Intended and Unintended Consequences of the Gabapentin Off-Label Marketing Lawsuit Among Patients With Bipolar Disorder

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ABSTRACT

Objective: The number of lawsuits accusing pharmaceutical companies of off-label marketing has risen in recent years. The impact of such lawsuits on drug prescribing and spending has not been examined. We evaluated a nationwide sample to determine whether the $430 million gabapentin off-label marketing lawsuit and accompanying media coverage affected gabapentin market share, substitution of other scientifically substantiated and unsubstantiated anticonvulsants, and anticonvulsant spending of Medicare/Medicaid patients diagnosed with bipolar disorder.

Method: Using a national 5% sample of Medicare recipients linked to Medicaid claims, we used an interrupted times series design to evaluate the impact of the lawsuit on monthly market share, utilization, and spending from January 1, 2001, to December 31, 2005.

Results: The start of the lawsuit was associated with a 28% relative reduction in gabapentin market share (from ~21% to ~15%) and a reduction in the rate of prescribing from 108 prescriptions per 1,000 patients per month before the start of the lawsuit to 90 by the end of follow-up ($P < .001$). We also observed increases in market share for 3 other anticonvulsants. Total anticonvulsant use and spending per 1,000 patients increased by 13% and 74%, respectively, after the intervention. The increase in anticonvulsant spending was equivalent to $7,554 per 1,000 patients per year higher than expected compared with the baseline trend ($P = .01$).

Conclusions: We conclude that the lawsuit resulted in a reduction in gabapentin market share, increased market share for other anticonvulsants, and substantially increased total anticonvulsant spending to approximately half of the settlement amount, not counting substitutions of newer drugs for other illnesses affected by the lawsuit. These findings support the need for further study of the effects of current lawsuits regarding off-label drug marketing.

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The number of government lawsuits accusing pharmaceutical companies of off-label marketing has risen in recent years.[1–3] Such lawsuits seek to recover costs of off-label drug use caused by illegal marketing.[4] These lawsuits are often accompanied by widespread coverage in the lay media. Negative media messages about medications have been shown to change prescribing patterns and sometimes reduce inappropriate drug use.[5–7] However, no studies have examined the impact of such lawsuits for off-label marketing (and accompanying media reports) on drug prescribing and spending. Negative publicity from the lawsuits in marketing campaigns can increase market share of competitors' products. We investigated the impact of the gabapentin off-label marketing lawsuit on gabapentin market share, substitution of alternative anticonvulsants with varying levels of evidence of efficacy in treating bipolar disorder, and changes in anticonvulsant spending in a nationwide sample of patients with bipolar disorder.

Off-label prescribing is common in many conditions, such as cancer, chronic pain management, and mental illnesses, because scientific evidence supporting the use of some drugs for unapproved indications may exist even in the absence of a US Food and Drug Administration (FDA) indication.[8,9] Physicians may judge medications to be effective for off-label indications in their practice despite the absence of scientific evidence because of similarities to other medications that have proven effective in the past. Although physicians can legally prescribe medications for off-label indications, it is illegal for companies to market a product for indications that are not FDA approved.[4,9] Regulation of off-label marketing through litigation has become increasingly prominent as pharmaceutical expenditures have grown. Given that policies that restrict use of unsubstantiated medications can increase spending due to substitution of more expensive similarly unsubstantiated medications, it is important to examine the intended and unintended consequences to such lawsuits.[10]

Brief History of the Lawsuit

Gabapentin is an anticonvulsant medication that was approved in 1993 for adjunctive treatment of epilepsy and, in 2002, for postherpetic neuralgia. By 2000, gabapentin annual sales had grown to blockbuster status (nearly $1 billion), the vast majority of which were for off-label indications, such as bipolar disorder, various pain disorders, amyotrophic lateral sclerosis, attention-deficit/hyperactivity disorder, migraine, drug and alcohol withdrawal seizures, restless leg syndrome, and monotherapy treatment for epilepsy.[11] In 1998, a former Parke-Davis employee filed a lawsuit against the company for illegally marketing gabapentin for use in off-label indications. According to media reports, through which prescribers and patients would become aware of the lawsuit, the lawsuit was later unsealed in 2002, and the US Department of Justice and several states joined as plaintiffs.[3] The plaintiffs sought reimbursement for the utilization that resulted from the illegal marketing. In 2004, Pfizer, having

purchased Parke-Davis, settled the lawsuit for $430 million, the largest off-label marketing settlement up to that time.

