Drug Saf (2015) 38:1169–1178
DOI 10.1007/s40264-015-0340-6

SHORT COMMUNICATION

Association of Attorney Advertising and FDA Action with Prescription Claims: A Time Series Segmented Regression Analysis

Elizabeth C. Tippett[1] · **Brian K. Chen**[2]

Published online: 18 September 2015
© Springer International Publishing Switzerland 2015

Abstract

Introduction Attorneys sponsor television advertisements that include repeated warnings about adverse drug events to solicit consumers for lawsuits against drug manufacturers. The relationship between such advertising, safety actions by the US Food and Drug Administration (FDA), and healthcare use is unknown.

Objectives To investigate the relationship between attorney advertising, FDA actions, and prescription drug claims.

Methods The study examined total users per month and prescription rates for seven drugs with substantial attorney advertising volume and FDA or other safety interventions during 2009. Segmented regression analysis was used to detect pre-intervention trends, post-intervention level changes, and changes in post-intervention trends relative to the pre-intervention trends in the use of these seven drugs, using advertising volume, media hits, and the number of Medicare enrollees as covariates. Data for these variables were obtained from the Center for Medicare and Medicaid Services, Kantar Media, and LexisNexis.

Results Several types of safety actions were associated with reductions in drug users and/or prescription rates, particularly for fentanyl, varenicline, and paroxetine. In most cases, attorney advertising volume rose in conjunction with major safety actions. Attorney advertising volume was positively correlated with prescription rates in five of seven drugs, likely because advertising volume began rising before safety actions, when prescription rates were still increasing. On the other hand, attorney advertising had mixed associations with the number of users per month.

Conclusion Regulatory and safety actions likely reduced the number of users and/or prescription rates for some drugs. Attorneys may have strategically chosen to begin advertising adverse drug events prior to major safety actions, but we found little evidence that attorney advertising reduced drug use. Further research is needed to better understand how consumers and physicians respond to attorney advertising.

Key Points

American consumers and physicians are exposed to multiple sources of drug safety information, including regulators, the media, and attorney advertising, but the effect of these various sources of information on prescription decisions is not well understood.

Attorneys appear strategic in their advertising purchasing decisions, and begin placing advertisements on adverse drug risks before major safety actions, when prescription rates are generally still increasing.

However, we find no evidence that attorney advertisements serve to disseminate drug safety information in a way that reduces drug prescription rates.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-015-0340-6) contains supplementary material, which is available to authorized users.

✉ Elizabeth C. Tippett
tippett@uoregon.edu

[1] School of Law, University of Oregon, 1221 University of Oregon, Eugene, OR 97405, USA

[2] Arnold School of Public Health, University of South Carolina, Columbia, SC, USA

1 Introduction

Attorneys sponsor television advertisements soliciting consumers for lawsuits against drug manufacturers. The advertisements typically include repeated warnings about adverse drug events [1]. Because most drugs in attorney advertisements have not been recalled [1], the advertisements have the potential to influence consumer and provider decisions regarding whether to prescribe or refill a drug. The effect of such advertisements is unknown.

We used Medicare prescription claims to examine the effect of attorney advertising and co-occurring US Food and Drug Administration (FDA) actions on prescription behavior. Second, we examined the association between FDA action and attorney advertising volume.

Figure 1 illustrates a conceptual model of how various sources of drug risk information may influence consumer and physician decisions. It also illustrates the relationships among these sources of information. The dotted lines represent relationships examined in our regressions. Of the multiple sources of drug safety information, we hypothesize that information from the FDA is perceived as the most credible source and attorney advertising is the least credible. Consistent with existing literature [2], we predict that regulatory or other safety action will decrease prescription fills. By contrast, we hypothesize that physicians and consumers disregard risk-related information from attorneys.

2 Methods

2.1 Study Design

2.1.1 Advertising Data

Television advertising data was obtained from Kantar Media for December 2008 to December 2009. The dataset included national network and cable advertisements, and advertisements targeted to the Boston and Atlanta media markets. The dataset was limited to attorney-sponsored advertising identified by Kantar as related to drugs or medical devices.

To account for audience size, national network and cable advertisements were weighted proportional to the average cost of network and cable programming in the sample. Locally targeted advertisements were weighted as network advertising because they were typically broadcast on the local affiliates of network stations (for example, the local ABC station). A single weighted unit of advertising refers to one broadcast of a network advertisement, and 2.5 broadcasts of an advertisement on cable television.

Boston and Atlanta were selected based on their size [3], as well as their geographic and demographic differences.

2.1.2 Prescription Data

The prescription data consisted of Medicare prescription drug claims for specified drugs by any beneficiary residing in the Boston and Atlanta media markets. The data were obtained from the Centers for Medicare and Medicaid Services (CMS), following institutional review board approval by the University of Oregon and a CMS privacy review. The dataset was limited to retail, rather than hospital or mail-in pharmacies to focus the analysis on decisions more likely to be time sensitive and consumer driven.

