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# Drug withdrawals and the utilization of therapeutic substitutes: The case of Vioxx

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ABSTRACT

The lack of research on how the 2004 safety-related withdrawal of the drug Vioxx affected consumer drug utilization or outcomes for competitors is a missed opportunity to learn from the largest drug withdrawal event in history. Our study fills this void using state-level repeated cross section data from the Medicaid State Drug Utilization (SDU) database of fee-for-service Medicaid claims for prescription drugs, and individual-level panel data from the Medical Expenditure Panel Survey (MEPS) which is a nationally representative survey that contains information on medication use across two years. We find that the withdrawal of Vioxx had both positive and negative effects for specific substitute drugs in its own class (COX-2s), and that it led to an overall increase in the usage of both its most direct competitor class (NSAIDs) and in a class of older similar therapy (Analgesics). We argue these shifts in drug usage represent what could be viewed as an appropriate response to the events. However, aggregate use of drugs in the COX-2 and related classes declined overall, suggesting that some consumers may have over-reacted to the withdrawal events in ways that lessened the health benefits they could receive from this family of drugs. These findings about medication utilization changes in response to negative information are highly relevant for policy design and for determining thresholds for regulatory interventions.


## 1. Introduction

The withdrawal of several blockbuster drugs from the market in the past decade (including Propulsid in 2000 and Vioxx in 2004) has led to increased public attention and concern about prescription drug safety and efficacy. Most recently, the pain medication Darvocet was voluntarily withdrawn from the market due to heart arrhythmia side effects, and the Food and Drug Administration (FDA) severely restricted access to the popular diabetes drug Avandia due to heart attack risk.[1] The effect of widely publicized withdrawal events on public perception of drug safety issues is part of a broader question regarding consumer responses to negative health information, on which a large literature exists in marketing, economics, psychology and public health. Yet there has been little research on consumer reaction to the withdrawal of prescription drugs due to safety concerns. The contribution of our paper is to provide the first study of the Vioxx (rofecoxib) withdrawal

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[1] Darvocet was withdrawn in November 2011 and restrictions on use of Avandia were effective that same month. Also in November 2011, the FDA removed approval of the chemotherapy drug Avastin for use in breast cancer patients – but it remains in the market for use in other cancers. Xigris, an injectible used to combat bacterial blood infections, was withdrawn from the market in October 2011 for lack of efficacy rather than safety concerns. Information on FDA drug safety warnings and drug withdrawals is available at http://www.fda.gov/Drugs/DrugSafety/.

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on usage of drugs in the same class and in competitor classes, and to expand the focus of drug withdrawal studies to consider effects on new outcomes beyond market shares: to prices, total expenditures, and product mix [specifically over-the-counter (OTC) and generic drugs].

The withdrawal of a drug due to safety concerns is a dramatic form of negative information about that particular product. In principal, however, such a withdrawal provides consumers and physicians with no new negative information about other drugs that remain in the market. Thus, we would expect to observe substitution toward remaining competitor brands, leading to an increase in their use (positive spillovers). However, if the withdrawal of one drug raises safety concerns about other drugs in the same class, even though they are not withdrawn, we may observe reduced use of this entire class of drugs (negative spillovers). If the affected drug class has close substitutes in another class of drugs (less likely to share chemical characteristics and thus less likely to be associated with the same negative information), consumers may substitute toward these drugs. The net effect on drug use in the affected class and in related classes will depend on the relative magnitude of these responses.

The withdrawal of Vioxx is a particularly rich example to test for positive and negative spillover effects. In addition to being the largest drug withdrawal event in history, Vioxx has a set of close substitutes within its class (COX-2 inhibitors) and among other drug classes. This provides us an opportunity to see how competitor drugs *within* the same class versus close competitors *outside* the class are affected by a drug withdrawal, facilitating analysis of a broad set of substitution or spillover effects from the withdrawal. Although not the primary focus of our paper, we also comment on the subsequent withdrawal of another drug in the same COX-2 inhibitor class (Bextra, valdecoxib) in early 2005.

