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EVALUATION OF SERIOUS BLEEDING SIGNALS DURING CONCOMITANT USE OF CLOPIDOGREL AND HYPNOTIC DRUGS

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Abstract

Background: In a previous drug-drug interaction (DDI) screening study intended to generate hypotheses, clopidogrel + either eszopiclone or zolpidem (vs. clopidogrel alone) were associated with serious bleeding.

Objectives: To confirm or refute these DDI signals and examine associations with other hypnotics in an independent population of United States Medicaid beneficiaries

Methods: We employed a bi-directional self-controlled case series design in eligible individuals concomitantly exposed to one of 12 hypnotics (precipitants, exposures of interest) plus either clopidogrel (the object drug) or pravastatin (the negative control object drug). The outcome was

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hospital presentation with serious bleeding. Using conditional Poisson regression, we calculated confounder-adjusted rate ratios (RRs) and 95% confidence intervals for serious bleeding during clopidogrel + precipitant use (vs. clopidogrel alone). To distinguish a DDI from a precipitant's inherent effect on bleeding, we divided effect measures by the adjusted RR for the corresponding pravastatin + precipitant pair to obtain ratios of RR (RRRs).

Results: Among 23,194 users of clopidogrel and 3,824 of pravastatin who experienced serious bleeding during an active prescription for one of these agents, confounder-adjusted RRRs for serious bleeding were 6.63 (0.39-113.01) and 0.77 (0.53-1.11) with eszopiclone and zolpidem, respectively, whereas confounder-adjusted RRRs for other hypnotics ranged from 0.18 (0.04-0.85) for triazolam to 1.79 (0.16-20.44) for zaleplon. Statistical imprecision therefore precluded us from confirming or refuting these prior signals with eszopiclone and zolpidem.

Conclusions: While we could not confirm or refute previously identified DDI signals, numerically elevated RRRs for serious bleeding with several clopidogrel + hypnotic pairs warrant further examination.

Keywords

drug interaction; hemorrhages; antiplatelet agents; hypnotics; pharmacoepidemiology

1. INTRODUCTION

Serious bleeding is one of the most concerning adverse events associated with the use of antiplatelet agents [1]. In a recent automated, high-throughput pharmacoepidemiologic drug-drug interaction (DDI) screening and hypothesis-generating study using a bi-directional self-controlled case series (SCCS) design, *Leonard et al.* examined the rate of serious bleeding for an individual receiving clopidogrel—a very widely-used antiplatelet agent and the object drug of interest—or pravastatin (i.e., negative control object drug) after initiating vs. not receiving a precipitant drug [2]. Two hypnotics—eszopiclone and zolpidem—were identified in that study as having a potentially increased risk of serious bleeding when used concomitantly with clopidogrel (ratios of rate ratios [RRRs] versus pravastatin for serious bleeding 1.99, 95% confidence interval [CI] 1.12-3.55 and 1.34, 1.11-1.62, respectively) [2]. DDIs between clopidogrel and hypnotics are not currently reported in product labeling or in commonly used DDI knowledge bases such as Lexicomp, Inc. or IBM Micromedex®, except for one between clopidogrel and trazodone [3]. With the increasing use of hypnotics in recent years [4], coupled with an aging population with high likelihood of receiving antiplatelet therapy [5], concomitant use of a commonly prescribed antiplatelet agent such as clopidogrel with a hypnotic may become more widespread. In fact, 2016 data from the United States (U.S.) Centers for Disease Control and Prevention identified >545,000 and >196,000 national office visits during which patients were concomitantly prescribed clopidogrel with zolpidem and with eszopiclone, respectively. The potential DDI signals between clopidogrel and these hypnotics thus raised concerns about patient safety and treatment outcomes. We sought to confirm or refute these signals in an independent database consisting of U.S. Medicaid beneficiaries from four states from 1999-2012, using the same bi-directional SCCS design and negative control object drug as the screening study to

minimize confounding and exposure trend bias, as well as quantitatively comparing clopidogrel findings [2].