Drugs were initially screened for inclusion based upon advertising volume. Drugs with fewer than 50 units of advertising were excluded. Drugs featured in advertisements broadcast predominantly or exclusively at the end of the sample period were also excluded. Several drugs were excluded, such as drugs not commonly prescribed to the elderly, over-the-counter drugs, drugs rarely prescribed outside of a hospital setting, recalled drugs, and those subject to FDA prescribing restrictions (e.g., rosiglitazone).

The drugs selected for the study were:

- metoclopramide (Reglan), a gut motility agent;
- fentanyl transdermal patch (Duragesic), an opioid analgesic;
- exenatide (Byetta), a drug for improving glycemic control in type 2 diabetes mellitus patients;
- varenicline (Chantix), a smoking cessation drug;
- pregabalin (Lyrica), an anticonvulsant;
- quetiapine (Seroquel), an antipsychotic; and
- paroxetine (Paxil), an antidepressant.

Several different manufacturers produce the fentanyl transdermal patch, some of which issued recalls in 2008 and 2009 owing to manufacturing defects. Patches produced by any manufacturer subject to a recall in 2008 or 2009 were excluded from the analysis. Patches from other manufacturers were included, but we included the "recall" indicator variable to identify the spillover effect of the recall and related attorney advertising on the remaining manufacturers. After our exclusion criteria described above, we included in the analytical dataset 85,043 Medicare beneficiaries who were prescribed at least one of the seven drugs in 2009.

2.1.3 Media Variable

The media variable was generated as the number of media items referencing the applicable drug using a search for US-based news on LexisNexis. The database includes

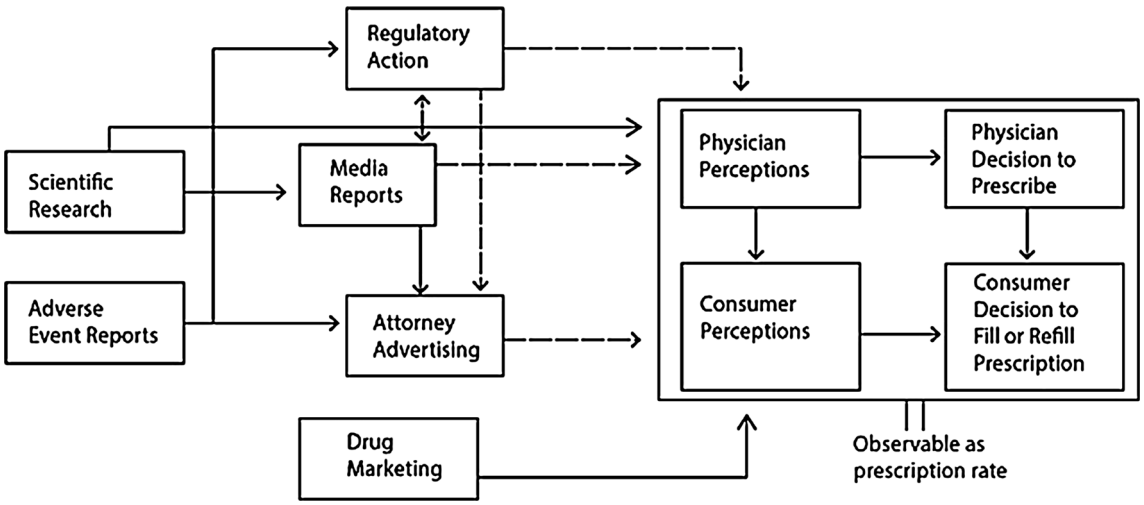

Fig. 1 Conceptual model of how various sources of drug risk information may influence consumer and physician decisions

hundreds of newswires, newspapers, web-based publications, magazines, and television news transcripts.

2.1.4 Regulatory and Safety Interventions

The regulatory variables were generated by reviewing FDA safety notices, press releases, and letters to the manufacturer posted online [4]. The date of the FDA regulatory action corresponded to the date of the safety notice or letter, or dates referenced in subsequent correspondence. Four regulatory variables were used: (1) FDA approval of a drug relabeling; (2) FDA notification to a manufacturer that a drug will be placed on Risk Evaluation and Mitigation Strategy status ("REMS demand"), or (3) subsequent approval of such REMS ("REMS approval"). (4) An additional safety action variable ("Recall") was created to reflect the 2009 recall of certain fentanyl patches [5]. We captured only safety actions that occurred in 2009. The date of the REMS demand for quetiapine could not be ascertained.

2.1.5 Number of Enrollees

The per-month number of Medicare enrollees was generated using publicly available datasets from CMS of county-level enrollment in Medicare Part D and Medicare Advantage plans [6]. The county-level enrollee data were matched with the zip code-based prescription data using a map illustrating the Boston and Atlanta media markets [7].

