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ORIGINAL RESEARCH ARTICLE

Adverse Event Reporting Patterns of Newly Approved Drugs in the USA in 2006: An Analysis of FDA Adverse Event Reporting System Data

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Abstract
Background The Weber effect states that adverse event (AE) reporting tends to increase in the first 2 years after a new drug is placed onto the market, peaks at the end of the second year, and then declines. However, since the Weber effect was originally described, there has been improvement in the communication of safety information and new policies regarding the reporting of AEs by healthcare professionals and consumers, prompting reassessment of the existence of the Weber effect in the current AE reporting scenario.
Objectives To determine the AE reporting patterns for new molecular entity (NME) drugs and biologics approved in 2006 and to examine these patterns for the existence of the Weber effect.
Methods Publicly available FDA Adverse Event Reporting System data were used to assess the AE reporting patterns for a 5-year period from the drug's approval date. The total number of annual reports from all sources, based on the report date, was plotted against time (in years).
Results In the period from 2006 to 2011, a total of 91,187 AE reports were submitted for 19 NMEs approved in 2006. The highest number of AE reports were submitted for varenicline tartrate ($N = 47{,}158$) and the lowest number for anidulafungin ($N = 161$). Anidulafungin was reported to have the highest proportion of death reports (36 %) and varenicline tartrate the lowest proportion (1.7 %). The classic Weber pattern was not observed for any of the 19 NMEs approved in 2006. While there was no one predominant pattern of AE report volume, we grouped the drugs into four general categories; the majority of drugs had either a continued increase in reports (Category A 31.6 %) or an N-pattern with reporting reaching an initial peak in year 2 or 3, declining and then beginning to climb again (Category B 42.1 %).
Conclusions and relevance There have been numerous changes in AE reporting, particularly a huge increase in overall annual report volume, since the Weber effect was first reported. Our results suggest that a Weber-type reporting pattern should not be assumed in the design or interpretation of analyses based on AE reports.

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1 Introduction

Post-marketing adverse event (AE) reporting trends are used by regulators and drug manufacturers to design and interpret drug safety studies based on AE reports in the context of assessing the evolving risk-benefit profile of a drug. When doing so, AE reporting for drugs, in the years immediately following approval, is often assumed to follow a particular pattern known as the 'Weber effect'. The Weber effect refers to a pattern of AE reporting with an increase in volume in the first 2 years after a new drug is placed onto the market, peaking in the second year, and then declining. This reporting phenomenon was first described by JCP Weber in 1984 when examining AE reporting patterns for seven non-steroidal anti-inflammatory drugs (NSAIDs) during their first 5 years of marketing in the UK [1].

Over the years, investigators have examined AE reporting trends in the US FDA Adverse Event Reporting System (FAERS) database for NSAIDs and other drug classes. Hartnell et al. [2] successfully replicated the Weber effect among AE reports for five NSAIDs, but in a similar study conducted by Wallenstein and Fife, only three of five NSAIDs demonstrated reporting patterns consistent with the Weber effect [3]. More recently, a study by McAdams et al. examined reporting trends among four angiotensin II receptor blocker medications. Not only did the authors fail to find reporting patterns consistent with the Weber effect for any of the drugs studied, but there was little consistency in reporting patterns across the medications [4]. Similar observation was found in a study of selective serotonin reuptake inhibitors [5]. Not only has AE reporting changed considerably since these studies were conducted, but each study was limited to a small number of drugs within a single therapeutic area. As a result, these studies do not provide enough evidence to support the existence of the Weber effect in the current US FAERS.

In recent years, AE reporting has dramatically increased [6]. The US FDA now receives approximately one and a half million AE reports annually. Concurrently with that rise, rapid employment of new technologies and the FDA's adoption of a transparency policy have accelerated the communication of safety information, which has had a large and inconsistent influence on AE reporting, particularly by the public or consumers. Given the rapid increase in overall reporting of AEs in the past decade and the significant impact of publicity on drug (and class)-specific reporting, can it be assumed that the AE reporting for a newly approved drug will follow a Weber-type pattern? Assuming the existence of the Weber effect has influenced the selection of comparator drugs (and time periods) in calculating reporting rates that may potentially lead to faulty interpretation of AE data [7, 8]. Therefore, we sought to examine the contemporary FAERS database to examine reporting patterns for the NME drugs and biologics approved by the FDA in 2006.