2. MATERIAL AND METHODS

2.1. Overview

We conducted a bi-directional SCCS study for each clopidogrel + hypnotic precipitant drug pair to examine the rate of serious bleeding in individuals treated with clopidogrel (i.e., object drug) during time exposed (i.e., focal windows) vs. unexposed (i.e., referent windows) to the precipitant, in comparison to the rate of serious bleeding in individuals treated with pravastatin (i.e., negative control object drug) during focal windows vs. referent windows. Cohort identification and statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

2.2. Data source

We used 1999-2012 U.S. Medicaid claims data from four states (California, Florida, New York, and Pennsylvania), supplemented with Medicare claims (including Part D Event Files for 2006-2012) for dually enrolled individuals.

2.3. Creating study cohorts of new users of clopidogrel and pravastatin

We constructed separate study cohorts for the object drug (i.e., clopidogrel) and the negative control object drug (i.e., pravastatin). Adults (age ≥18 years) with a 183-day baseline period of continuous Medicaid enrollment and devoid of clopidogrel (or pravastatin) prescriptions were eligible. We then utilized pharmacy claim dates and days' supply values to build object drug (or negative control object drug) exposure episodes consisting of ≥1 dispensed prescription for clopidogrel (or pravastatin). We allowed a grace period between consecutive pharmacy claims for the object drug and at the end of the terminal dispensing, calculated as 20% of the days' supply of the object drug and rounded up to the nearest integer, assuming that patients achieved 80% adherence.

2.4. Defining observation and baseline periods

For each new user of clopidogrel or pravastatin meeting aforementioned inclusion criteria, object drug-specific observation periods began with initiation of the object drug and were censored at the earliest of the following: 1) lapsed of exposure to object drug (after allowing for a grace period, defined above), 2) switching to a therapeutic alternative (i.e., ticlopidine, prasugrel, or ticagrelor for clopidogrel, and another statin for pravastatin), 3) Medicaid disenrollment, 4) end of study period, or 5) death. We defined focal windows as days exposed to both object and precipitant drugs and referent windows as days exposed to the object drug only. We defined indeterminate windows as days exposed to the object drug following lapsed exposure to a precipitant (defined by the days' supply of the most recent precipitant claim) and days during which there was concomitant use of ≥2 hypnotics.

The baseline period was defined as the 183 days immediately preceding yet excluding the observation period start date. As mentioned above, we required the baseline period to be devoid of an interruption in Medicaid coverage and a dispensing for the object or negative

control object drug under study. We did not exclude from study object episodes preceded by a baseline dispensing for an alternative antiplatelet or statin, which permitted us to study second- and later-line therapies.

2.5. Defining exposure of interest and time-varying covariates

The exposure of interest was concomitant use of a hypnotic drug, defined as doxepin, estazolam, eszopiclone, flurazepam, lorazepam, quazepam, ramelteon, temazepam, trazodone, triazolam, zaleplon, or zolpidem (i.e., precipitant drugs [6]) during an active prescription for either clopidogrel (i.e., the object drug [6]) or pravastatin (i.e., the negative control object drug [6]). Exposure to hypnotics was also defined using pharmacy claims for these drugs, similar to the aforementioned definition of exposure to the object drug.

We employed a bi-directional self-controlled case series (SCCS) design, which inherently eliminates confounding by time-invariant factors within individual [7]. Additional time-varying variables that could potentially be confounders were selected through disjunctive cause criterion [8] and included exposure to drugs that may increase the risk of serious bleeding on current day or within previous 30 days, drugs that may interact with clopidogrel on current day or within previous 14 or 30 days, drugs that are gastroprotective on current day or within previous 30 days, other hypnotics used within prior 30 days, acute infection on current day or within previous 14 days, ischemic or cerebrovascular disease on current day or ever prior (i.e., during the current observation period, baseline period, or any available data preceding the baseline period), serious bleeding event ever prior, and long-term care residence on current day or within previous 30 days (Tables A.2 and A.3).