We examine the effect of Vioxx's withdrawal in two separate analyses. To study the aggregate effects of the withdrawal on drug usage patterns, we turn to a universe of claims from a particular set of consumers – Medicaid fee-for-service enrollees. The Medicaid database we have assembled allows us to study the impact of the withdrawal in a population with known insurance characteristics, using a near universe of drug purchases (including covered OTC medications). A further advantage of the Medicaid data is that it is reported quarterly, allowing us to closely target drug usage changes in the database to the Vioxx withdrawal date. We use these data to examine the impact of the Vioxx withdrawal on aggregate usage, product mix and total expenditures in the COX-2 and related drug classes.

One shortcoming of the Medicaid data is that it reports state-level prescription reimbursements rather than individual usage patterns. While our analysis is able to control for other state-level covariates such as changes in the Medicaid population, it may be desirable to validate that the effects seen in the aggregate are also present in individual usage decisions. To accomplish this, we use data from the Medical Expenditure Panel Survey (MEPS) to study individuals' drug usage patterns among those who were using Vioxx or competitor drugs, before and after the withdrawal event. Due to the differences in risks faced by the elderly and younger users, we examine these patterns separately for all age groups and then, separately, for the elderly. This type of analysis is novel to the literature, as prior withdrawal events did not yield adequate sample size to examine individual users of the withdrawn product (Cawley and Rizzo, 2008).

Market withdrawal of prescription drugs due to safety concerns is relatively uncommon but not exceedingly rare, and the pace of drug withdrawals appears to be accelerating in recent years. Wysowski and Swartz (2005) find that from among nearly 6000 drugs approved for use during 1969–2002, 75 were withdrawn from the market by 2005. Olson (2008) reports that between 1997 and 2001 alone, 12 drugs were withdrawn from the market. Fontanarosa et al. (2004) calculate that the rate of drug withdrawals (as a percent of drugs in the market) increased from 1.56% during the years 1993–1996 to 5.35% during 1997–2001.[2] These trends of increased drug withdrawals are not altogether surprising in the wake of the Prescription Drug User Fee Act (PDUFA) of 1992 and its renewals, which directs the FDA to increase the timeliness of new drug approvals. This creates a shift of regulatory emphasis away from lengthy premarket testing of drug safety toward post-marketing surveillance and withdrawal of drugs that prove to be unsafe. In this policy environment, understanding consumers' reactions to drug withdrawals is important for informing future FDA actions.

Consumers may have difficulty assessing the appropriate level of risks implied by the withdrawal of a drug from the market, particularly for related drugs that remain in the market. As a result, consumers may fail to react appropriately to the withdrawal. Some research suggests that new risk information may receive excessive weight in consumer decisions, or that consumers may oversimplify the implications of risk information due to cognitive limitations (Magat and Viscusi, 1992). By studying the impact of the Vioxx withdrawal on quantities purchased, product mix, and expenditures, we study outcomes relevant to researchers and to policy makers.

In the remainder of the paper we first provide background on the Vioxx withdrawal events, describe prior relevant work, and lay out our hypotheses. We next describe the Medicaid data and the empirical tests of hypotheses regarding effects of the Vioxx withdrawal on aggregate usage patterns, and present our findings. We then describe our MEPS data analysis to examine effects of the Vioxx withdrawal on individual usage patterns. A final section summarizes and concludes.

[2] Qureshi et al. (2011) find only a 3.6% safety withdrawal rate for new molecular entities (NMEs) introduced between 1980 and 2009, but their data show that withdrawals for safety reasons make up a larger percentage of all drug discontinuations since 1990 (29%) compared to the 1980s (15%).