2 Methods

This study is based on all AE reports received by the FDA from January 1, 2006 onwards and released in the publicly available version of the FAERS database. We focused on the AE reporting patterns of all the NME drugs approved in 2006 for a 5-year period immediately following their approval for marketing in the USA. NME (or innovator) drugs were chosen because, as they are the first in their class, their AE patterns would not be influenced by the safety experience or ongoing safety concerns with prior drugs within the same class. Drugs with very low-volume reporting (less than 10 reports in the month) and newly approved drug combinations in which the active ingredient existed in other previous formulations were excluded.

Because these drugs were approved over the course of the year, annual counts of AE reports were determined for each drug beginning at its approval date. All reports with FDA receipt dates (report date) from the drug approval date through the fourth consecutive quarter were accumulated into the year 1 counts. This was repeated to calculate the number of reports received annually. Follow-up reports were not counted. While it is possible that the FDA may have received duplicate reports of the same AE (e.g., if reported by multiple sources and/or through multiple channels), no attempt was made to identify or exclude duplicate reports.

We analyzed the overall AE reporting trend for all drugs from 2006 to 2011 and the reporting pattern for all NME drugs approved during 2006, over their first 5 years on the market. Noncumulative counts of annual AE reports were plotted against time (in years from approval) based on the report date. Drugs were categorized based on the pattern of reporting over the 5-year period, regardless of the absolute report volume. AE reports were also described by the distribution of report and patient demographic characteristics including the report type (direct and expedited), and whether the patient died (death as an outcome). Data were analyzed using QScan-FDA (DrugLogic Inc., Reston, VA, USA).

3 Results

There were 22 NME drugs approved in 2006 (Table 1) [9]. Three drugs (avobenzone, ecamsule, and octocrylene, Kunecatechins, and a combination of Bismuth Biskalcitrate, metronidazole, and tetracycline hydrochloride) were excluded based on low-volume reporting and being part of a combination with drugs approved previously. The drugs included in the study span a variety of therapeutic areas.

In the period from 2006 to 2011, a total of 2,202,676 AE reports were submitted to the FDA for all marketed drugs and biologics, and a consistent annual increase was observed in the overall AE reporting over the study period (Fig. 1). For the 19 NME drugs included in this study, 91,187 AE reports were submitted to the FDA within their first 5 years of marketing in the USA (Table 1).

Among the drugs in this study, the highest number of AE reports were submitted for varenicline tartrate ($N = 47{,}298$) and the lowest number for anidulafungin ($N = 164$). Table 2 provides a descriptive summary of the AE reports by drug based on the total number of reports, report type, and death (reported as a patient outcome). In our study, 11 of the drugs had expedited reporting rates

Table 1 New molecular entity drugs approved in 2006 included in the study

Generic name	Indication	Date of approval	Review classification	Route of administration
Alglucosidase alfa	Pompe disease (glycogen storage disease type II)	4/28/06	BLA	IV
Anidulafungin	*Candida* fungal infections	2/17/06	S	IV
Ciclesonide	Seasonal and perennial allergic rhinitis	10/20/06	S	Nasal spray/intranasal
Darunavir ethanolate	HIV-1 infections	6/23/06	P	PO
Dasatinib	Imatinib-resistant chronic myeloid leukemia	6/28/06	P, O	PO
Decitabine	Myelodysplastic syndrome	5/2/06	S, O	IV
Idursulfase	Enzyme replacement therapy for patients with Hunter syndrome	7/24/06	BLA	IV
Lubiprostone	Chronic idiopathic constipation	1/31/06	S	PO
Paliperidone	Schizophrenia	12/19/06	S	PO
Panitumumab	Treatment of metastatic carcinoma of the colon or rectum	9/27/06	BLA	IV
Posaconazole	Fungal infections	9/15/06	P	PO
Ranibizumab	Neovascular (wet) age-related macular degeneration	6/30/06	BLA	IO
Ranolazine	Chronic angina	1/27/06	S	PO
Rasagiline mesylate	Idiopathic Parkinson's disease	5/16/06	S	PO
Sitagliptin phosphate	Type II diabetes mellitus	10/16/06	S	PO
Sunitinib malate	Gastrointestinal stromal tumor, renal cell carcinoma, pancreatic neuroendocrine tumor	1/26/06	P	PO
Telbivudine	Hepatitis B virus	10/25/06	S	PO
Varenicline tartrate	Smoking cessation	5/10/06	P	PO
Vorinostat	Progressive, persistent, or recurrent cutaneous T-cell lymphoma	10/6/06	P, O	PO