2.2 Analysis

The prescription drug claims were analyzed at (1) the month-level (with the natural log of the total number of drug users in that month as the dependent variable), and (2) the patient-month level, where the dependent variable was set to 1 if a patient had a prescription for a given drug in that month, or set to 0 otherwise. The first specification is meant to investigate the changes in monthly number of users, whereas the second is intended to detect the monthly changes in prescription rates among our selected cohorts. Each drug was analyzed separately owing to potential heterogeneity in the effect of advertisements, as well each drug's unique set and timing of safety interventions.

We employed a segmented regression analysis to evaluate the effect of time-delimited interventions (here, safety actions) using longitudinal data [8]. The methodology allows us to detect pre-safety intervention trends, level changes at the time of safety intervention, and changes in the post-intervention trend relative to the pre-intervention trend in the outcome variables of interest. The pre-safety intervention trend variable was coded as a counter that starts at 1 in January and ends at 12 in December 2009. The level change, or post-safety intervention variable, was coded as a categorical variable equal to 0 in all pre-safety intervention months, and 1 in all months after the safety intervention. To estimate the change in slope post-intervention relative to the period before the intervention, we included a post-intervention month counter that is 0 until the intervention and begins counting the number of months after the intervention until the final month of the study period. (For example, if an intervention occurred in May 2009, the month counter variable would have values 0, 0, 0, 0, 1, 2, 3, 4, …, 8 for January to December 2009). The analysis also included log ad volume, log media hits, and log Medicare enrollees as additional explanatory variables.

Statistical analyses were carried out using Stata version 13.1.

3 Results

3.1 Safety Action as a Predictor of Attorney Advertising Volume

Although regulatory action was not a selection criterion for inclusion, all seven drugs were subject to one or more safety actions in 2009. For all drugs, attorney advertising volume began increasing before FDA actions, often peaking in conjunction with an official FDA safety action. Table 1 illustrates the sequence of safety actions relative to peak attorney advertising volume and peak media hits for each drug.

Regressions using safety actions as a predictor of attorney ad volume illustrate the correlation in timing between attorney advertising volume and safety actions (Table 2). Only some produced statistically significant coefficients, unsurprising given the small sample size (because advertising volumes vary by city and month, there are only 12 monthly data points per city for each drug). For many drugs, attorney advertisements rose sharply when FDA actions occurred, and fell after the safety actions. See for example, metoclopramide (Boston), fentanyl (Boston), pregabalin, quetiapine (Atlanta), and varenicline. All these drugs have positive coefficients for the post-safety action variable, and a negative coefficient for the associated change in slope post-safety-action variable. Paroxetine is the only drug for which we find no positive correlation between advertising volume and safety actions. Attorney advertising volume for metoclopramide and paroxetine was already on an upward trend before the first safety actions in the analysis. The early metoclopramide advertising may have been spurred by a Supreme Court ruling favorable to plaintiffs suing drug manufacturers [9]. The opposite signs for metoclopramide relabeling in Boston and Atlanta result from the different timing of peak advertising volume. The paroxetine-related advertising may have related to a prior relabeling in January 2009, which could not be estimated in the model [10].

3.2 Correlation Between Media Hits and Safety Actions

Our regressions also show a high degree of correlation in timing between safety actions and media hits for many of the FDA safety actions (Table 3). Five out of seven of the drugs had a positive pre-intervention slope, although the results were mostly not statistically significant. This result is consistent with the interpretation that media attention on drug safety risks preceded official action by the FDA. Media hits also increased, with statistical significance at least at the 10 % level, after FDA relabeling for all three drugs subject to this regulatory action. This result reflects subsequent media coverage of FDA action.

3.3 Safety Action, Media Hits, and Attorney Advertising Volume as Predictors of the Number of Prescription Users and Prescription Rates

Table 4 presents the results for changes in the monthly number of users. Recalls and relabeling are associated with statistically significant decreases in the number of users in one or more drugs despite the small number of observations (12 per drug). For example, fentanyl experienced a 9.09 % ($p < 0.05$) reduction in drug users following the recall ("Post-Recall"), and a 5.53 % ($p < 0.01$) decrease in the slope of growth ("change in post-recall slope"). For varenicline, the relabeling is associated with a much larger immediate decrease in users (−86.6 %, $p < 0.05$, "Post-Relabel"). The trend in the number of paroxetine users fell 5.14 % ($p < 0.05$) following a relabeling ("Change in post-relabel slope"). For most drugs, the media variables and attorney advertising variables did not produce significant results in this specification.

Graphs illustrating the relationship among attorney advertising, media hits, and the number of users show attorney advertising rising as users increased (Figs. 2, 3). Both advertising and media hits appear to respond to, and in some cases precede, regulatory action (Figs. 2, 3).

Table 5 shows the results of our prescription rate model with individual fixed effects. All drugs had an increasing pre-safety action trend in prescription rates, which was likely a result of the data structure. By construction, the data include a panel of all Medicare beneficiaries with at least one prescription in 2009 of the various drugs studied. However, not everyone in our cohort received a prescription in the initial months of the data. Therefore, the initial months may have had a smaller number of patients with a prescription than the later months.