## 2. Background

### 2.1. The Vioxx withdrawal

Vioxx is a COX-2 inhibitor, a type of non-steroidal anti-inflammatory agent (NSAID) that acts on the COX-2s enzymes which are responsible for inflammation. Unlike other NSAIDs (which will henceforth be referred simply to as 'NSAIDs', excluding COX-2s), COX-2 inhibitors do not display gastrointestinal side-effects. This feature, first reported in leading medical journals in 1999, led to the widespread popularity of these drugs. These studies showed much lower gastrointestinal complications with COX-2 use compared to other NSAIDs drugs such as ibuprofen or naproxen. The risk of gastrointestinal complications from NSAIDs use among the elderly is particularly high, leading to many excess hospitalizations and deaths among this population (Ray et al., 1990). However, the COX-2 drugs do not have greater efficacy in treating pain and inflammation; in this regard they are very similar to the older NSAIDs drugs (Griffin, 2000).

Vioxx was introduced in 1999, entering the market soon after the entry of the first COX-2 inhibitor, Celebrex. Another competitor, Bextra, entered the market in 2002. These three drugs were the only competitors in the COX-2 class, and became blockbuster drugs for their manufacturers as the class soared in popularity. Soon after its introduction, Vioxx became one of the best selling prescription drugs in the US, and the COX-2 class on the whole accounted for nationwide sales of $5.5 billion by 2004.

The COX-2 drug class suffered a major setback in September 2004 when Vioxx was voluntarily withdrawn from the market by its manufacturer (Merck) due to tests which revealed that extended exposure to Vioxx caused increased risk of heart attacks. These dangers had been apparent in initial studies (VIGOR) that compared Vioxx to naproxen in 2000, but it appeared that heart attacks occurred among high-risk patients (who should have been taking aspirin to reduce their risk). Scientists interpreted the greater heart attack risk associated with Vioxx as appearing because naproxen lowered risks of heart attacks (Mukherjee et al., 2001).[3] In 2004, editors at the *New England Journal of Medicine* realized that there was more information available from this study that the authors did not take into account, including information that adverse cardiac events occurred in low-heart-risk patients as well. Merck voluntarily withdrew the drug in response to new information, from both internal studies and the FDA studies (Stolberg, 2004).[4] These studies heightened awareness about the coronary side-effects of COX-2 drugs and the NSAIDs in general.

Pfizer voluntarily withdrew Bextra from the market in April 2005 following an FDA request; evidence from meta-analysis of earlier studies revealed that Bextra also increased heart attack risk. Some researchers suggested that Bextra more-than-doubled heart attack risk, which would make it even riskier than Vioxx. However, the validity of the science was controversial, as demonstrated by a decision earlier in 2005 by an advisory panel that had (narrowly) recommended Bextra remain in the market.

At the same time as the Bextra withdrawal, the FDA called for a "black box" warning label on Celebrex, the remaining COX-2 medication on the market. The black box warning is the most stringent warning placed in the labeling of a prescription drug medication, used to indicate an extremely serious risk (Murphy and Roberts, 2006). The prominently displayed box is particularly used in cases where the FDA finds a specific risk of death.[5] The label for Celebrex was required to state that it can increase cardiovascular problems, but that the lowest doses could be used safely for short periods of time.

Coincident with the Celebrex warning, the FDA also called for stronger warning labels on all NSAIDS.[6] While not as strong as a black box label, these warnings provide consumers with more specific information regarding the risk of ulcers, heart attacks, and strokes associated with the use of these drugs. The required language specifically warns that the elderly are at greater risk for serious gastrointestinal problems.[7] One exception to the labeling requirement was made for the NSAID sub class of Salicylates – including aspirin – which has pain-relief and anti-inflammatory properties and is also a platelet inhibitor with benefits for cardiovascular health.

As a result of the confluence of events surrounding the Bextra withdrawal, it is impossible to study this event in the same way as the Vioxx event. However, while we focus on the Vioxx withdrawal in our paper, we also comment on effects seen from the combination of the withdrawal and warnings of April 2005 involving Bextra and all COX-2 and NSAIDs. The timing of the events we study is the following: Vioxx was withdrawn on September 30th 2004 which is the end of the 3rd quarter of 2004; on April 7th 2005 (mid-2nd quarter of 2005), Bextra was withdrawn and Celebrex and NSAID labels were ordered.