Objective

In this study, we hypothesized that the lawsuit, accompanied by widespread media coverage of the case (hereafter referred to as "the lawsuit") from competing manufacturers, resulted in a reduction in prescribing of gabapentin. We chose to test this hypothesis in a population with bipolar disorder because gabapentin's off-label use for this indication was unsupported in the scientific literature.[12–14] In 2000, two randomized controlled trials[12,13] were published that concluded that gabapentin was no different than placebo in the treatment of bipolar disorder. We further hypothesized that reductions in use of gabapentin would result in substitution of other anticonvulsants that may or may not have proven efficacy in the treatment of bipolar disorder. Finally, we hypothesized that such medication substitution would lead to increased spending within the anticonvulsant class.

METHOD

Study Design

We used an interrupted time series design to evaluate the effect of the lawsuit on changes in level and trend of anticonvulsant market share and spending in patients with bipolar disorder. In a national experiment in which a control group is impossible, interrupted time series is the strongest quasi-experimental design available because it can control for preexisting levels and trends of outcomes during the preintervention period when evaluating immediate changes in trends after the start of an intervention.[15]

Data

Using a merged dataset of a national 5% sample of Medicare (public insurance for the elderly and disabled) recipients and Medicaid (public health insurance for the low-income population) claims data from January 1, 2001, to December 31, 2005, we identified a continuously enrolled, dually eligible population over the age 18 years based on monthly enrollment data from Medicare and Medicaid. Continuous enrollment was defined as being enrolled in both Medicaid and Medicare in all months during the study period. We further analyzed Medicaid prescription drug claims for this population to measure anticonvulsant market share, utilization, and spending. These claims included a unique patient identifier, National Drug Code, date of dispensing, the number of units provided (number of tablets, for example), days' supply, and amount reimbursed.

The Harvard Pilgrim Health Care Institutional Review Board approved the study, waiving consent because our study was conducted with de-identified patient data from a large administrative claims data set.

Study Population

The study population contains many of the sickest patients with bipolar disorder, a large number of whom qualify as permanently disabled.[16] We limited the cohort to patients who had at least 1 inpatient or 2 outpatient diagnoses of bipolar disorder (*ICD-9-CM* codes 296.0, 296.1, 296.4–296.7, 296.89, and 301.11) at any point during the study period.[17,18] Diagnoses of bipolar disorder were accepted from the first diagnostic field in a claim.

Information regarding sex, age, and race of the study population were taken from the Medicare 5% sample data. Unique medications at baseline included medications for both physical and mental health and were taken from the claims data based on previously validated methods.[19]

Clinical Points

- Federal lawsuits against pharmaceutical companies for off-label psychotropic prescribing may cause unintended substitutions of newer drugs that could raise rather than lower costs.
- Litigation intended to recover government health care costs of off-label use of psychoactive medications for serious mental illness should educate physicians regarding the most efficient and effective substitute drugs.

Study Intervention Index Date

The intervention was indexed when the lawsuit began in March 2002 (Figure 1).[20] In order to identify trends in media reports of the lawsuit, we conducted a search of the LexisNexis database[20] for newspaper articles and newswires that contained the words *Neurontin* and *off-label* between January 1, 1996, and December 31, 2005. The search yielded 196 articles, of which 29 were excluded because they were unrelated to the lawsuit. The first of many reports on this topic appeared in March 2002, shortly after the case was unsealed.[21] Almost all coverage occurred in newspapers or newswires; television coverage was rare.

In June 2003, 15 months following the start of the lawsuit, the anticonvulsant lamotrigine was approved for bipolar maintenance by the FDA.[22] Since this event would most likely affect anticonvulsant market share, we included this new indication in our analysis as a second intervention during the study period.

