UNIVERSITY of MARYLAND
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Adverse outcomes associated with concurrent gabapentin, opioid, and benzodiazepine utilization: A nested case-control study

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Background

- Gabapentin and opioids are both indicated for pain management
- Benzodiazepines are often prescribed for the management of anxiety and insomnia among individuals with pain conditions
- Opioids and Benzodiazepines are known to be independently associated with respiratory depression, and gabapentin has recently been linked to similar adverse respiratory outcomes.
- Despite emerging safety concerns regarding gabapentin and the increased likelihood of co-prescriptions of gabapentin with opioids and benzodiazepines, little is known about adverse consequences associated with concurrent use of all three medication classes.

Objectives

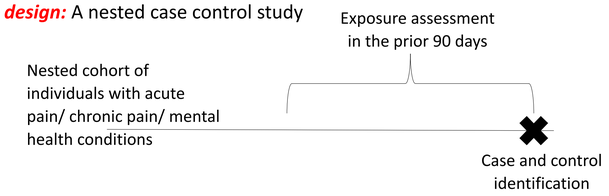
The goal of this study is to quantify the associations between concurrent therapy involving gabapentin, opioids, and benzodiazepines and public health outcomes —respiratory depression events, opioid-related overdose events

Methods

Data source: 5% random sample of 2013-2016 Chronic Conditions Data Warehouse (CCW) Medicare data

Study population: Disabled individuals with diagnoses of acute pain (AP), chronic pain (CP), or mental health (MH) conditions and who had continuous Medicare Parts A, B and D coverage in the 6-months prior to and 12-months following the cohort entry date. Cohort entry date was defined as the date of the earliest prescription fill for gabapentin, opioids, and benzodiazepines. Those with cancer diagnosis, chronic kidney disease, or receiving hospice benefits were excluded, as were individuals who had respiratory depression /opioid overdose in the pre-cohort entry period.

Study design: A nested case control study



Main outcome: Main outcomes were respiratory depression and opioid-related overdose. Cases were beneficiaries within the nested cohort with the outcome of interest and controls were those cohort without any of the outcomes of interest (in the 12-months post cohort entry).

Main independent variable: Concurrent medication utilization was assessed based on an overlap of at least one day in the days supplied of prescriptions for gabapentin (GABA), opioids (OP), and/or benzodiazepines (BZD): GABA+OP+BZD, GABA+OP, and OP only users

Statistical analysis: We utilized a disease risk score to summarize the relationship between covariates and outcome. Incident density sampling was used to match each case with up to 4 controls on: disease risk score, age, race, dual eligibility status, sex, and cohort entry year. Multivariable conditional logistic regression was used to estimate the association between outcomes and concurrent medication use

Results

Table 1. Characteristics of matched cases and controls in cohort (respiratory depression)