S standard review drug, *P* priority review drug, *O* orphan drug, *BLA* biologic license applications, *IV* intravenous, *PO* per oral, *IO* intraocular

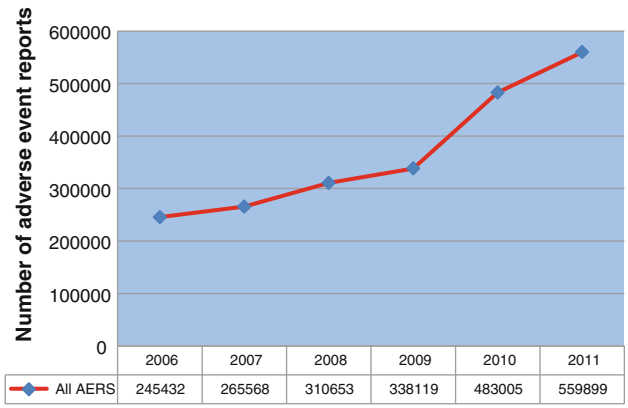

Fig. 1 Overall adverse event reporting trend for all marketed drugs from 2006 to 2011

greater than 80 %. Expedited reports are the reports of unexpected and serious AEs that manufacturers (sponsors) are required to report to the FDA within 15 calendar days. Direct reports come to the FDA by the health professionals, consumers, and sources other than the drug's manufacturer. In our study, the proportion of direct reports was in the range of 0.8 % for alglucosidase alfa to 15.3 % for decitabine. Anidulafungin was reported to have the highest proportion of death reports (36 %) and varenicline tartrate the lowest proportion of death reports (1.7 %).

Based on the resulting reporting patterns, the drugs were grouped into four broad categories: category A included those drugs that had continuously increasing numbers of AE reports over the 5-year period; category B drugs demonstrated an N-pattern of reporting (increasing to a peak in reports [in year 2 or 3], followed by a decline and then subsequently increasing again); category C drugs reached a plateau in reporting within the first several years, before report volume began to increase again; and category D included all remaining drugs (no common reporting pattern). Figures 2, 3, 4, 5 illustrate the reporting patterns for the drugs included in the study. Some drugs ($N = 6$, 31.6 %) showed a continuous increase in AE reports during the 5 years following FDA approval (category A). These drugs included anidulafungin, ciclesonide, darunavir, lubiprostone, sunitinib, and vorinostat. Eight drugs (42.1 %) that showed an initial rise in report volume after approval, followed by a decline before AE report volume began to increase again (Category B). Among the drugs in Category B, alglucosidase alfa, decitabine, paliperidone,

Table 2 Descriptive results for the 19 new molecular entity drugs approved in 2006

