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Changes in emergency department visits for zolpidem-attributed adverse drug reactions after FDA Drug Safety Communications

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Abstract

Purpose: To identify possible changes in U.S. emergency department (ED) visits from zolpidem-attributed adverse drug reactions (ADRs) after 2013 Food and Drug Administration (FDA) Drug Safety Communications (DSCs), which notified the public about FDA's new dosing recommendations for zolpidem.

Methods: We estimated the occurrence of ED visits from zolpidem-attributed ADRs using nationally representative, public health surveillance of medication harms (National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, 2010–2017). We estimated the number of zolpidem prescriptions using IQVIA National Prescription Audit, 2010–2017. We calculated rates of ED visits for zolpidem-attributed ADRs per 10 000 dispensed zolpidem prescriptions and identified time trends and potential inflection points using joinpoint regression. For comparison, we repeated these analyses for sedating antidepressants commonly used to treat disordered sleep (trazodone, doxepin, and mirtazapine).

Results: The best-fit regression model for rates of ED visits for zolpidem-attributed ADRs by 6-month intervals identified a single inflection point in the second half of 2014 ($P = .024$) with a 6.7% biannual decrease from 2010 to 2014 ([−13.1%, 0.3%], $P = .059$) and a 13.9% biannual increase from the second half of 2014 through 2017 ([−1.1%, 31.3%], $P = .068$). No change or inflection points were identified for rates of ED visits for sedating antidepressant-attributed ADRs.

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AUTHOR CONTRIBUTIONS

Study concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: A.I.G. and E.H.Z. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: A.I.G. and M.C.L. Administrative, technical or material support: All authors. Supervision: A.I.G., E.H.Z. and D.S.B.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. Funded solely by the U.S. Department of Health and Human Services, which had no role in study design; collection, analysis, and interpretation of data; writing the report; and decision to submit the report for publication.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Conclusions: While there was a nominal decline in the rate of ED visits for ADRs in the time period before and for 18 months after FDA's 2013 zolpidem DSCs, the decrease was not sustained, and thus questions remain concerning the long-term impact of the zolpidem DSCs on ADRs.

Keywords

adverse drug reactions; drug safety communications; drug-related side effects; emergency department visit trends; pharmacoepidemiology; prescribing trends; United States Food and Drug Administration; zolpidem

1 | INTRODUCTION

The U.S. Food and Drug Administration (FDA) issues Drug Safety Communications (DSCs)[1] to disseminate new safety information about approved drugs, alerting patients and health care professionals about new risks, or signals of new risks, so they can make informed decisions about use of the drugs.[2] Zolpidem, a commonly prescribed sedative/hypnotic insomnia drug, was the subject of DSCs in January and May 2013, as FDA recommended lowering the bedtime dose of zolpidem, due to concerns of incomplete elimination and next morning impairment; FDA also warned that patients who take zolpidem extended-release should not drive the next day.[3,4] Analysis of U.S. commercially insured persons has shown statistically significant, though clinically unremarkable, increase in low-dose and decrease in high-dose zolpidem dispensing after the DSCs.[5] Whether these intended changes have reduced harm remains unknown.[5]

To evaluate the impact of the zolpidem DSCs on patient harm, we used nationally representative public health surveillance data (a) to estimate numbers of emergency department (ED) visits due to zolpidem adverse drug reactions (ADRs) and (b) to identify possible changes in estimated prescription-based rates of ED visits for ADRs before and after the zolpidem DSCs.

2 | METHODS

2.1 | DATA SOURCES AND COLLECTION METHODS

National estimates of ED visits for zolpidem ADRs were obtained using eight years of data (1 January 2010 through 31 December 2017) from 60 hospitals participating in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project. NEISS-CADES is an active public health surveillance system based on a nationally representative, size-stratified probability sample of hospitals with at least six beds and 24-hour EDs in the United States and its territories.[6]

Trained NEISS-CADES data abstractors reviewed clinical records of every ED visit to identify clinician-diagnosed medication harms. Abstractors recorded implicated pharmaceuticals, patient demographics, intent of pharmaceutical use, narrative descriptions of the event, clinician diagnoses, laboratory testing, treatments administered, and discharge disposition. NEISS-CADES data collection and analysis has been deemed a public health surveillance activity and did not require IRB approval.[7]

National estimates of brand-name and generic zolpidem prescriptions dispensed at outpatient retail and long-term care pharmacies were obtained from the 2010–2017 IQVIA National Prescription Audit (NPA). NPA aggregates prescription data from 50 400 retail pharmacies across the United States, representing approximately 90% of all retail prescription activity, and an additional 1930 pharmacies serving long-term care facilities. NPA uses a proprietary algorithm to project national-level estimates of dispensed prescriptions.[8]