	Acute Pain		Chronic Pain		Mental Health	
Variables	**Cases (N=3,795)**	**Controls (N=14,730)**	**Cases (N=4,322)**	**Controls (N=16,804)**	**Cases (N=2,637)**	**Controls (N=10,199)**
Age, N (%)						
<65	2,524 (66.5)	9,869 (67)	2,839 (65.7)	11,128(66.2)	1,877 (71.2)	7,318 (71.8)
>65+	1,271 (33.5)	4,861 (33)	1,483 (34.3)	5,676 (33.8)	760 (28.8)	2,881 (28.3)
Gender, N (%)						
Females	2,352 (62)	9,181(62.3)	2,639 (61.1)	10,328(61.5)	1,743 (66.1)	6,800 (66.7)
Males	1,443(38)	5,549(37.7)	1,683(40)	6,476 (38.5)	894 (33.9)	3,399 (33.3)
Ethnicity, N (%)						
White	3,027 (79.8)	111,879(80.6)	3,458 (80)	13,562(80.7)	2,218 (84.1)	8,649 (84.8)
Black	572(15.1)	2,162 (14.7)	651(15.1)	24,80 (14.8)	309(11.7)	1,155 (11.3)
Others	196 (5.2)	689 (4.7)	213 (4.9)	762 (4.5)	110 (4.2)	395 (3.9)
Dual eligibility, N (%)	2,517 (66.3)	9,792 (66.5)	2,823 (65.3)	11,008(65.5)	1,846 (70)	7,159 (70.2)
Chronic pain, N (%)	2,960 (78)	11,357 (77.1)	----------	----------	2,471 (93.7)	9,539 (93.5)
Acute pain, N (%)	-------	--------	3,614 (83.6)	13,747(81.8)	2,219 (84.2)	8,465 (83)
Mental Health, N (%)	2,230 (58.8)	8,454 (57.4)	2,501 (57.9)	9,410 (56)	----------	----------
Substance Use disorder, N (%)	297 (7.8)	1,081 (7.3)	325 (7.5)	1,228 (7.3)	241 (9.1)	856 (8.4)
Benzodiazepines, N (%)	1,167 (30.8)	4,256 (28.)	1,341 (31)	4,957 (29.5)	1,063 (40.3)	3,908(38.3)
Gabapentin, N (%)	986 (26)	3,535 (24)	1,113 (25.8)	4,054 (24.1)	749 (28.4)	2,727 (26.7)
Opioids, N (%)	2,594 (68.4)	9,869 (67)	3,003 (69.5)	11,427 (68)	1,906 (72.3)	7,241 (71)
Number of Outpatient visits, N (%)						
None	15 (0.4)	72 (0.5)	19 (0.4)	90 (0.5)	----------	36 (0.4)
1-10	764(20.1)	3,264 (22.1)	1,013 (23.4)	315 (21.1)	324 (12.3)	2,103 (20.6)
>10	3,016 (79.5)	11,394 (77.4)	3,290 (76.1)	12,434 (74)	2,127 (80.7)	8,060 (79)
Number of Inpatient visits, N (%)						
None	2,990 (78.8)	11,912 (80.9)	3,460 (80.1)	13,779 (82)	2,045 (77.6)	8,066 (79.1)
1	563 (14.8)	2,128 (14.5)	609 (14.1)	2,178 (13)	412 (15.6)	1,508 (14.8)
>1	242 (6.4)	690 (4.7)	253 (5.9)	840 (5)	180 (6.8)	625 (6.1)

P-values for all matched case and control comparisons are >0.05
All percentages are column percentages

Table 2. Characteristics of matched cases and controls in cohort (opioid-related overdose)