New molecular entity	Total number of reports *N*	Outcome reported as death *N* (%)	Report type *N* (%)	
			Direct	Expedited
Alglucosidase alfa	646	212 (32.8)	5 (0.8)	578 (89.5)
Anidulafungin	164	59 (36.0)	8 (4.9)	136 (82.9)
Ciclesonide	511	21 (4.1)	29 (5.7)	405 (79.3)
Darunavir ethanolate	2,275	277 (12.2)	47 (2.1)	1,936 (85.1)
Dasatinib	2,088	401 (19.2)	268 (12.8)	1,258 (60.3)
Decitabine	700	204 (29.1)	107 (15.3)	493 (70.4)
Idursulfase	292	56 (19.2)	4 (1.4)	288 (98.6)
Lubiprostone	742	27 (3.6)	108 (14.6)	499 (67.3)
Paliperidone	4,861	184 (3.8)	175 (3.6)	4,328 (89.0)
Panitumumab	1,821	373 (20.5)	77 (4.2)	1,527 (83.9)
Posaconazole	669	199 (29.8)	34 (5.1)	569 (85.1)
Ranibizumab	4,371	714 (16.3)	116 (2.6)	3,996 (91.4)
Ranolazine	910	82 (9.0)	79 (8.7)	406 (44.6)
Rasagiline mesylate	718	31 (4.3)	25 (3.5)	394 (54.9)
Sitagliptin phosphate	13,475	453 (3.4)	474 (3.5)	4,765 (35.4)
Sunitinib malate	8,759	2,494 (28.5)	355 (4.1)	7,490 (85.5)
Telbivudine	314	33 (10.5)	2 (0.6)	300 (95.5)
Varenicline tartrate	47,298	800 (1.7)	3,766 (8.0)	14,228 (30.1)
Vorinostat	573	128 (22.3)	75 (13.1)	442 (77.1)

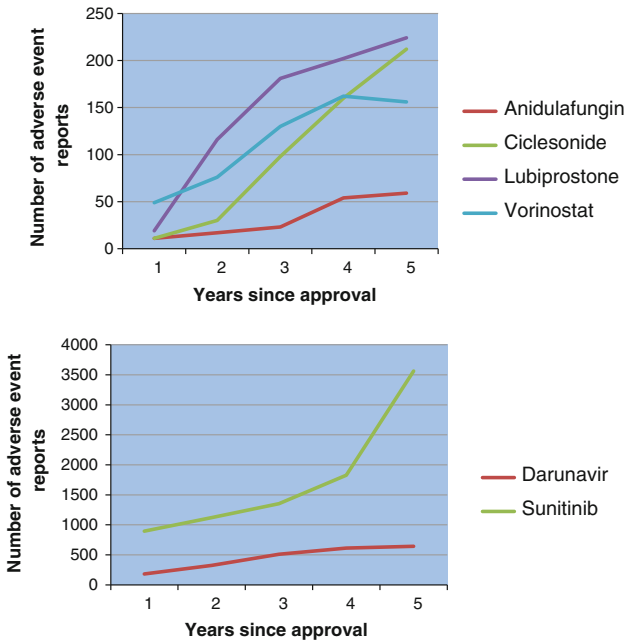

Fig. 2 Adverse event reporting trend for drugs in Category A ($N = 6$)

ranolazine, and varenicline had a peak in reporting in the second year post-approval, while dasatinib, posaconazole, and rasagiline peaked in the third year. Two drugs were included in category C, which was defined by an initial rise in reporting, which then plateaued for 2 or more years before report volume began to increase again. The drugs in this category included ranibizumab and panitumumab. Panitumumab did not have a distinct increase; the number of reports was relatively constant in the first 4 years post-approval, but report volume dramatically rose from the fourth to the fifth year. The remaining drugs, idursulfase, sitagliptin, and telbivudine, exhibited unique AE reporting profiles (Category D, miscellaneous). Idursulfase had a peak in the fourth year, with a drop in the number of reports in the fifth year. AE report volume for telbivudine increased from the first to the second year of marketing, remained constant (plateaued) over the next 2 years, and then declined in the fifth year.

Five drugs (alglucosidase alfa, sitagliptin, sunitinib, telbivudine, and varenicline) approved in 2006 were required to have a Risk Evaluation and Mitigation Strategy (REMS) in the later years [10]. Sitagliptin, telbivudine, and sunitinib were relieved from the REMS requirement after 2011. We found that drugs having a REMS did not have a unique pattern as compared with drugs that did not have a REMS. Alglucosidase alfa and varenicline have reporting pattern B, sunitinib has reporting pattern A, and sitagliptin and telbivudine have reporting pattern D. Alglucosidase alfa, idursulfase, panitumumab, and ranibizumab are all biologics. Our study did not find any consistency in the reporting patterns for these biologics. Of 19 drugs, 12 drugs