This rising trend, however, was often halted or mitigated by subsequent safety actions. In the prescription rate specification, all safety actions were either associated with a reduction in the level or trend, or both, in the prescription rate. The great majority of the reductions varied between 2 and 5 % in the prescription rate (see Table 5). For metoclopramide, an FDA relabel was associated with a reduction in the post-relabel trend by 2.45 % ($p < 0.001$) ("Change in post-relabel slope"). Fentanyl experienced a drop in the post-recall prescription rate of 2.62 % ($p < 0.001$) ("Post-Recall") and a decrease (−1.74 %, $p < 0.01$) in the post-recall trend ("Change in post-recall slope"). The trend of exenatide prescription decreased relative to the previous period by 3.05 % ($p < 0.001$) ("Change in post-REMS demand slope") after the REMS

Table 1 Relative timing of safety actions, media items, and attorney advertising

	2008	2009 (month of year)											
Drug		**Jan.**	**Feb.**	**Mar.**	**Apr.**	**May**	**Jun.**	**Jul.**	**Aug.**	**Sept.**	**Oct.**	**Nov.**	**Dec.**
Vareniclide (Chantix)	REMS Demand 5/6/2008							*RELABEL* **MEDIA**	**ADS** (Bos, Atl)		*REMS Approval*		
Quetiapine (Seroquel)	REMS Demand[b]	**ADS** (Bos)			**ADS** (Atl)								*REMS Approval* **MEDIA**
Pregabalin (Lyrica)	REMS Demand 12/16/2008				*RELABEL*		**ADS** (Bos, Atl)			**MEDIA**			
Metoclopramide (Reglan)			*REMS Demand*				*RELABEL*	**ADS** (Atl)	*REMS Approval*	**MEDIA**	**ADS** (Bos)		
Exenatide (Byetta)								**ADS** (Bos, Atl)			*REMS Demand*	**MEDIA**	
Paroxetine (Paxil)		*RELABEL*		**ADS** (Bos, Atl)			**MEDIA**	*RELABEL*					
Fentanyl (Duragesic)	Relabel 2/7/2008 Recalls 2/12/2008 2/17/2008 3/1/2008 8/8/2008 12/31/2008						**ADS** (Bos, Atl)		*RECALL* **MEDIA**				

REMS risk evaluation and mitigation strategy

[a] Media refers to month of peak media hits for references to the drug

[b] The precise date of this regulatory action could not be ascertained from public sources

[c] Ads refers to the month of peak attorney advertising for the applicable city: Boston or Atlanta

announcement. For varenicline prescriptions, the FDA relabel was associated with both a level change (−5.72 %, $p < 0.001$) ("Post-relabel") and slope reduction in the prescription rate (−2.86 %, $p < 0.001$) ("Change in post-relabel slope"). Similarly, for paroxetine, the FDA relabel was associated with both a level change (−0.577 %, $p < 0.1$ only) ("Post-Relabel") and slope reduction (−2.65 %, $p < 0.01$) ("Change in post-relabel slope") in the prescription rate. We were unable to estimate simultaneously the impact of REMS approval and advertising volume for quetiapine, likely because the approval occurred at the end of the study period and advertising volume increased concurrently with the FDA action.

Attorney advertising was positively associated with prescription rate ($p < 0.01$) for five of the seven drugs, suggesting that advertising and prescription rate moved in the same direction. The relative timing of peak attorney advertising, peak media hits, and regulatory action varied. (Table 1). Peak attorney advertising preceded peak media coverage for five of the seven drugs, suggesting that attorneys began advertising before media coverage peaked. Peak media coverage corresponded with regulatory action for three drugs, and immediately followed regulatory action for two drugs (Table 1). Peak attorney advertising was considerable for several drugs. For example, 119 weighted units of attorney advertisements about varenicline were broadcast nationally in August 2009, where one unit represents one network advertisement broadcast or 2.5 cable advertisement broadcasts (Supplementary Table).

4 Discussion

Our findings provide some support for the conceptual model presented in the Introduction. Regulatory action appears to spur attorney advertising and reduce prescription claims. The positive correlation between attorney advertising and prescription rates suggests that physicians and consumers do not reduce drug use as a result of attorney advertising. Instead, this positive correlation is consistent with an interpretation that both attorney advertisements and prescription rates rose in the period before a safety action, and both fell in the period after the safety action.