Outcomes

All study outcomes were calculated at monthly time intervals to allow the use of an interrupted times series design. We measured monthly market share as the fraction of total monthly prescription fills of anticonvulsants that each anticonvulsant represented. We chose to measure market share because it best reflects changes in relative use of individual products within a drug class. We also measured overall utilization of anticonvulsant therapy and utilization of gabapentin. We counted a month as a "use month" if that month was included between the dispense date and through date on a prescription. When looking at utilization, we counted each

Figure 1. Cumulative Number of News Articles in LexisNexis National Sample[20] on Gabapentin Off-Label Marketing Lawsuit: 1996 to 2005

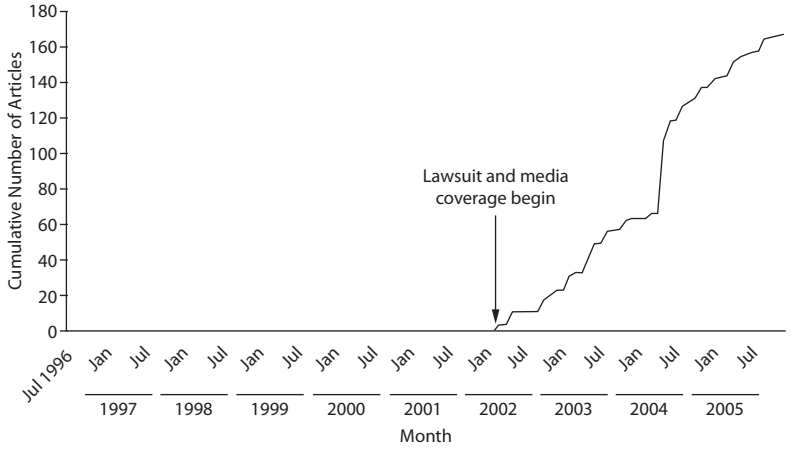


Table 1. Baseline Characteristics of Study Cohort of Medicare and Medicaid Beneficiaries With Bipolar Disorder

	Study Cohort (N = 3,004)	
Characteristic	n	%
Women	1,852	62
Age at baseline, y		
20–34	536	18
35–54	1,665	55
55–64	345	12
65+	458	15
Race, white	2,499	83
Medication use[a]		
Antipsychotics	1,987	66
Lithium	744	25
Anticonvulsants	1,915	64
Antidepressants	2,384	79
Antianxiety	1,874	62
	Mean	SD
No. of unique medications[b]	10.77	0.117

[a]Number of people who filled a prescription in each drug class at any point during the study period.
[b]Number of unique medications filled among the study population during the first year of the observation period.

use month as a prescription. In order to characterize the level of scientific evidence of efficacy among the anticonvulsant medications used to treat bipolar disorder, we referred to the treatment recommendations from the National Institute of Mental Health as well as several literature reviews. We identified several older anticonvulsants, including divalproex sodium, valproic acid, and carbamazepine, that were either approved for bipolar disorder or had been scientifically substantiated in the literature through publication of double-blind, randomized control trials that included results of efficacy in bipolar disorder.[23,24] We also classified 3 anticonvulsants (topiramate, levetiracetam, and oxcarbazepine) as lacking evidence of efficacy for bipolar disorder.[25] Finally, we included lamotrigine, which gained approval as a maintenance treatment in bipolar disorder during the study period.[22–24,26,27]

We defined the following measures to describe spending. Using the pharmacy reimbursed amount, we defined total anticonvulsant spending per 1,000 prescriptions per month, spending for each anticonvulsant per 1,000 prescriptions per month, and anticonvulsant spending per 1,000 people per month.

Analysis

We estimated population-level changes in anticonvulsant market share and spending using interrupted time series regression models.[15] Using 14 months of data prior to the lawsuit, we established a baseline level and slope of market share and spending for anticonvulsants per 1,000 patients per month. We used segmented linear regression to evaluate changes in slopes and levels of anticonvulsant market share, utilization, and spending after the start of the lawsuit (March 2002) and the FDA approval of lamotrigine for bipolar maintenance (June 2003), controlling for preintervention trends in market share and spending. In the segmented regression, we controlled for serial autocorrelation and excluded all nonsignificant ($P > .05$) terms from the models by using backward elimination. We used SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina), to conduct these analyses.

RESULTS

Descriptive Statistics

Table 1 describes several baseline characteristics of the study patients (N = 3,004). The mean age was 48 years, ranging from 21 to 92. Women comprised 62% of the population, and 83% of the patients were white. During the first year of the study period, patients took a mean of 10.8 unique medications.