2.2 | DEFINITIONS

Zolpidem ADR cases included allergic reactions, non-allergic adverse reactions, or secondary effects of drug administration (eg, choking on a pill), which were explicitly attributed to the use of zolpidem. ED visits for ADRs involving the sedating antidepressants trazodone, doxepin, or mirtazapine were used as a comparison group; these medications are also commonly used for managing insomnia[9] (eg, 80% of trazodone prescriptions are given for insomnia)[10] and were not the subject of DSCs in 2010–2017 (unlike eszopiclone, which was subject to a DSC in 2014).[11]

2.3 | STATISTICAL ANALYSIS

NEISS-CADES cases are weighted based on inverse probability of selection, adjusted for non-response and hospital non-participation and post-stratified to account for changes in the number of U.S. ED visits each year.[6] Nationally estimated (projected) numbers and proportions of ED visits for ADRs, with corresponding 95% confidence intervals (CIs), were calculated using the SURVEYMEANS procedure in SAS 9.4 (SAS Institute). Cumulative 8-year (2010–2017) estimates and corresponding CIs were divided by 8 to calculate average annual estimates and CIs, accounting for weighting and complex sample design. Cumulative estimates less than 1200, based on fewer than 20 cases, or with coefficients of variation greater than 30% were considered statistically unstable and are not shown.

Biannual 2010–2017 prescription-based rates of ED visits for zolpidem ADRs were calculated and accompanying 95% CIs for rate estimates were calculated incorporating the variance of the numerator, ED visits for zolpidem ADRs. Because of the large sample size and high pharmacy participation rate, the variance of NPA estimates was considered negligible. The same calculations were performed for the comparator group. Using Joinpoint software (National Cancer Institute, Bethesda, Maryland),[12] piecewise (segmented) regression was employed to calculate average change in estimated 2010–2017 biannual rates of ED visits for zolpidem and comparator ADRs, and identify potential inflection points.

3 | RESULTS

Based on 644 NEISS-CADES surveillance cases, there was an annual average of 5281 estimated ED visits for zolpidem ADRs in 2010–2017 (ranging from 7309 [95% CI, 4314–10 304] to 2697 [95% CI, 1403–3990] estimated visits in 2010 and 2014, respectively), accounting for 0.5% (95% CI, 0.4%–0.5%) of estimated ED visits for ADRs from all medications (Table 1). Approximately two-thirds (67.6%; 95% CI, 61.6%–73.7%) of estimated zolpidem ADR visits were made by patients aged ≥50 years. Most estimated

zolpidem ADR visits were made by females (61.2%). Zolpidem was the only medication implicated in an estimated two-thirds (65.7%) of zolpidem ADR visits, and nearly all (95.4%) zolpidem ADR visits involved a non-allergic adverse reaction. Hospitalization was required in 25.1% of estimated zolpidem ADR visits.

Visits for ADRs involving the sedating antidepressants were similar in estimated frequency to those from zolpidem (5223 annually), but approximately half of the visits (53.7%; 95% CI, 48.7%–58.7%) involved patients aged <50 years and half (53.7%) involved females. The estimated proportion of visits that required hospitalization (24.8%) was similar to that for zolpidem; but sedating antidepressant visits involved a significantly higher proportion of allergic reactions compared to zolpidem (12.8% vs 4.0%). The annual estimates for both groups were similar when only non-allergic adverse reactions were included (Table S1).

Between 2010 and 2017, the projected number of prescriptions dispensed for zolpidem decreased by 25.8%, ranging from 41.8 million in 2010 and 42.4 million in 2012, to 31.0 million in 2017, whereas prescriptions dispensed for all comparator sedating antidepressants increased: trazodone, 20.2 million to 33.8 million; doxepin, 2.0 million to 3.0 million; and mirtazapine, 9.2 million to 13.2 million, in 2010 and 2017, respectively.

The estimated rates of ED visits per 10 000 dispensed prescriptions were similar for ADRs involving zolpidem (1.4; 95% CI, 1.0–1.7) and the sedating antidepressants (1.3; 95% CI, 1.0–1.6) during 2010–2017. The best-fit regression model of zolpidem-attributed prescription-based ED visit rates by 6-month intervals identified a single inflection point in the second half of 2014 ($P = .024$). From 2010 to 2014, the trend decreased at 6.7% biannually ([−13.1%, 0.3%], $P = .059$); and then increased at 13.9% biannually from the second half of 2014 through 2017 ([−1.1% to 31.3%], $P = .068$) (Figure 1A). No change or inflection points were identified for sedating antidepressant ED visit rates (Figure 1B).