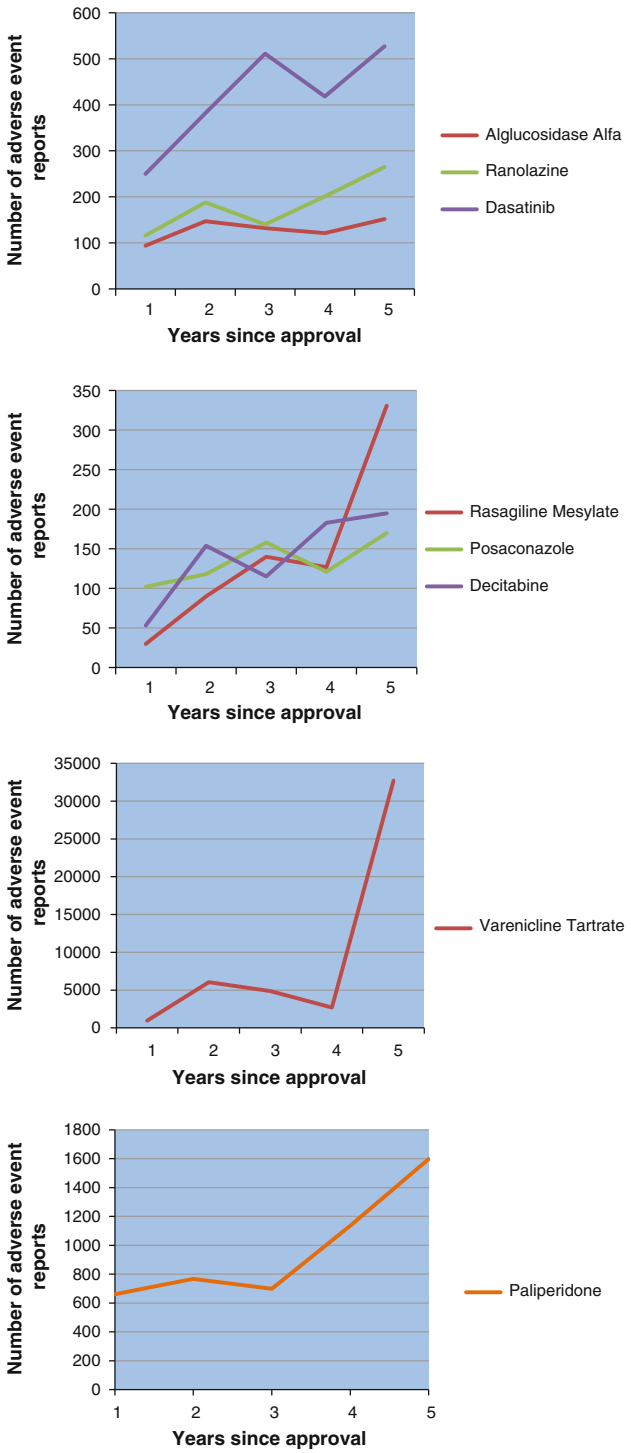

Fig. 3 Adverse event reporting trend for drugs in Category B ($N = 8$)

are administered orally, and 7 other drugs are administered by a non-oral (intravenous, intranasal, or intraocular) route of administration. No consistency was observed in the AE reporting patterns according to route of administration.

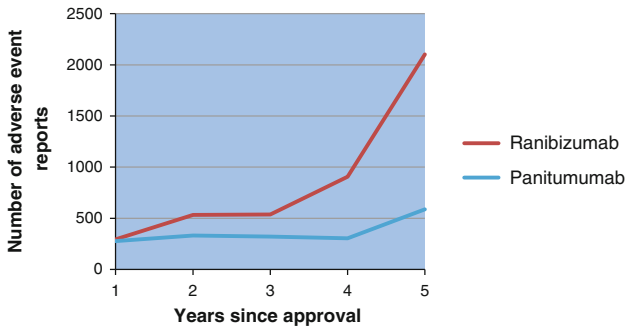

Fig. 4 Adverse event reporting trend for drugs in Category C ($N = 2$)