2.6. Identifying outcomes

The composite outcome of interest was serious bleeding—including gastrointestinal bleeding, nontraumatic intracranial hemorrhage, or epistaxis—ascertained by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) discharge diagnoses appearing in the principal position on an inpatient or emergency department claim (positive predictive values: 81% [9], 77-94% [10-12], and 58.8% [13], respectively) (Table A.1).

2.7. Statistical analysis

We used conditional Poisson regression to calculate confounder-adjusted rate ratios (RRs) with 95% CIs for serious bleeding occurrence during use of object drug + precipitant drugs (vs. object drug alone). To quantitatively compare clopidogrel findings to the negative control object drug, we divided the adjusted RR for each clopidogrel-precipitant pair by the adjusted RR for the corresponding pravastatin-precipitant pair to obtain the RRR and its 95% CI, adjusting for covariates [6]. This served to distinguish a potential DDI from a precipitant's inherent effect on bleeding.

Additional analyses were performed to clarify the association between exposure and outcome through stratification by mutually exclusive focal window segments of 0-15, 16-30, 31-60, 61-120, and 121-180 days since concomitant use of object and precipitant drugs. To assess for potential violation of the independent events assumption underlying the SCCS

design, we conducted a sensitivity analysis limited to subjects with only one outcome during the observation period. Additional analyses included unidirectional left (i.e., excluding observation time before the first focal window) and right censoring (i.e., excluding observation time after the first focal window) to evaluate the potential for immortal time bias and reverse causation bias potentially introduced by the bidirectional design [14]; limiting to subjects alive throughout the entire observation period; modifying the grace period length for the object drug; and increasing the clopidogrel-free baseline period from 183 to 365 days. We considered an association to be present if both the RR for the clopidogrel-hypnotic drug pair *and* the RRR for the clopidogrel-hypnotic drug pair divided by the corresponding pravastatin-hypnotic drug pair were statistically significantly elevated.

This study was approved by the Institutional Review Board of the University of Pennsylvania (protocol #827561).

3. RESULTS

We identified 23,194 users of clopidogrel and 3,824 of pravastatin who experienced serious bleeding during an active prescription for one of these agents. Individuals in the clopidogrel group had a median age of 75.5 years (interquartile range [IQR] 66.5-83.0) at the start of observation, compared to 72.1 years (IQR 62.0-80.1) in the pravastatin group (Table 1). The plurality of individuals in both groups were female, white, and resided in California. Table 2 shows the adjusted RRs for serious bleeding for each object-precipitant drug pair, as well as the RRRs for these precipitants used with clopidogrel vs. pravastatin as the negative control object drug. Quazepam was dropped from the final analysis as no pravastatin users exposed to this benzodiazepine experienced a serious bleeding event. Neither the RR for zolpidem (0.97, 95% CI 0.85-1.09), nor the RRR for zolpidem using pravastatin as the negative control object drug (0.77, 95% CI 0.53-1.11) suggested an elevated risk. The RR for eszopiclone was nonsignificantly elevated (1.61, 95% CI 0.92-2.82), while the RRR was too imprecise to provide any useful information (6.63, 95% CI 0.39-113.01). The RR for temazepam was modestly elevated (1.34, 95% CI 1.12-1.60), while the RRR that used pravastatin as a negative control object drug was attenuated and non-significant (1.24, 95% CI 0.67-2.73). No other RRRs were statistically elevated, and several of the 95% CIs were quite wide and included large values.

We observed similar results in all sensitivity analyses and did not identify an increased risk of serious bleeding with concomitant use of clopidogrel and precipitant hypnotic drugs, as shown in Tables A.4-A.6. When expanding the clopidogrel-free baseline period from 183 to 365 days or when decreasing and increasing grace periods of the object drug (i.e., assuming 90% adherence and 70% adherence, respectively), we also obtained similar findings. Additionally, when stratifying by focal window segments, we identified no statistically significant RRRs for serious bleeding.

4. DISCUSSION

Statistical imprecision precluded us from confirming or refuting prior signals of a potential interaction between zolpidem or eszopiclone and clopidogrel leading to serious bleeding [2].