4 | DISCUSSION

After FDA issued two zolpidem DSCs in 2013, zolpidem dispensing decreased from 42 million prescriptions in 2012 to 31 million in 2017. Some prescribers may have switched patients from this sedativehypnotic to a sedating antidepressant, as prescriptions for sedating antidepressants increased consistently from 2010 to 2017. We observed a transient, nominal decline in the estimated number and rate of zolpidem-attributed ED visits for ADRs in the United States after FDA issued two zolpidem DSCs in 2013. However, the decline in zolpidem ADR visits reversed after 2014. No changes in the rate of ED visits for ADRs attributed to sedating antidepressants were observed.

Initial decreases in the estimated numbers of ED visits for zolpidem ADRs and rates of ED visits for zolpidem ADRs are consistent with recent analyses of the impact of these two 2013 zolpidem DSCs on prescribing, which reveal a short-lived uptick in social media coverage and inconsistently communicated DSC content in traditional media, in addition to a small decrease (13%) of high-dose zolpidem dispensing soon after the DSCs.[5,13–15] The decline in zolpidem prescriptions since 2013 could be related to factors other than the DSCs, although exploring these other mechanisms is outside the scope of this report.

4.1 | Limitations

These surveillance data based on 644 cases likely underestimate the total number of zolpidem harms because only events diagnosed and treated in EDs are included. Visits involving medication errors, non-therapeutic use, and accidental ingestions by young children were not included, but these are unlikely to be affected by the DSCs. Rate calculations could have been affected by changes in representativeness of either the NEISS or IQVIA samples over time or secular trends in ED usage or pharmacy dispensing over time. The rate of ED visits due to the comparator was unchanged throughout the study period, suggesting significant surveillance artifacts are less likely. Joinpoint was used for this exploratory analysis, but with additional years of follow-up an interrupted time series analysis, accounting for complex sample design, may be able to better characterize the change in slope and level of effect after the DSCs.

5 | CONCLUSIONS

FDA disseminates emerging drug safety information via DSCs and other communications strategies under the assumption that these strategies increase health care professionals' and public awareness and ultimately decrease adverse outcomes. Because a nominal decline in the rate of ED visits for zolpidem-attributed ADRs was observed in the time period before and for 18 months after FDA's 2013 zolpidem DSCs, and because the decrease was not sustained, questions remain concerning the long-term impact of zolpidem DSCs. Future investigations of the impact of DSCs for other products are likely needed to determine if DSCs require reinforcement for sustained impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Evaluation of the impact of the U.S. FDA's Drug Safety Communications (DSCs) can support FDA as it develops, disseminates, and implements future safety communication approaches.
- FDA issued two DSCs in January and May 2013, notifying the public about the new dosing recommendations for zolpidem.
- An estimated 3000 to 7000 annual ED visits in the United States were for zolpidem-attributed adverse drug reactions (ADRs) in 2010–2017.
- Even though there was a nominal decline in the rate of ED visits for zolpidem-attributed ADRs after FDA's 2013 DSCs, the decrease was non-statistically significant and not sustained.

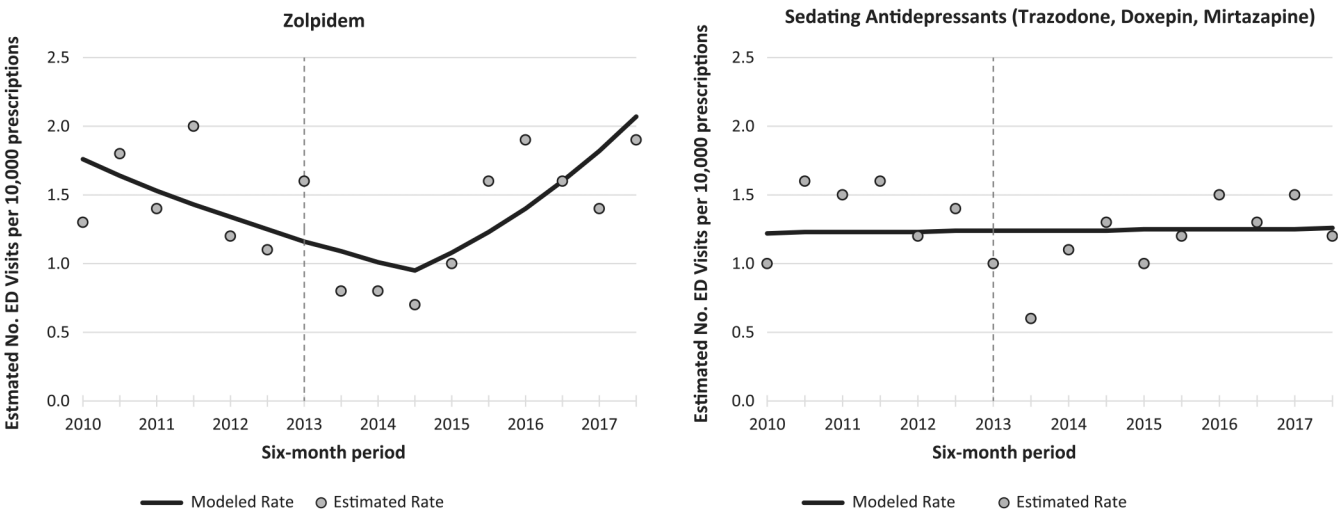

FIGURE 1.