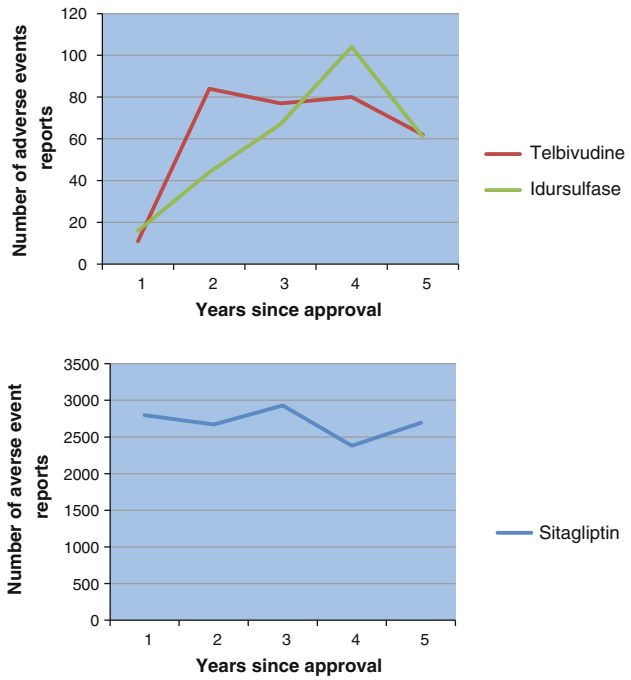

Fig. 5 Adverse event reporting trend for drugs in Category D ($N = 3$)

4 Discussion

Since the concept of the Weber effect, in which physician interest and reporting of newly observed AEs was highest during the first couple of years a drug was on the market, was introduced more than two decades ago in the UK, the existence and applicability of the Weber effect in the contemporary US FAERS has been questioned [11]. In addition to an exponential increase in report volume, particularly among non-healthcare professionals, the AE reporting requirements and coding of adverse reactions have changed in the US and UK since the 1980s. Safety information is available more rapidly to an expanded audience, with increased transparency and rapid dissemination of safety issues being investigated by the FDA, and

the use of the Internet and social media to rapidly disseminate safety information. Not only was a Weber-type AE pattern not demonstrated among recently approved drugs, there was no distinct AE reporting pattern following drug approval in the USA [2, 3].

The results of our study do not support the existence of the Weber effect in contemporary AE reporting in the USA, on the contrary, no one pattern of AE reporting predominated. All NMEs approved in 2006 had an AE report volume rise during the first year or two following approval (as would be expected because the baseline would be at or near zero prior to approval). Following this initial rise from the origin, AE reporting during those first 5 years of marketing diverged into four key patterns: (A) a continuous increase in reports or an interruption in the increase characterized by (B) a brief decline, (C) a plateau before the increase in AE report resumed, or (D) no specific pattern. A statistical test was not used to group drugs into these four patterns, because the objective of this study was to observe the existence of a distinct peak in AE reporting in the second year followed by a continuous decline, and not to show if one group differs from the other based on reporting.

In previous studies examining the Weber effect, the rise of AE reporting in the second year of postmarketing was attributed by study authors to the increase in the sale of drugs, which were used by a more diverse group of people following approval. The number of AE reports then was expected to decline, regardless of any increase in prescription volume, as physicians were less motivated to report AEs because of their familiarity with the drug and its AE profile [2, 3]. McAdams et al. calculated AE report volume as a function of drug use by prescription data from US retail pharmacies. They observed that this AE reporting rate peaked at the end of the first year and declined thereafter, approximating a Weber-type pattern, although they did not observe the Weber effect in AE report volume [4]. While it would seem obvious that AE reporting would be high in proportion to sales when sales and reports both begin at or near zero (creating an initial upward slope in the AE reporting rate) followed by a period in which sales increase disproportionally compared with AE reports (leading to downward slope of the curve), Wallenstein and Fife did not observe a Weber-type pattern among four NSAIDs when plotting AE reporting rates using prescriptions as a denominator [3]. Here, we reported AE reporting patterns, which are raw frequencies or counts of case reports, and not AE reporting rates, which would be calculated as a function of estimated sales or use.