Gabapentin and Anticonvulsant Market Share

During the 14 months prior to the lawsuit, gabapentin was the second-most-prescribed medication (behind divalproex sodium) to the study population, representing 21.4% of anticonvulsant prescriptions. During this baseline period, gabapentin market share remained stable between 21.4% and 22.6%. However, gabapentin market share declined suddenly

Figure 2. Market Share of Selected Anticonvulsants in the Dually Eligible Population With Bipolar Disorder: Gabapentin, Lamotrigine, and Unapproved Drugs

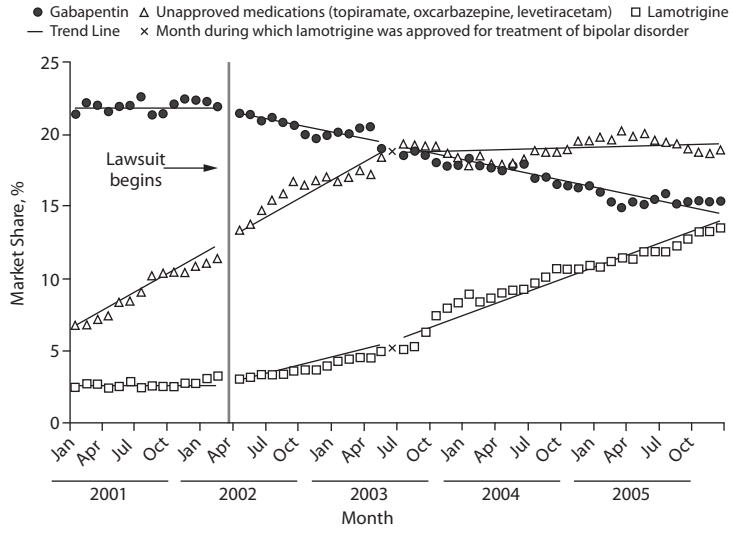
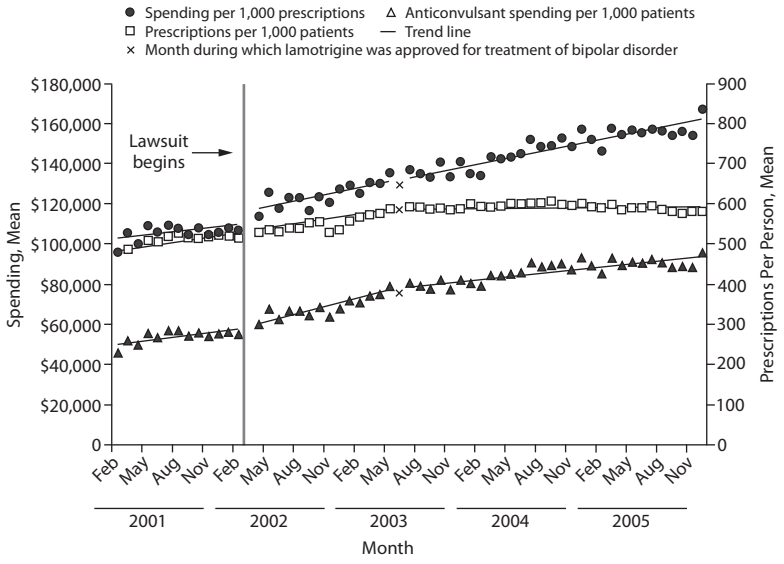


Figure 3. Overall Spending and Utilization of Anticonvulsant Drugs Among the Dually Eligible Bipolar Population



after the start of the lawsuit (Figure 2) to 15.4% by the end of the study period, representing a relative change of −28% in market share (trend change = −0.16% market share per month, $P < .001$). In terms of gabapentin utilization among the study population, there was a reduction in the rate of prescribing from 108 prescriptions per 1,000 patients per month before the start of the lawsuit to 90 prescriptions per 1,000 patients per month by the end of follow-up (data not shown here).