Although wide CIs are present for many of our estimates, numerically elevated RRRs for serious bleeding with several other clopidogrel + hypnotic pairs warrant further examination in larger datasets.

Potential pharmacokinetic mechanisms may support previously identified signals of increased serious bleeding when clopidogrel is co-prescribed with either zolpidem or eszopiclone [2]. Clopidogrel is metabolized to its inactive metabolite primarily by the liver carboxylesterase 1 (CES1) pathway [15]. Limited data suggest that zolpidem has some inhibitory effect on hydrolase activities of p-nitrophenyl acetate by the recombinant human CES1 [16], which could result in more clopidogrel prodrug being available for conversion to its active metabolite, leading to an increased antiplatelet effect and bleeding risk. Similarly, zopiclone has been shown to have some inhibitory effect on recombinant human CES1; thus, we might expect its stereoisomer eszopiclone to have the same effect to a certain extent and also potentiate clopidogrel's antiplatelet effect by inhibiting the CES1 pathway [17]. Unfortunately, we were unable to confirm or refute an increased risk of serious bleeding when either zolpidem or eszopiclone were used concomitantly with clopidogrel in this study due to statistical imprecision.

5. CONCLUSION

Overall, while we were able to rule out an increased risk greater than 10% with concomitant use of clopidogrel and zolpidem, we could neither confirm nor refute the earlier DDI signal for serious bleeding with co-prescribed clopidogrel and eszopiclone [2] based on our findings due to statistical imprecision. Of note, the trend towards increasing serious bleeding risk observed in several other clopidogrel + hypnotic drug pairs among this study population warrants further examination in larger datasets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

[1]. Buccheri S, Capodanno D, James S, Angiolillo DJ, Bleeding after antiplatelet therapy for the treatment of acute coronary syndromes: a review of the evidence and evolving paradigms, Expert Opin Drug Saf 18(12) (2019) 1171–1189. [PubMed: 31623473]

[2]. Leonard CE, Zhou M, Brensinger CM, Bilker WB, Soprano SE, Pham Nguyen TP, Nam YH, Cohen JB, Hennessy S, Clopidogrel Drug Interactions and Serious Bleeding: Generating Real-World Evidence via Automated High-Throughput Pharmacoepidemiologic Screening, Clin Pharmacol Ther 106(5) (2019) 1067–1075. [PubMed: 31106397]

[3]. IBM Micromedex, 2020. https://www.micromedexsolutions.com/home/dispatch. (Accessed August 3, 2020).

[4]. Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB, Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care survey 1999-2010, Sleep 37(8) (2014) 1283–93. [PubMed: 25083008]

[5]. Simms AD, Batin PD, Kurian J, Durham N, Gale CP, Acute coronary syndromes: an old age problem, J Geriatr Cardiol 9(2) (2012) 192–6. [PubMed: 22934104]

[6]. Hennessy S, Leonard CE, Gagne JJ, Flory JH, Han X, Brensinger CM, Bilker WB, Pharmacoepidemiologic Methods for Studying the Health Effects of Drug-Drug Interactions, Clin Pharmacol Ther 99(1) (2016) 92–100. [PubMed: 26479278]

[7]. Petersen I, Douglas I, Whitaker H, Self controlled case series methods: an alternative to standard epidemiological study designs, BMJ 354 (2016) i4515. [PubMed: 27618829]

[8]. VanderWeele TJ, Shpitser I, A new criterion for confounder selection, Biometrics 67(4) (2011) 1406–13. [PubMed: 21627630]

[9]. Schelleman H, Bilker WB, Brensinger CM, Wan F, Yang YX, Hennessy S, Fibrate/Statin initiation in warfarin users and gastrointestinal bleeding risk, Am J Med 123(2) (2010) 151–7. [PubMed: 20103024]

[10]. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF, Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors, Med Care 43(5) (2005) 480–5. [PubMed: 15838413]

[11]. Arnason T, Wells PS, van Walraven C, Forster AJ, Accuracy of coding for possible warfarin complications in hospital discharge abstracts, Thromb Res 118(2) (2006) 253–62. [PubMed: 16081144]