### 2.2. Related literature

There is a large body of literature related to consumers' reactions to negative information about products. Much of this literature has focused on retail markets including foods, chemical cleaners, furniture, and other products for which

[3] http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf.

[4] An advisory panel recommended in 2005 that Vioxx be returned to the market because of disagreement about the risks versus benefits, but Merck has not decided to return the product to market.

[5] Requiring a black box warning also restricts the types of advertising that can be used for the drug.

[6] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm.

[7] This statement also appears in the Celebrex labeling.

standardized warnings are provided in a product label.[8] The research examines whether product labels are utilized and understood by consumers, and results generally support the hypothesis that such labeling is informative. Studies of consumer recollection of product labeling or warning information show that warnings are remembered and affect intended use or actions in relation to the good (e.g., Viscusi et al., 1986; Smith and Johnson, 1988; Zarkin and Anderson, 1992). Product labeling has also been found to affect relative market shares in the directions expected if consumers make use of available information (Ippolito and Mathios, 1990; Burton and Biswas, 1993; Mathios, 2000; Heiman and Lowengart, 2008).[9]

In prescription drug markets, negative product information may be relayed to physicians, to consumers, or to both parties. FDA regulation of direct-to-consumer advertising requires drug manufacturers to include extensive information about adverse side effects in their drug advertisements. The FDA also releases physician advisories and requires warning labels on prescription drug products themselves, which provide negative information at the point of prescribing or sale. Empirical studies of the effectiveness of FDA-provided information, through label changes and doctor advisories, show mixed results, with some studies finding no significant effects on prescribing (e.g., Soumerai et al., 1987) and others finding significant (although generally modest) declines in prescribing (e.g., Guo et al., 2003). Several recent papers examining the case of black box warnings on antidepressants find that there was a significant decline in the use of pediatric antidepressants following the suicidality warnings placed on those medications in 2004.[10]

Physicians and consumers may also receive information about prescription drugs through reporting of clinical trial results in medical journals and/or the popular press. Azoulay (2002) studies the effect of scientific information stemming from clinical trials on the market shares of prescription drugs, using data from the anti-ulcer drug market. The study finds that a greater stock of clinical evidence regarding a drug's efficacy increases the drug market share, and concludes that clinical research provides information to the market and helps to shape product market competition.[11]

A more precise and unequivocally negative signal about a product's safety occurs when the product is recalled from the market. There are many cases of products being partially or temporarily recalled, for example, because specific manufacturing lots are damaged, or one component part requires repair or replacement. Less commonly, a product is entirely withdrawn from the market due to safety concerns. In such cases the recall provides a strong negative signal about the product; but its signal about the manufacturer and about related products, competitors, or the industry is less clear. A product recall could lead to either negative demand spillovers or positive demand spillovers for other products and firms.

Studies of temporary or partial product recalls find that these events significantly reduce both the demand for the product (Crafton et al., 1981; Hartman, 1987) and the share price of the affected firm (Mitchell, 1989; Govindaraj et al., 2004). Such studies commonly find that the affected firm's share price decline exceeds the direct costs of the recall and lost sales, leading researchers to conclude that there are significant reputation penalties for product recalls. Spillover effects appear to vary with circumstances: in the case of automobile recalls, research suggests no effects on competitors (Hoffer et al., 1994; Hartman, 1987), but Govindaraj et al. (2004) find positive spillover effects for tire manufacturers from the Bridgestone tire recall.

Results for drug recalls are similarly mixed. Mitchell (1989) finds negative spillover effects for other OTC drugs from the Tylenol recall, but in general the existing research finds weaker spillover effects in drug withdrawal events (Jarrell and Peltzman, 1985; Hoffer et al., 1988). Dranove and Olsen (1994) study 18 events that provide negative information in prescription drug markets and find that there are no significant spillover effects on competitors' drug sales, but significant negative spillover effects on competitors' share prices. The authors conjecture that negative spillover effects on share prices arise from the market's anticipation of increased regulation.