According to Weiss et al. [6], in recent years, there has been a tremendous rise in the AE reporting to the FDA. Weiss et al. observed that there was an annual increase of 11.3 % in AE volume reporting from 2000 to 2010. This overall increase of AE reporting very likely influences the reporting pattern of each individual drug. Driven by the rise in AE reports during the past decade, once AE reporting stabilizes for a newly approved drug, contrary to what would be expected based on the Weber effect, the new expected baseline or underlying pattern would be that of increasing AE report volume. Indeed, this was observed in this study during the first 5 years of marketing for the majority of drugs. However, data from the later years will be required to ascertain if the AE reporting continues to rise over time.

Factors such as publicity, regulatory actions, REMS, a new indication or change in the formulation or marketing strategy can affect AE reporting, which can contribute to the diversity of the reporting patterns that we have observed. Improvement in technology and involvement of media has led to more accessible health information and increased awareness among the public regarding reporting of AEs. Wallenstein and Fife also observed the increase in drug publicity before the second peak of the AE reporting for NSAIDs [3]. Regulatory actions by the FDA can also lead to changes in the AE reporting pattern. In the case of varenicline, the FDA required Pfizer to resubmit a large number of AE reports they had received for varenicline (from 2007 to 2010) in a manner that caused a large spike in reports in the FAERS database (Fig. 3) [12]. Approval of new indications [4, 5] or a change in the formulation [13] has been shown to increase the reporting of AEs. In our study, ranibizumab gained a new indication in June 2010 (the fourth year after approval) for macular edema following retinal vein occlusion [14]. There was an increase in the AE reports in the fifth year for this drug (Fig. 4), which may have been to some extent attributed to this new indication. Similarly, increases in AE reporting temporally associated with the marketing of a new formulation or a new indication were observed for some other drugs such as anidulafungin, ciclesonide, and dasatinib, but not for drugs such as decitabine, lubiprostone, paliperidone, and ranolazine. Hartnell et al. [5] also observed that marketing strategies of the drug manufacturers could affect the reporting patterns of selective serotonin reuptake inhibitors. Our study did not address this observation and could be addressed by future studies.

Studies have been published that compare AE reporting rates between drug classes and interpret these differences without fully considering the implications of reporting patterns on absolute and relative reporting rates [8, 15]. AE reporting for each drug is differentially affected by various reporting factors. Because the AE reporting does not always follow a set Weber effect pattern, conclusions regarding safety profiles of the drugs based on a comparison of drug AE reporting rates may be misleading.

5 Conclusion

This study did not observe the typical 'Weber' reporting pattern for any of the NMEs approved in 2006, but instead found a number of general reporting patterns among which two predominate: (1) continually increasing reporting and (2) an initial peak or plateau in reporting in years 2–3, before continuing to rise. Because AE reporting is clearly influenced by factors other than time since approval, differences in reporting of particular AEs across drugs cannot be presumed to reflect a true difference in AEs. Interpreting studies that compare AE reporting (or estimated reporting rates) across drugs, within or between classes should be undertaken with the greatest of caution, especially before taking any regulatory action.

Author's contributions Pankdeep Chhabra and Xing Chen: study design, data analysis, interpretation of data, and manuscript preparation; they had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Sheila Weiss: study design, interpretation of data, and manuscript preparation. Qscan-FDA was provided for this research through an in-kind donation from Druglogic, Inc. to the Center for Drug Safety, University of Maryland School of Pharmacy.

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Sheila Weiss: Consulted for directly, served on the advisory board, served on a grant or contract (as a principal investigator or as an investigator), consulted with their legal representatives as an expert, and/or worked as an employee in the last 3 years: University of Maryland, Johns Hopkins School of Public Health, Georgetown University, National Cancer Institute, DrugLogic Inc., United Healthcare/Optum, Pfizer, Bayer, Esai, Novartis, Amgen, Biogen Idec, and Roche.

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