[12]. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, Goldberg RJ, Gurwitz JH, A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data, Pharmacoepidemiol Drug Saf 21 Suppl 1 (2012) 100–28. [PubMed: 22262598]

[13]. Delate T, Jones AE, Clark NP, Witt DM, Assessment of the coding accuracy of warfarin-related bleeding events, Thromb Res 159 (2017) 86–90. [PubMed: 29035718]

[14]. Farrington P, Whitaker H, Ghebremichael Weldeselassie Y, Self-Controlled Case Series Studies: A Modelling Guide with R, Chapman and Hall/CRC 2018.

[15]. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, Altman RB, Klein TE, Pharmacogenomics knowledge for personalized medicine, Clin Pharmacol Ther 92(4) (2012) 414–7. [PubMed: 22992668]

[16]. Shimizu M, Fukami T, Nakajima M, Yokoi T, Screening of specific inhibitors for human carboxylesterases or arylacetamide deacetylase, Drug Metab Dispos 42(7) (2014) 1103–9. [PubMed: 24751575]

[17]. Thomsen R, Rasmussen HB, Linnet K, Consortium I, In vitro drug metabolism by human carboxylesterase 1: focus on angiotensin-converting enzyme inhibitors, Drug Metab Dispos 42(1) (2014) 126–33. [PubMed: 24141856]

Table 1.

Baseline characteristics of individuals under study who experienced at least one serious bleeding event

		Object drug	
		Clopidogrel	**Pravastatin**
Number of persons		23,194	3,824
Person-days of observation time, median per individual (IQR)		97.0 (36.0-285.0)	130.0 (49.0-364.0)
Person-days of observation time, total		5,630,601	1,069,942
Person-days exposed to a precipitant drug		1,034,742	152,035
Person-days unexposed to a precipitant drug		4,595,859	917,907
Outcome occurrences during observation time, total		19,530	3,487
Outcome occurrences during person-days exposed to a precipitant drug, total		3,546	558
Outcome occurrences during person-days unexposed to a precipitant drug, total		15,984	2,929
Demographic characteristics			
Age in years at start of observation time, median (IQR)		75.5 (66.5-83.0)	72.1 (62.0-80.1)
Female sex, n (%)		14,068 (60.7%)	2,306 (60.3%)
Race	White	11,349 (48.9%)	1,724 (45.1%)
	Black	3,783 (16.3%)	600 (15.7%)
	Hispanic/Latino	3,584 (15.5%)	612 (16.0%)
	Other/Unknown	4,478 (19.3%)	888 (23.2%)
State of residence	CA	8,540 (36.8%)	1,932 (50.5%)
	FL	5,831 (25.1%)	699 (18.3%)
	NY	6,270 (27.0%)	822 (21.5%)
	PA	2,553 (11.0%)	371 (9.7%)
Nursing home resident at start of observation time, n (%)		919 (4.0%)	65 (1.7%)
Exposure to precipitant drugs in person-days of observation time (%)			
Doxepin	unexposed	5,600,276 (99.5%)	1,063,084 (99.4%)
	exposed	20,260 (0.4%)	3,746 (0.4%)
	indeterminate	10,065 (0.2%)	3,112 (0.3%)
Estazolam	unexposed	5,626,789 (99.9%)	1,069,367 (99.9%)
	exposed	2,723 (0.0%)	445 (0.0%)