Our research relates most closely to that of Cawley and Rizzo (2008), who examine the effects of seven prescription drug withdrawals during the period 1997–2001 on consumers' use of remaining drugs in the same class. Using individual-level data from the MEPS, for the majority of cases the authors find that withdrawal of a drug is associated with negative spillover effects to other drugs in the class. Specifically, patients display lower utilization rates and lower take-up rates of other non-withdrawn medications in the same class following the year of the withdrawal event. However, this finding does not occur in all cases, and some competitor drugs experience positive spillovers. The authors find that in the case of heartburn and cholesterol drugs there are competitive benefits, while there are negative spillovers in the other classes (including obesity, pain, hypertension, and irritable bowel syndrome) examined. They argue that withdrawn drugs with larger market shares, fewer substitutes, and safety problems that are unique within the class will be more likely to exhibit positive spillovers.

We examine the effects of the Vioxx withdrawal and related events on the market for the remaining competitor drugs. Our study contributes to the literature by examining a case that has a unique information structure. The magnitude of the Vioxx withdrawal and the strong inter-relatedness of the affected drug classes provide a rich environment for studying the effects of negative information in the prescription drug market. Our study also adds to prior research by examining product

[8] Hieke and Taylor (2012) provide a review of the large literature on nutrition labels.

[9] There is also a large body of literature examining the formatting of labels and warnings, which concludes that both format and specific information content are important in affecting outcomes (e.g., Magat et al., 1988; Smith et al., 1990; Wansink, 2003; Russo et al., 1996; Heiman and Lowengart, 2008). Moreover, giving too much information can actually cause consumers to make poorer decisions (Keller and Staelin, 1987; Malhotra, 1982).

[10] Busch and Barry (2009) provide a summary; see also Busch et al. (2010) and Parkinson et al. (2012).

[11] A more recent example is the Cleveland Clinic study of Avandia's cardiovascular risks in 2007, after which it was noted that the sales of Avandia declined (Harris, 2010).

mix and overall expenditures in the affected markets, and by using a longitudinal sample of Vioxx users to examine usage patterns among competitor drugs after the withdrawal.

### 2.3. Hypothesized responses

In general, the Vioxx withdrawal is expected to have negative spillover effects on usage for drugs thought to share similar risks, and positive spillover effects on competitor products seen as unaffected by the risks associated with the withdrawn drug. Vioxx was shown to be associated with fatal risks, and drugs with similar pharmacology may have suggested the same risks to consumers of other COX-2 drugs, even though they were not subject to the withdrawal action in September 2004. Additionally, COX-2 drugs (even absent the fatality risks) had been shown to have relatively small or no increased efficacy over older NSAIDs drugs; the main benefit was a reduction in the risk of stomach bleeding for certain long-term uses. This benefit affected a relatively small number of patients, but was particularly important for elderly patients.

Given this information, the Vioxx withdrawal is expected to have negative spillovers for Bextra and Celebrex, but positive spillovers for the NSAIDs which are substitutes for reducing inflammation but act through different physiological mechanisms. We may also observe an increase in usage of Analgesics, since these drugs are often recommended for osteoarthritis therapy due to bleeding risks for the elderly associated with NSAIDs (Griffin, 2000). The 2005 withdrawal of Bextra, and simultaneous requirements for stronger warning labels on Celebrex and the entire class of NSAIDs, will further reduce the usage of Celebrex, and NSAIDs. This should lead to additional substitution toward competitor drugs in the Analgesics and Salicylates (aspirin) classes, which were not affected by the stronger warning labels. We examine aggregate and individual usage variations to provide evidence on these changes.

We further analyze the aggregate data to examine the effects of the Vioxx withdrawal on drug mix and expenditures in competitor classes. The NSAIDs, Salicylates, and Analgesics classes include many older products, and there is a range of generic and OTC alternatives available in these classes. We may see more use of OTC or generic products for inflammation relief if these classes are seen as safer competitors due to the withdrawal; alternatively, usage may shift to branded prescription products in competitor classes if they are viewed as providing stronger or more effective benefits. The availability of generic and OTC drugs also leads to large differences in average prices by class. These price differences suggest a strong potential for prescription cost savings in the aftermath of the Vioxx withdrawal if usage shifts away from COX-2s.