Figure 2 shows a market share comparison of gabapentin, lamotrigine, and the unapproved anticonvulsants during the study period. Lamotrigine utilization remained stable at 2.5% during the baseline period. After the start of the gabapentin lawsuit, the trend in lamotrigine market share increased immediately by 0.19% market share per month ($P < .001$) and continued to increase after it received FDA approval for bipolar disorder treatment, reaching a market share of 13.5% by the end of the observation period. Figure 2 also shows that the market share for the unapproved anticonvulsants (topiramate, oxcarbazepine, and levetiracetam) increased consistently from the start of the study period. The upward monthly market share trend of 0.43% ($P < .001$) continued after the start of the lawsuit and then decreased after lamotrigine received an FDA indication for bipolar disorder (trend change = −0.41%, $P < .001$). This finding suggests that prescribers did not reduce off-label prescribing within this drug class as a result of the lawsuit. Overall, it appears that lamotrigine and the unapproved anticonvulsants offset much of the decline in gabapentin market share. The market share for the older approved anticonvulsants steadily declined during the baseline period (baseline trend = −0.32% market share per month, $P < .001$), and this decline slowed after the intervention (trend change = 0.24% market share per month, $P = .01$) (data not shown).

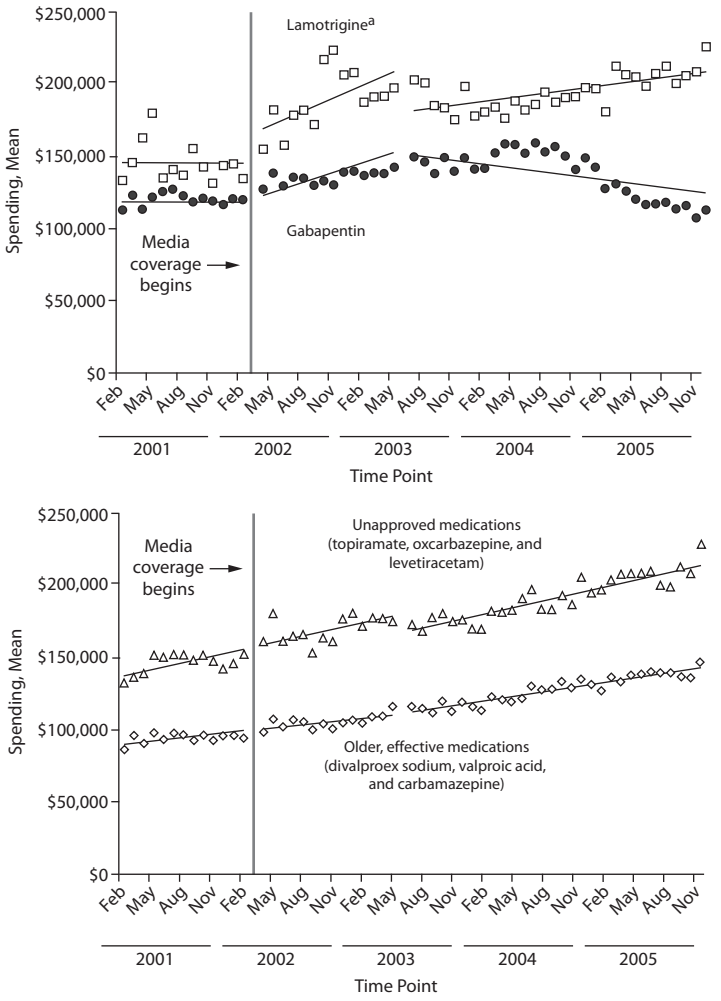
Anticonvulsant Use and Spending

Figure 3 shows the monthly utilization of anticonvulsants per 1,000 bipolar patients, mean monthly spending per 1,000 anticonvulsant prescriptions, and mean monthly spending on anticonvulsant treatment per 1,000 patients from February 2001 to December 2005. Prior to the start of the lawsuit, monthly spending on anticonvulsants was consistently rising by $655.70 per 1,000 patients each month. This upward trend further increased after the start of the lawsuit (trend change = $629.50 per 1,000 patients per month, $P = .01$). The dramatic increase in the trend of anticonvulsant spending per 1,000 patients continued until lamotrigine was approved 14 months after the start of the lawsuit (see Figure 3). This trend change accounts for an $8,184 increase in anticonvulsant spending per 1,000 patients compared with expected spending based on the baseline trend over the 13-month period before lamotrigine was approved for bipolar disorder.