Table 2 Correlations between attorney advertising volume and safety actions

Dep Var: attorney advertising volume (weighted unit)	(1) Metoclopramide (Reglan)	(2)	(3) Fentanyl (Duragesic)	(4)	(5) Exenatide (Byetta)	(6)	(7) Pregabalin[a] (Lyrica)	(8)	(9) Quetiapine (Seroquel)	(10)	(11) Varenicline (Chantix)	(12)	(13) Paroxetine (Paxil)	(14)
	Boston	Atlanta	Boston	Atlanta	Boston	Atlanta	Boston	Atlanta	Boston	Atlanta	Boston	Atlanta	Boston	Atlanta
Media items	−0.711 (1.170)	−0.302 (0.906)	0.0492 (0.155)	0.130 (0.148)	0.111 (0.117)	0.105 (0.117)	0.0339* (0.0171)	0.0339* (0.0171)	0.0236 (0.117)	0.381* (0.165)	−0.690* (0.308)	−0.661 (0.335)	−0.555 (0.463)	−0.568 (0.469)
Pre-intervention slope	35.15** (11.88)	37.48** (8.434)	−0.886 (6.402)	−2.285 (7.145)	−0.171 (1.716)	−0.218 (1.697)	−0.372 (0.273)	−0.372 (0.273)	4.695*** (1.334)	6.069** (2.295)	−5.087 (3.914)	−3.307 (2.852)	7.337 (13.60)	7.433 (13.72)
Post-recall	–	–	14.22 (31.52)	−8.970 (32.82)										
Change in post-recall slope	–	–	−9.692 (7.709)	−2.360 (7.858)										
Post-REMS demand	−7.284 (51.23)	−19.54 (38.31)			−17.77 (19.98)	−17.57 (20.22)								
Change in post-REMS demand slope					2.665 (7.540)	2.772 (7.657)								
Post-relabel	119.9* (52.91)	−110.8* (40.56)					11.60* (6.112)	11.60* (6.112)			183.7** (54.72)	174.8** (62.12)	−18.45 (31.41)	−17.46 (31.34)
Change in post-relabel slope	86.31** (24.47)	133.6*** (18.54)					−0.499 (0.927)	−0.499 (0.927)			−44.47* (17.86)	−43.35* (20.21)	−14.51 (16.86)	−14.96 (16.98)
Post-REMS approval	−50.94 (100.3)	−262.5** (80.39)							12.47 (16.43)	55.73* (27.73)	69.11*** (13.81)	64.21** (18.95)		
Change in post-REMS approval slope	63.30 (40.01)	161.4*** (30.87)							2.070 (13.06)	−36.22* (17.84)	19.04 (19.24)	17.96 (22.22)		
Constant	−29.47 (18.87)	−35.06* (14.17)	64.07** (21.24)	34.15 (20.69)	26.72** (8.058)	27.28*** (7.772)	2.629 (1.405)	2.629 (1.405)	35.73** (13.84)	25.16 (22.15)	70.94*** (14.86)	56.75*** (12.60)	45.45 (32.27)	46.30 (32.71)
Observations	12	12	12	12	12	12	12	12	12	12	12	12	12	12
R-squared	0.648	0.885	0.314	0.346	0.213	0.207	0.49	0.49	0.681	0.578	0.871	0.868	0.391	0.393

(Dep Var: Attorney advertising volume (weighted units))—Weighted units of attorney advertising

Robust standard errors in parentheses

REMS risk evaluation and mitigation strategy

* $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$

[a] Results for Boston and Atlanta are identical for pregabalin because attorney advertising volume was identical in both cities

Table 3 Correlations between media hits and safety actions

Dep Var: media items	(1) Metoclopramide (Reglan)	(2) Fentanyl (Duragesic)	(3) Exanatide (Byetta)	(4) Pregabalin (Lyrica)	(5) Quetiapine (Seroquel)	(6) Varenicline (Chantix)	(7) Paroxetine (Paxil)
Pre-intervention slope	−5.700 (8.188)	24.25* (10.55)	0.583 (4.559)	−11* (5.485)	2.030 (3.548)	0.686 (5.207)	13.91 (8.334)
Post-recall	30 (24.19)		0 (51.48)				
Change in slope post-recall			9.417 (20.43)				
REMS demand	45.80** (13.72)			17.17 (31.52)		134.0* (56.84)	−9.019 (29.28)
Change in slope post-REMS demand	−19.30* (8.188)			15.30 (8.811)		−49.19* (23.42)	−21.51** (8.495)
Post-relabel	15.40 (34.22)				−159.0*** (23.58)	13.83 (34.90)	
Change in slope post-relabel	23** (7.632)				109.0*** (3.548)	55* (22.84)	
Post-REMS approval		−46.82 (62.34)					
Change in slope post-REMS approval		−28.35 (18.89)					
Constant	13.70 (8.188)	23.57 (32.51)	50.75* (25.55)	77.67*** (12.67)	85.73*** (18.84)	36.60 (22.42)	3.800 (25.54)
Observations	12	12	12	12	12	12	12
R-squared	0.257	0.449	0.097	0.051	0.404	0.515	0.52

(Dep Var: media items)—Number of media items referencing the applicable drug

Robust standard errors in parentheses

REMS risk evaluation and mitigation strategy

* $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$

The results showing a reduction in drug use after safety actions are consistent with previous studies on FDA warnings regarding adverse events [2, 11–15]. Other studies observed "high levels of provider awareness regarding…labeling changes", [2] which is consistent with the negative effect of relabeling on use observed here. Where a warning was limited to a certain subpopulation taking the drug, previous studies also observed a "spillover" effect on non-targeted populations [2, 16, 17]. A similar spillover effect was observed in our study, where a recall as to a particular fentanyl manufacturer produced a decrease in prescription for other manufacturers.