		Object drug	
		Clopidogrel	Pravastatin
	indeterminate	1,089 (0.0%)	130 (0.0%)
Eszopiclone	unexposed	5,606,359 (99.6%)	1,067,628 (99.8%)
	exposed	14,672 (0.3%)	1,438 (0.1%)
	indeterminate	9,570 (0.2%)	876 (0.1%)
Flurazepam	unexposed	5,609,149 (99.6%)	1,062,585 (99.3%)
	exposed	13,807 (0.2%)	4,882 (0.5%)
	indeterminate	7,645 (0.1%)	2,475 (0.2%)
Lorazepam	unexposed	5,374,099 (95.4%)	1,038,147 (97.0%)
	exposed	132,347 (2.4%)	19,010 (1.8%)
	indeterminate	124,155 (2.2%)	12,785 (1.2%)
Ramelteon	unexposed	5,623,881 (99.9%)	1,069,481 (100.0%)
	exposed	2,918 (0.1%)	30 (0.0%)
	indeterminate	3,802 (0.1%)	431 (0.0%)
Temazepam	unexposed	5,364,517 (95.3%)	1,040,865 (97.3%)
	exposed	183,339 (3.3%)	20,438 (1.9%)
	indeterminate	82,745 (1.5%)	8,639 (0.8%)
Trazodone	unexposed	5,430,109 (96.4%)	1,033,750 (96.6%)
	exposed	133,066 (2.4%)	24,336 (2.3%)
	indeterminate	67,426 (1.2%)	11,856 (1.1%)
Triazolam	unexposed	5,611,512 (99.7%)	1,066,288 (99.7%)
	exposed	12,309 (0.2%)	2,346 (0.2%)
	indeterminate	6,780 (0.1%)	1,308 (0.1%)
Zaleplon	unexposed	5,617,535 (99.8%)	1,066,530 (99.7%)
	exposed	7,608 (0.1%)	2,165 (0.2%)
	indeterminate	5,458 (0.1%)	1,247 (0.1%)
Zolpidem	unexposed	5,083,515 (90.3%)	989,939 (92.5%)
	exposed	397,849 (7.1%)	58,934 (5.5%)
	indeterminate	149,237 (2.7%)	21,069 (2.0%)

CA: California; FL: Florida; IQR: interquartile range; NY: New York; PA: Pennsylvania

Table 2.

Adjusted[†] rate ratios and ratios of rate ratios for serious bleeding by object-precipitant drug pair

Precipitant			**RR (95%CI) for precipitant during use of clopidogrel**	**RR (95%CI) for precipitant during use of pravastatin**	**RRRs (95%CI)**
Benzodiazepine receptor agonists	Benzodiazepine hypnotics	Estazolam	1.04 (0.18-5.91)	ND	ND
		Flurazepam	0.77 (0.38-1.53)	0.59 (0.18-2.01)	1.29 (0.32-5.23)
		Lorazepam	1.10 (0.92-1.33)	1.37 (0.82-2.28)	0.81 (0.47-1.40)
		Temazepam	**1.34** (1.12-1.60)	1.08 (0.60-1.95)	1.24 (0.67-2.31)
		Triazolam	0.84 (0.44-1.61)	**4.73** (1.15-19.52)	0.18 (0.04-0.85)
	Non-benzodiazepine z-drugs	Eszopiclone	1.61 (0.92-2.82)	0.24 (0.02-3.91)	6.63 (0.39-113.01)
		Zaleplon	1.41 (0.70-2.82)	0.79 (0.08-8.14)	1.79 (0.16-20.44)
		Zolpidem	0.97 (0.85-1.09)	1.25 (0.89-1.77)	0.77 (0.53-1.11)
Melatonin receptor agonist		Ramelteon	0.88 (0.25-3.11)	ND	ND
Tricyclic antidepressant		Doxepin	1.03 (0.53-2.00)	0.94 (0.10-8.60)	1.10 (0.11-11.01)
Serotonin Reuptake Inhibitor/Antagonist		Trazodone	1.07 (0.82-1.38)	0.93 (0.49-1.76)	1.15 (0.58-2.30)

CI: confidence interval; ND: not detectable; RR: rate ratio; RRR: ratio of rate ratios

[†]Adjusted for drugs that may increase the risk of serious bleeding on current day or within previous 30 days, drugs that may interact with clopidogrel on current day or within previous 14 or 30 days, drugs that are gastroprotective on current day or within previous 30 days, other hypnotics used within prior 30 days, acute infection on current day or within previous 14 days, ischemic or cerebrovascular disease on current day or ever prior, serious bleeding event ever prior, and long-term care residence on current day or within previous 30 days (more details in Tables A.2 and A.3)