Rates of emergency department (ED) visits for adverse drug reactions from zolpidem (Panel A) and sedating antidepressants (Panel B). Estimated biannual rates of ED visits per 10 000 prescriptions indicated by scatter plot and modeled rates indicated by a solid line. January and May 2013 Zolpidem FDA Drug Safety Communications indicated by a dashed vertical line. For zolpidem, A, the best-fit piecewise (segmented) regression model identified a single inflection point in the second half of 2014 ($P = .024$), a non-significant decrease of 6.7% biannually from 2010 to 2014 ($P = .059$) and a non-significant increase of 13.9% biannually from the second half of 2014 through 2017 ($P = .068$). For the comparator sedating antidepressants trazodone, doxepin, and mirtazapine, B, the best-fit regression model identified zero inflection points ($P = .22$ for one inflection point model and $P = .16$ for two-inflection point model). Excludes 28 cases where the zolpidem (6) or sedating antidepressant (22) was the third or fourth drug implicated, for valid comparison across years, as reporting of third and fourth implicated drugs did not begin until 2016.

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TABLE 1

Numbers of cases and national estimates of emergency department visits for adverse drug reactions from zolpidem and selected sedating antidepressants, by case characteristics—United States, 2010–2017[a]

	Zolpidem[b]			Sedating antidepressants (trazodone, mirtazapine, doxepin)[b]		
		Annualized national estimate			Annualized national estimate	
Characteristic	**Cases, No.**	**No. (95% CI)**	**% (95% CI)**	**Cases, No.**	**No. (95% CI)**	**% (95% CI)**
Age (years)						
<10	2	~	~	6	~	~
10–19	21	207 (85–328)	3.9 (1.6–6.2)	64	429 (284–574)	8.2 (5.8–10.6)
20–34	67	602 (370–835)	11.4 (7.8–15.0)	134	1167 (793–1540)	22.3 (18.5–26.2)
35–49	114	869 (609–1129)	16.5 (13.2–19.7)	140	1193 (902–1484)	22.8 (19.6–26.1)
50–64	175	1502 (1089–1916)	28.4 (25.0–31.9)	169	1356 (976–1737)	26.0 (22.5–29.5)
65–79	159	1217 (852–1583)	23.0 (19.0–27.1)	69	647 (391–904)	12.4 (8.8–16.0)
≥80	106	852 (513–1191)	16.1 (12.1–20.2)	61	413 (208–618)	7.9 (4.7–11.1)
Sex						
Female	387	3233 (2412–4054)	61.2 (57.1–65.3)	347	2807 (1992–3621)	53.7 (48.9–58.6)
Male	257	2048 (1501–2595)	38.8 (34.7–42.9)	296	2417 (1882–2951)	46.3 (41.4–51.1)
Number of implicated medications						
One	431	3470 (2615–4325)	65.7 (60.4–71.0)	370	2919 (2237–3600)	55.9 (50.6–61.2)
Two or more	213	1811 (1251–2371)	34.3 (29.0–39.6)	273	2304 (1615–2994)	44.1 (38.8–49.4)
Adverse reaction type[c]						
Non-allergic adverse reaction	619	5038 (3775–6300)	95.4 (93.2–97.6)	554	4549 (3410–5688)	87.1 (83.6–90.5)
Allergic reaction	20	209 (102–315)	4.0 (2.0–5.9)	87	668 (445–892)	12.8 (9.4–16.2)
Discharge disposition						
Hospitalized[d]	180	1327 (755–1899)	25.1 (17.8–32.4)	162	1293 (851–1736)	24.8 (19.7–29.8)
Not hospitalized	464	3955 (3022–4887)	74.9 (67.6–82.2)	481	3930 (2990–4870)	75.2 (70.2–80.3)
Total	644	5281 (3987–6575)	100	643	5223 (3961–6485)	100

[a]Case counts and estimates are from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC. Cumulative estimates less than 1200, based on fewer than 20 cases, or with coefficients of variation greater than 30% are considered statistically unstable and are not shown (~).

[b]Excludes emergency department visits involving medication errors, accidental ingestions by children <11 years old, and nonmedical use (self-harm, abuse, use not as directed, and use with unclear intent).

[c] Not shown: seven cases of emergency department visits for pill-induced dysphagia or aspiration (n = 5 zolpidem cases; n = 2 sedating antidepressant cases).

[d] Includes inpatient admissions, observation admissions, and transfers to other hospitals.

Abbreviation: CI, confidence interval.