https://doi.org/10.7812/TPP/16-169.
National Center for Injury Prevention and Control, 2017. CDC Compilation of Benzodiazepines, Muscle Relaxants, Stimulants, Zolpidem, and Opioid Analgesics with Oral Morphine Milligram Equivalent Conversion Factors, 2017 Version. Centers for Disease Control and Prevention, Atlanta, GA.
Paulozzi, L.J., 2012. Prescription drug overdoses: a review. J. Safety Res. 43, 283–289. https://doi.org/10.1016/j.jsr.2012.08.009.
Paulozzi, L.J., Strickler, G.K., Kreiner, P.W., Koris, C.M., 2015. Controlled substance prescribing patterns — prescription behavior surveillance system, eight states, 2013. Surveill. Summ. 64, 1–14. https://doi.org/10.15585/mmwr.ss6409a1.
See, S., Ginzburg, R., 2008. Choosing a skeletal muscle relaxant. Am. Fam. Physician 78, 365–370.
Shonesy, B.C., Williams, D., Simmons, D., Dorval, E., Gitlow, S., Gustin, R.M., 2019. Screening, Brief Intervention, and Referral to Treatment in a Retail Pharmacy Setting: The Pharmacist's Role in Identifying and Addressing Risk of Substance Use Disorder. J. Addict. Med. 1. https://doi.org/10.1097/ADM.0000000000000525.
Warner, M., Chen, L.H., Makuc, D.M., Anderson, R.N., Miniño, A.M., 2011. Drug poisoning deaths in the United States, 1980–2008. NCHS Data Brief 1–8.