Our results showing the association between REMS demands or REMS approvals and prescription add to the existing literature on FDA safety actions. In 2007, Congress passed the Food and Drug Administration Amendments Act, which expanded the FDA's power to regulate post-marketing surveillance of drugs through REMS demands and approvals [18, 19]. The effect of REMS on prescription claims has not previously been examined. In our study, we found that a REMS demand was associated with a reduction in the post-REMS-demand trend for exenatide (Table 5). The inconsistencies in the effect (negative and statistically significant for varenicline but statistically insignificant for metoclopramide) from a REMS approval may suggest that consumer and/or providers had already responded to the associated risk information through prior FDA actions for some of these drugs. Indeed, metoclopramide already had multiple safety actions in the same year.

Our results showing a correlation between attorney advertising, safety actions, and prescription behavior add to the limited literature regarding attorney advertising [20–22]. A small survey of female urology patients found a high level of consumer exposure to attorney advertising: the majority of respondents reported that they first learned about a medical device through attorney advertising [22]. The high volume of advertising observed for several of the drugs in this study suggest that consumers may likely be exposed to attorney advertising. We also show that attorneys often time their advertising with media mentions and safety actions.

Table 4 Association between log monthly number of users and regulatory actions, attorney advertising volume, and media items

Dep Var: log number of users per month	(1) Metoclopramide (Reglan)	(2) Fentanyl (Duragesic)	(3) Exenatide (Byetta)	(4) Varenicline (Chantix)	(5) Pregabalin (Lyrica)	(6) Quetiapine (Seroquel)	(7) Paroxetine (Paxil)
Log media items	−0.0188 (0.0687)	0.00483 − 0.0377	0.0850 (0.0830)	0.143** (0.0365)	−0.0327** (0.00753)	−0.0743 (0)	−0.00416 (0.0264)
Log advertising volume	−0.00589 (0.0468)	0.0130 (0.0413)	−0.0204 (0.158)	0.160** (0.0298)	0.0260 (0.0120)	0.0206 (0)	−0.00303 (0.0103)
Log medicare enrollees	0.0135 (0.146)	−0.108 (0.135)	0.123 (0.298)	0.415* (0.152)	−0.0301 (0.0530)	−0.0258 (0)	−0.0985 (0.0470)
Pre-intervention slope	0.0833 (0.0347)	0.0539*** (0.0115)	0.0612*** (0.00973)	0.189*** (0.0140)	0.0103* (0.00269)	0.0549 (0)	0.0447** (0.0122)
Post-recall		−0.0909** (0.0255)					
Change in post-recall slope		−0.0553*** (0.00937)					
Post-REMS demand			−0.209 (0.228)				
Change in post-REMS demand			−0.0827 (0.0450)				
Post-relabel	0.270 (0.157)			−0.866** (0.161)			0.0498 (0.0360)
Change in post-relabel slope	−0.106 (0.0599)			0.0173 (0.0438)			−0.0514** (0.0164)
Post-REMS approval	−0.0219 (0.0920)			−0.189** (0.0426)			
Change in post-REMS approval	0.0132 (0.0706)			−0.188* (0.0625)			
Constant	7.760* (2.215)	9.166*** (1.732)	3.373 (3.518)	−0.285 (1.995)	9.062*** (0.695)	10.17 (0)	10.47*** (0.672)
Observations	11	11	12	12	7	5	11
R-squared	0.981	0.986	0.918	0.987	0.891	1	0.952

(Dep Var: log number of users per month)—The natural logarithm of the total number of Medicare beneficiaries in Boston and Atlanta that filled a prescription for the applicable drug in the applicable month

REMS risk evaluation and mitigation strategy

* $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$

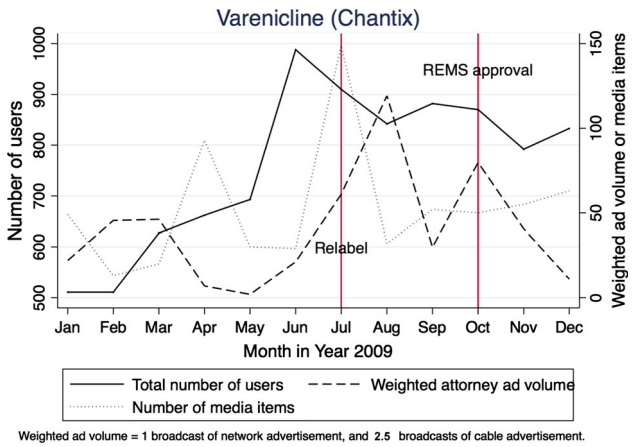

Fig. 2 Prescription rate, attorney advertising, and media items for varenicline (Chantix). *REMS* risk evaluation and mitigation strategy