The increase in anticonvulsant spending per 1,000 patients was largely due to substitution of expensive anticonvulsants as well as increased spending per prescription of gabapentin

and lamotrigine. The trend in gabapentin spending increased by $2,281 per 1,000 prescriptions per month ($P < .001$ after the intervention). Lamotrigine spending increased in both trend (trend change = $3,035 per 1,000 prescriptions per month, $P < .001$) and level (level change = $1,745 per 1,000 prescriptions per month, $P < .001$) (Figure 4). Figure 4 also shows that the spending on the unapproved anticonvulsants was increasing $1,356 per 1,000 prescriptions per month before the lawsuit, and this trend persisted after the lawsuit began. Spending on the older, commonly used standby anticonvulsants was increasing $748 per 1,000 prescriptions per month ($P < .001$) and continued to increase after the lawsuit.

Figure 4. Monthly Spending per 1,000 Prescriptions for all Anticonvulsants in the Dually Eligible Population With Bipolar Disorder: Gabapentin; Lamotrigine; Unapproved Drugs; and Older, Effective Medications



[a]Lamotrigine is displayed separately because it gained an approval for bipolar maintenance during the study period.

DISCUSSION

The importance of understanding the relationships between off-label lawsuits and media coverage, marketing, prescribing patterns, and drug spending grows as off-label marketing lawsuits become more frequent.[28,29] In the case of gabapentin, our results indicate that the lawsuit and accompanying media coverage corresponded with a decrease in market share of gabapentin, substitution of newer and expensive anticonvulsants, and an increase in overall spending on anticonvulsants.

Our results also suggest that illegal off-label marketing lawsuits have both intended and unintended consequences. Consistent with the US Department of Justice's intent to protect public insurers from fraudulent prescribing of gabapentin, the intended consequences of the lawsuit included a decrease in gabapentin market share as well as the substitution of alternative anticonvulsants. However, as soon as information about the lawsuit was made available through media and marketing, there was a long-term, unintended increase in spending on anticonvulsants, which included a mix of scientifically substantiated and unsubstantiated products. In this case, the increase in spending on anticonvulsant use most likely exceeded the settlement amount. On the basis of the national annual prevalence of bipolar disorder (2.6%)[30] and the observed approximate increase in spending immediately following the intervention ($7,554 per 1,000 patients per year, $P = .01$), we estimated that the increase in spending on anticonvulsants during the observed postintervention period was well over $200 million: about half of the $430 million gabapentin settlement amount, not counting many unmeasured substitutions in other illnesses affected by the lawsuit.

Despite evidence from physician self-report that off-label use of gabapentin in bipolar disorder was unaffected by the lawsuit,[31] our results show a reduction in use of gabapentin from 21.4% to 15.4% market share (28% relative reduction) after the lawsuit, following a period of stable use during the baseline period.

The relative decrease in gabapentin use did not coincide with a decline in overall anticonvulsant use; we showed that the market share of other anticonvulsants increased or continued to grow after the intervention. This increase is not surprising because of previous studies that show the decline in use of 1 drug after regulatory changes is often offset by increasing utilization of other substitute drugs.[10,32,33] Lamotrigine, an off-label, brand-name anticonvulsant that later received an indication for bipolar disorder in 2003 (more than a year after the gabapentin lawsuit), was one of the drugs that experienced the highest increase in market share.

The use of the unapproved anticonvulsants, which included 3 brand name medications with no indication for bipolar disorder, also continued to increase substantially after the intervention. Thus, many prescribers shifted from 1 scientifically unsubstantiated product to both substantiated and unsubstantiated products. The continued use of off-label prescribing indicates that the negative coverage did not result in a generalized reduction in off-label medication use. It is not surprising that the lawsuit was not associated with an increase in market share of older, generic medications that are not generally promoted as intensely as branded medications by the pharmaceutical industry.[34]

Monthly anticonvulsant spending per 1,000 patients increased 74% after the start of the lawsuit. Since a major driver of the lawsuit was state Medicaid program reimbursement of excess spending for off-label gabapentin use from 1994 to 2002, the increase in spending for anticonvulsants was unexpected.