We further analyze the individual data to examine drug usage changes for patients over age 65. This age group benefited disproportionately from long-term use of the COX-2 drugs, so they were more exposed to the risks publicized by the Vioxx withdrawal. This age group also faces greater gastrointestinal health risks from the use of NSAIDs. As a result, we expect to observe stronger negative spillover effects of the Vioxx withdrawal and the NSAIDs warnings events among this age group, and differences in changes in their drug usage patterns.

## 3. Analysis of aggregate-level responses

### 3.1. State Medicaid data

The primary source of data for our analysis is the Medicaid State Drug Utilization (SDU) records provided by the Centers for Medicaid and Medicare (CMS) from data submitted by states.[12] Under the Medicaid Drug Rebate Program, drug manufacturers have agreements to receive Federal funding for outpatient drugs dispensed by state Medicaid programs. Forty-nine states and the District of Columbia are included in the program (Arizona is excluded), and agreements are in place with over 550 pharmaceutical companies. In order to calculate rebate amounts, each state submits data on drug usage under Medicaid to CMS each quarter. (Note that the rebate information itself is not reported publicly.)

The SDU provides data on drug reimbursements in each state for the entire population insured under the fee-for-service Medicaid program, constituting an average of 55 million beneficiaries per year in our study period. The SDU data records the total number of prescriptions and amounts reimbursed under Medicaid for each state and quarter by national drug code (NDC). The SDU data include covered OTC[13] drugs, prescription drugs, and both generic and branded drugs.

Medicaid data provides an advantage over other aggregated data on drug expenditure or usage trends; all drugs are prescribed under a specific insurance program, with known pharmacy benefit characteristics and known population characteristics. Although there is no reason to expect *a priori* that characteristics of the Medicaid population or the programs change immediately at the time of the COX-2 withdrawal events in ways that affect the use of anti-inflammatory medications, we include controls for population and state program characteristics (such as the age structure of the beneficiary population) in our regression analysis to ensure that our results do not inadvertently pick up such influences. SDU data also provides

[12] The SDU data have been used in prior research (Duggan and Scott Morton, 2006); nevertheless, we conducted additional analysis to confirm the quality of the data for our research. We examined the percent of drugs that we could match with Multum, aggregated individual prescription data, compared totals to published CMS totals, and compared trends of aggregate drug use in the SDU data to those seen in national totals for the classes of interest. The results, available from the authors, lead us to believe that the SDU data are suitable for use in our analysis.

[13] States differ in the extent to which OTC drugs are reimbursable under Medicaid. However, there has not been a substantial change in this coverage over time within a given state during our time period. See National Pharmaceutical Council, various years.

**Table 1**
Drug class data by year.

| | 2001 | 2002 | 2003 | 2004 | 2005 |
|---|---|---|---|---|---|
| Number of prescriptions | | | | | |
| COX-2 | 7,870,970 | 7,988,188 | 7,518,005 | 6,868,426 | 2,502,577 |
| Analgesics | 5,312,975 | 5,099,107 | 4,818,702 | 5,155,259 | 5,666,861 |
| Salicylates | 201,445 | 187,266 | 173,158 | 172,945 | 194,316 |
| NSAID | 9,352,785 | 9,998,705 | 10,523,835 | 11,423,642 | 13,616,537 |
| All drugs | 459,560,510 | 500,910,879 | 529,154,584 | 568,440,920 | 594,530,053 |
| Percent of prescriptions for branded drugs | | | | | |
| COX-2 | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| Analgesics | 64.8% | 38.7% | 2.3% | 0.7% | 0.5% |
| Salicylates | 4.2% | 3.0% | 1.8% | 0.6% | 0.4% |
| NSAID | 13.9% | 8.2% | 7.8% | 7.2% | 8.9% |
| All drugs | 54.8% | 52.8% | 50.9% | 49.4% | 47.3% |
| Amount reimbursed per prescription | | | | | |
| COX-2 | $85.09 | $89.72 | $93.09 | $99.24 | $102.88 |
| Analgesics | $24.73 | $23.75 | $13.38 | $11.28 | $10.72 |
| Salicylates | $25.99 | $27.58 | $26.39 | $27.43 | $26.00 |
| NSAID | $22.81 | $6.83 | $6.57 | $6.90 | $11.29 |
| All drugs | $53.55 | $57.19 | $60.05 | $64.91 | $66.98 |
| Total amount reimbursed | | | | | |
| COX-2 | $669,740,837 | $716,700,227 | $699,851,085 | $681,622,596 | $257,465,122 |
| Analgesics | $131,389,872 | $121,103,791 | $64,474,233 | $58,151,322 | $60,748,750 |
| Salicylates | $5,235,556 | $5,164,796 | $4,569,640 | $4,743,881 | $5,052,216 |
| NSAID | $213,337,026 | $68,291,155 | $69,141,596 | $78,823,130 | $153,730,703 |
| All drugs | $24,611,136,136 | $28,648,099,445 | $31,774,092,259 | $36,899,973,626 | $39,824,486,014 |