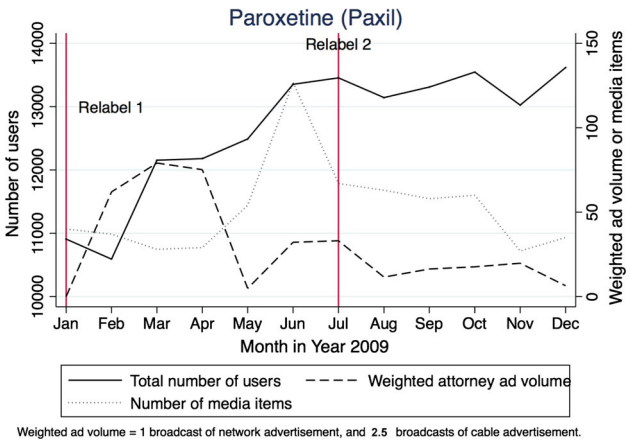

Fig. 3 Prescription rate, attorney advertising, and media items for paroxetine (Paxil)

Table 5 Association between prescription rates and regulatory actions, attorney advertising volume, and media items

Dep Var: = 1 if patient filled a prescription during the month	(1) Metoclopramide (Reglan)	(2) Fentanyl (Duragesic)	(3) Exenatide (Byetta)	(4) Varenicline (Chantix)	(5) Pregabalin (Lyrica)	(6) Quetiapine (Seroquel)	(7) Paroxetine (Paxil)
Log media items	−0.00448*** (0.00165)	0.00172 (0.00371)	0.0150* (0.00766)	0.00828* (0.00449)	0.0125*** (0.00238)	−0.00573 (0.00458)	−0.00168 (0.00273)
Log ad volume	0.00719 (0.00296)	0.00975*** (0.00225)	0.0143 (0.00979)	0.0153*** (0.00275)	0.0138*** (0.00128)	0.0274*** (0.00199)	0.00586*** (0.00118)
Log medicare enrollees	0.470* (0.240)	−0.134 (0.153)	0.0934 (0.522)	−1.128*** (0.282)	−0.708* (0.430)	0.243*** (0.0873)	−0.391* (0.205)
Pre-intervention slope	0.0163*** (0.00239)	0.0223*** (0.00138)	0.0183*** (0.00316)	0.0357*** (0.00260)	0.00664*** (0.00108)	0.0169*** (0.000747)	0.0285*** (0.00127)
Post-recall		0.0262*** (0.00599)					
Change in post-recall slope		0.0174*** (0.00238)					
Post-REMS demand			−0.0410 (0.0269)				
Change in post-REMS demand slope			0.0305*** (0.0114)				
Post-relabel	0.0831*** (0.00861)			0.0572*** (0.0176)			−0.00577* (0.00312)
Change in post-relabel slope	−0.0245*** (0.00548)			0.0286*** (0.00636)			0.0265*** (0.00170)
Post-REMS approval	−0.00505 (0.00570)			−0.0293** (0.0127)			
Change in post-REMS approval slope	0.00413 (0.00540)			0.00352 (0.00732)			
Constant	−5.674* (2.998)	1.908 (1.897)	−1.033 (6.464)	13.93*** (3.483)	9.333* (5.382)	−2.618** (1.079)	5.239** (2.538)
Observations	159,940	100,578	8,868	41,664	84,098	165,613	259,930
R-squared	0.014	0.012	0.012	0.013	0.003	0.012	0.008
No. of patients	14,540	8,721	739	3,472	12,014	32,275	23,630

(Dep Var: = 1 if patient filled a prescription drug during the month)——A dummy variable equal to one if Medicare beneficiary within the panel filled a prescription for the applicable drug in the applicable month

Robust standard errors in parentheses

REMS risk evaluation and mitigation strategy

* $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$

The short duration and the observational nature of our analysis limit our ability to draw causal inferences for the relationship between attorney advertising and prescription. Nonetheless, we found no evidence of a negative correlation between attorney advertising and prescription claims, in contrast to the negative relationship observed between several safety actions and the number of users and/or prescription claims. Our findings are consistent with an interpretation that consumers and providers likely disregard attorney advertising, and make decisions based on other information. As previously noted, the positive correlation in the prescription rate specification is likely owing to attorneys' timing of advertising placement near FDA actions.

5 Limitations

This preliminary study has several limitations. The dated quality of the dataset fails to reflect recent changes in advertising or media consumption practices. The study was limited to Medicare beneficiaries, an older cohort whose response to risk information and media consumption patterns may not be representative of the general population [23]. Future research on attorney advertising is needed to examine how other demographics respond, and to measure the impact of attorney advertising on websites and social media.