This study has several limitations. Our datasets did not allow us to measure pharmaceutical spending on marketing for anticonvulsants. Marketing to psychiatrists for gabapentin was essentially discontinued after the publication of the 2 negative randomized controlled trials[35] and may have contributed to the stability in use of gabapentin during the initial period of this study. However, there was most likely an increase in marketing of other anticonvulsant drugs in anticipation of decreased gabapentin use. We also could not account for changes to state Medicaid pharmacy benefits. For example, several state Medicaid programs implemented prior authorization policies that included gabapentin, but these programs were implemented near the end of our study period after the lawsuit was settled in 2004 and were unlikely to affect our results.[35] Like lamotrigine, several antipsychotics (risperidone, quetiapine, ziprasidone, and aripiprazole)[36] were approved for bipolar disorder during the study period. Since these approvals could potentially influence our outcomes, we conducted a sensitivity analysis in which we included new bipolar medication approvals that occurred during the study period as interventions and evaluated changes in drug-specific market share and spending using all bipolar drugs in the denominator for market share. This analysis did not change our conclusions with regard to the anticonvulsant drug class, so we chose to exclude these interventions in the study. Also, we recognize that the publication of 2 studies[12,13] suggesting that gabapentin was not efficacious may have affected prescribing of gabapentin; however, these studies occurred before our baseline period, when gabapentin use was flat and stable. Spending was based on pharmacy reimbursement, so we could not account for rebates. We did not have any information about physician specialty, so we were unable to distinguish between anticonvulsants prescribed by psychiatrists and those prescribed by general practitioners. However, other studies of this population indicate that most patients with bipolar illness are generally treated by mental health specialists.[37] Another limitation was that the preintervention period was relatively short; however, use of all medications was very stable and easy to model with the available data. We recognize that the dually eligible population with bipolar disorder is a particularly vulnerable subpopulation among those diagnosed with the disorder. While we believe that the general pattern of substitution effects in the general population may be similar, further study is needed to generalize our findings beyond this population.

In 2006, a year after our study period ended, Medicare Part D, the largest change to Medicare coverage since its inception, was implemented. Under this policy, the dually eligible population was transitioned from state Medicaid pharmacy benefits to regional Part D drug plans. Since both state Medicaid pharmacy benefits and Part D Plans vary widely in their formularies and cost-containment strategies, we believe it would be very interesting to evaluate a more recent lawsuit to observe whether similar intended and unintended consequences of this type of litigation would occur during the Part D era.

The US Department of Justice continues to sue pharmaceutical companies for off-label marketing practices. AstraZeneca, Pfizer, and Serono recently settled cases for hundreds of millions of dollars.[28,29,38] In 2010, Novartis settled a lawsuit accusing Novartis of marketing oxcarbazepine for off-label use in bipolar disorder.[1] The impact of these later lawsuits and their accompanying media coverage on prescribing practices remains unknown. On the basis of these results, the gabapentin lawsuit was associated with both intended and unintended changes in drug utilization and spending. This finding highlights the need for more comprehensive consideration of potential consequences when the US Department of Justice and states negotiate these important settlements. We found that both on-label and off-label anticonvulsants substituted for gabapentin use, and spending increases for other anticonvulsants eclipsed the reimbursement to states for off-label gabapentin use. These findings suggest the need for further study of lawsuits for the pharmaceutical marketing of off-label indications. We suggest that, in these types of lawsuits, the US Department of Justice communicates with relevant health care provider and specialty organizations rather than rely on media reports as a primary means of disseminating information about an illegal marketing case. With knowledge of such a case, the health care provider organizations could inform prescribers about the litigation and reinforce that prescribers should refer to treatment guidelines for the disease of interest when making decisions about off-label prescribing. A narrow regulatory approach that does not consider the prescribing needs and substitution behavior of clinicians may not be effective in decreasing the use of scientifically unsubstantiated drugs and may increase rather than decrease overall spending.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), divalproex sodium (Depakote and others), gabapentin (Neurontin, Gralise, and others), lamotrigine (Lamictal and others), levetiracetam (Keppra and others), lithium (Lithobid and others), oxcarbazepine (Trileptal and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), topiramate (Topamax and others), valproic acid (Stavzor, Depakene, and others), ziprasidone (Geodon and others).

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Additional information: The Medicare/Medicaid dataset used in this study is owned by the Centers for Medicare and Medicaid Services. The data reside at Jen Associates, Inc, and can be obtained by contacting Dan Gilden (phone: 617-686-5578; e-mail: dmg@jen.com).

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