	Acute Pain		Chronic Pain		Mental Health	
Variables	**Cases (N=371)**	**Controls (N=1,339**	**Cases (N= 412)**	**Controls (N=1,493)**	**Cases (N=326)**	**Controls (N=1,165)**
Age, N (%)						
<65	308(83)	1,120 (83.6)	345 (83.7)	1,254 (84)	276 (84.7)	1,003 (86.1)
>65+	63 (17)	219 (17)	67 (16.3)	5239(16)	50 (15.3)	162(13.9)
Gender, N (%)						
Females	230 (62)	842 (62.9)	259 (62.9)	1935 (62.6)	206 (63.2)	744 (63.9)
Males	141(38)	497 (37.1)	153(37.1)	558 (37.4)	120 (36.8)	421 (36.1)
Ethnicity, N (%)						
White	326 (87.9)	1,201 (89.7)	361 (87.6)	1,331(89.2)	297 (91.1)	1,085 (84.8)
Black	----------	110 (8.2)	----------	132 (8.8)	29(8.9)	80 (16.2)
Others	----------	28 (2.1)	----------	30 (2)	----------	----------
Dual eligibility, N (%)	261 (70.4)	956 (71.4)	283 (68.7)	1,046(70.1)	239 (73.3)	858 (73.7)
Chronic pain, N (%)	360 (97)	1,291 (96.4)	----------	----------	307 (94.2)	1,070 (92)
Acute pain, N (%)	----------	----------	364 (88.4)	1,290(86.4)	288 (88.3)	988 (84.8)
Mental Health , N (%)	282 (76)	951 (71)	301 (73.1)	1,054(70.5)	----------	----------
Substance Use disorder, N (%)	142(38.3)	428 (32)	155 (37.6)	507 (33.6)	133 (40.8)	419(36)
Benzodiazepines, N (%)	187 (50.4)	603(45)	209 (50.7)	684 (45.8)	181 (55.5)	593 (50.9)
Gabapentin, N (%)	131 (35.3)	409 (30.6)	139 (33.7)	435 (29.1)	107 (32.8)	333 (28.6)
Opioids, N (%)	301 (81.1)	1,053 (78.6)	335 (81.3)	1,167(78.2)	261 (80.1)	899 (77.2)
Number of Outpatient visits, N (%)						
1-10	27(7.3)	147 (11)	66 (16)	315 (21.1)	27 (8.3)	139 (11.9)
>10	321 (86.5)	1,085 (81)	345 (83.7)	1,194 (80)	278 (85.3)	944 (81)
Number of Inpatient visits, N (%)						
None	266 (71.7)	1,037 (77.5)	302 (73.3)	1,183(79.2)	230 (70.6)	868 (74.5)
1	71 (19.1)	209 (15.6)	74 (18)	224 (13.3)	64 (19.6)	196 (16.8)
>1	34 (9.2)	93 (7)	36 (8.7)	112 (7.5)	32 (9.8)	101 (8.7)

P-values for all matched case and control comparisons are >0.05
All percentages are column percentages

Table 3. Association between concurrent medication utilization and adverse outcomes

		Respiratory depression		Opioid-related Overdose	
Cohort	**Medication category**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
AP	GABA+OP+BZD	**1.62 (1.45-1.80)**	**1.35 (1.19-1.52)**	**3.51 (2.75-4.47)**	**1.43 (1.04-1.98)**
	GABA+OP	**1.23 (1.12-1.34)**	**1.10(1.03-1.18)**	**1.60 (1.23-2.08)**	1.21 (0.90-1.70)
	OP only	reference	reference	reference	reference
CP	GABA+OP+BZD	**1.56 (1.41-1.72)**	**1.24 (1.11-1.38)**	**3.24 (2.56-4.09)**	**1.47 (1.07-2.00)**
	GABA+OP	**1.22 (1.21-1.33)**	**1.06 (1.01-1.12)**	**1.63 (1.27-1.95)**	**1.23 (1.04-1.48)**
	OP only	reference	reference	reference	reference
MH	GABA+OP+BZD	**1.37 (1.22-1.54)**	**1.16 (1.02-1.32)**	**2.56 (1.99-3.28)**	**1.44 (1.04-2.00)**
	GABA+OP	**1.27 (1.13-1.42)**	0.98 (0.86-1.12)	**1.48 (1.10-2.00)**	1.29 (0.90-1.85)
	OP only	reference	reference	reference	reference

Significant findings highlighted in red
Adjusted for all matched variables in Tables 1 or 2 and the following: lung disease, diabetes, MI, heart failure, seizures, dementia, hypertension, liver disease, CVA, Muscle relaxants, pregabalin, sedatives

Conclusions

- Concurrent GABA+OP+BZD use was associated with greater than 40% and 15% increased odds of opioid-related overdose and respiratory depression across all cohorts.
- Among individuals with CP, concurrent GABA+OP was associated with significantly higher odds of both opioid-related overdose and respiratory depression.
- Given widespread incorporation of gabapentin into several pain management protocols and further, its increasing utilization among those with psychiatric conditions, the benefits, and risks of gabapentin co-prescribing with opioids and/or benzodiazepines should be weighed by clinicians in these settings

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