*Source*: Medicaid state drug utilization dataset, aggregated at the class level using the Multum-Lexicon classification system.

the advantage of quarterly reporting, which allows changes in drug usage to be more precisely related to the timing of drug withdrawal or warning events. Because all covered prescriptions are reported, the SDU data permit an examination of the substitution of drug use within and across drug categories.

The SDU data as released from CMS includes the FDA-designated NDC, a standardized code identifying each drug name (including generics) by dispensing method and dosage. We use the Lexicon database developed by Multum Information Services to match each NDC code in the SDU data with a database of drug categories and characteristics. Using the Multum Lexicon identifiers, each drug-dose-form combination listed separately in the CMS data is aggregated to the level of a brand or generic name across dose and form of administration, and further aggregated into drug classes. Our analysis includes four Multum drug categories: COX-2 inhibitors (code 278) including Bextra, Celebrex, and Vioxx; non-steroidal anti-inflammatories (NSAIDs, code 61) such as ibuprofen, which are the closest therapeutic substitutes for COX-2 drugs; Salicylates (code 62) such as aspirin; and Analgesics (code 59), a class of pain relievers that do not have anti-inflammatory properties but are nonetheless often a recommended for those with higher risk of gastrointestinal bleeding (Griffin, 2000).[14]

For drug classes other than the COX-2, we aggregate data from the SDU into the drug class level for our regression analysis, after merging the Multum classifications into the CMS data by NDC code.[15] We chose the class level (for example, Salicylates) instead of the brand or molecule level (e.g. aspirin) for our empirical analysis, because our hypothesis examines aggregate class-level effects. When aggregating the data to the class level, we also calculate the prescription-weighted average for the share of prescriptions that are for drugs defined in the Multum Lexicon as being OTC or generic.

Our data time period spans from the first quarter of 2001 through the fourth quarter of 2005. While CMS provides data from periods more recent than 2005, these data are not comparable to the 2001–2005 period due to the implementation of Medicare Part D in 2006, which transferred prescription drug coverage for individuals eligible for both Medicaid and Medicare (dual-eligibles) out of this database (Bruen and Miller, 2008).

For our study period, the SDU contains 4704 individual drug names in our four drug classes of interest, each followed in 49 state markets[16] over the 20 quarters between 2001 and 2005. This comprises approximately 114.7 million dispensed prescriptions, at a total cost of $4.92 billion to the states, including $3.2 billion in reimbursements for COX-2 drugs alone. Table 1 displays the number of prescriptions for each drug class, the percent of prescriptions for branded drugs, the average amount reimbursed per prescription, and the total amount reimbursed per year. For comparison purposes, the table also

[14] On average, 96.5% of all drug-dose-unit combinations in the CMS data successful matched by NDC code with the Lexicon data, meaning that we are unable to discern the drug class for 3.5% of all CMS entries.