The 1-year sample period limited the study's ability to account for seasonal fluctuations in prescription patterns. It

also prevented us from measuring additional FDA disclosures to the public through public comment periods, and FDA actions that occurred in the year before the study period (see Table 1). In 2008, varenicline, quetiapine, and pregabalin experienced a REMS demand, and fentanyl was subject to several recalls. These actions may have influenced both prescription claims and attorney advertisements, particularly in the initial months of 2009, but their effect could not be accounted for using our segmented regression analyses. Moreover, the short duration of the study prevented us from accurately classifying new vs. prevalent drug users to study the potentially differential responses to attorney advertising between these two groups. The high degree of correlation between advertising volume and safety actions made it difficult to disentangle the effects of advertising vs. regulatory actions on prescriptions. Finally, the dataset did not allow us to distinguish between changes in prescription rates attributable to physician decisions from those made by consumers.

6 Conclusion

Our principal conclusion is that several safety interventions appeared to have the predicted negative impact on drug prescription in our study. Our preliminary report does not show that attorney advertisements reduced drug use.

Acknowledgments Job Chen contributed to the data analysis for this project.

Compliance with Ethical Standards

Funding This project was funded in part with a Faculty Research Award by the University of Oregon's Office of Research, Innovation and Graduate Education. This research was also funded in part by LizT Consulting LLC.

Conflict of interest Elizabeth Tippett is the sole proprietor of LizT Consulting LLC. Elizabeth Tippett and Brian Chen have no other conflicts of interest that are directly relevant to the content of this study.

References

1. Tippett EC. Medical advice from lawyers: an analysis of attorney advertising for drug injury lawsuits. Am J Law Med. 2015;41(1):7–48.
2. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. Med Care. 2012;50(6):466–78.
3. Nielsen. Local television market universe estimates. Available from: http://www.nielsen.com/content/dam/corporate/us/en/newswire/uploads/2009/08/2009-2010-dma-ranks.pdf.
4. Drugs@FDA. FDA approved drug products. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed 24 Feb 2015.
5. Watson announces limited recall of fentanyl transdermal system, published August 7, 2009. Available from: http://phx.corporate-ir.net/phoenix.zhtml?c=65778&p=irol-newsArticle&ID=1318770. Accessed 24 Feb 2015.
6. Centers for Medicare and Medicaid Services, Monthly Enrollment by Contract/Plan/State/County. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MCRAdvPartDEnrolData/Monthly-Enrollment-by-Contract-Plan-State-County.html. Accessed 13 June 2015.
7. SeventhPoint, Nielsen DMA—Designated Market Area Regions 2012–2013. Available from: http://seventhpoint.com/images/pdfs/2012-2013%20Large%20DMA%20Map.pdf. Accessed 13 June 2015.
8. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299–309.
9. Wyeth v. Levine, 129 S.Ct. 1187 (2009).
10. Food and Drug Administration, Letter to GlaxoSmithKline from Thomas Laughren, January 30, 2009. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/020031s061,020936s038,020710s025ltr.pdf. Accessed 11 May 2015.
11. Wax D, Doshi A, Hossain S, et al. Changing patterns of postoperative nausea and vomiting prophylaxis drug use in an academic anesthesia practice. J Clin Anesth. 2007;19:356–9.
12. Starner CI, Schafer JA, Heaton AH, et al. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Manag Care Pharm. 2008;14(6):523–31.
13. Habib AS, Gan TJ. The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia. J Clin Anesth. 2008;20:35–9.
14. Smalley W, Shatin D, Wysowski DK et al. Contraindicated use of Cisapride. JAMA. 2000;284(23):3036–9.
15. Karpel JP, Peters JI, Szema AM, et al. Differences in physicians'-self-reported knowledge of, attitudes towards, and responses to the black box warning on long-acting beta-agonists. Ann Allergy Asthma Immunol. 2009;103:304–10.
16. Valuck RJ, Libby AM, Orton HD, Morrato EH et al. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry. 2007;164(8):1198–205.
17. Dorsey ER, Rabbani A, Gallagher SA et al. Impact of FDA black box advisory on antipsychotic medication use. Arch Intern Med. 2010;170(1):96–103.
18. Food and Drug Administration Amendments Act of 2007, Pub. Law 110-85, § 505–1.
19. Chen BK, Yang T. Post-marketing surveillance of prescription drug safety: past, present and future. J Legal Med. 2013;34(2):193–213.
20. Juurlink DN, Park-Wyllie LY, Kapral MK. The effect of publication on Internet-based solicitation of personal-injury litigants. Can Med Assoc J. 2007;177(11):1369–70.
21. Tenggardjaja CF, Moore CK, Vasavada SP, Li J, Goldman HB. Evaluation of patients'-perceptions of mesh usage in female pelvic medicine and reconstructive surgery. Urology. 2015;85:326–32.
22. Koski ME, Chamberlain J, Rosoff J, et al. Patient perception of transvaginal mesh and the media. Urology. 2014;84(3):572–82.
23. The Pew Research Center for the People and the Press. Trends in news consumption: 1991—2012. In changing news landscape, even television is vulnerable. Available from: http://www.people-press.org/files/legacy-pdf/2012%20News%20Consumption%20Report.pdf. Accessed 4 May 2015.