[15] Pediatric medications within these classes were identified by a licensed pharmacist contracted for this study, and dropped from the data before aggregating by drug class, since these are beyond the interest of this study.

[16] The state is the natural unit of observation since Medicaid programs are administered at the state level. The markets include 48 states and Washington DC. Arizona data is not reported in the SDU and Tennessee is only partially reported, and thus these states are excluded from our sample.

**Table 2**
Summary statistics, state medicaid dataset.

| Variable | Observations | Mean | Std. dev. |
|---|---|---|---|
| Number of prescriptions | 3850 | 29,780 | 57,369 |
| Reimbursement per prescription | 3850 | $41.47 | $32.02 |
| Total reimbursement amount | 3850 | 128,000,000 | 343,000,000 |
| Percent of prescriptions that are OTC (excluding COX-2) | 2887 | 0.3695 | 0.2306 |
| Percent of prescriptions that are generic (excluding COX-2) | 2887 | 0.5287 | 0.1671 |
| Percent of beneficiaries in fully capitated managed care | 3850 | 0.4590 | 0.3053 |
| Percent of beneficiaries age 65 and over | 3850 | 0.0751 | 0.0263 |
| Percent of beneficiaries age 18 and under | 3850 | 0.6042 | 0.0608 |
| State has preferred drug List (indicator) | 3850 | 0.3540 | 0.4783 |

*Source*: Prescription data from Medicaid State Drug utilization dataset; beneficiary data from Current Population Survey; preferred drug list indicators from the National Pharmaceutical Council.

displays these statistics for all prescriptions in the SDU. Over time, patterns in the aggregate data are distinct from those in the four drug classes of interest, confirming the changes observed after the Vioxx withdrawal do not reflect general trends in Medicaid prescriptions.

There were over 7 million prescriptions for COX-2 drugs throughout most years across the data, falling precipitously to 2.5 million prescriptions by 2005. NSAIDs are more popular than the COX-2 class; Analgesics are nearly as popular and usage remains strong through 2005; but prescription-strength Salicylates (aspirin) are relatively uncommon in the data. The COX-2 drugs are only available in branded form, but the other classes are populated primarily by generics in most years. The percent of prescriptions for branded NSAIDs and branded Analgesics declines over the period, but use of branded NSAIDS increases again in 2005.

The availability of generic versions of older drugs has a strong impact on average reimbursement amount per prescription: COX-2 drugs are just over 3 times as expensive as the average drug in other classes in 2001, but by 2005 the rise in COX-2 costs and the decline in average costs in other classes equates to COX-2 prices that are nearly 10 times the expense of the average NSAID or Analgesic prescription, and four times more expensive than a Salicylate prescription. Due to the changing patterns of usage over the period, overall Medicaid reimbursements for these four drug classes decline over time from just above $1 billion in 2001, to just below $500 million in 2005.

To control additional aspects of our data, we add state-level data on Medicaid populations and program characteristics that may also affect the use of medications to the SDU drug database. We calculate and add to our database state-by-year estimates of the age distribution of Medicaid beneficiaries by categories (under age 18, those between age 19 and 64 and those age 65 and older) from the Current Population Survey (CPS). We also calculate the percent of Medicaid beneficiaries in fully-capitated managed care contracts by state and year, whose prescriptions are not included in the SDU data, from administrative totals published by CMS. We obtain state-by-year measures of Medicaid prescription drug regulations from the National Pharmaceutical Council (NPC) annual publications. Table 2 presents summary statistics for key variables in the final dataset.

### 3.2. Trends in Medicaid data

We present a descriptive look at trends in SDU data around the time of the COX-2 withdrawal events. Fig. 1 shows quarterly national Medicaid data on the total number of prescriptions of each of the COX-2 brands. The Medicaid series for the withdrawn drugs terminates at the dates of their respective withdrawals from the market (2004:3 and 2005:2), confirming that our data correctly captures these events. The graph also shows sales of Celebrex decline after the Bextra withdrawal, suggesting a negative spillover effect, or an effect of the stronger warning label placed on all COX-2 medications

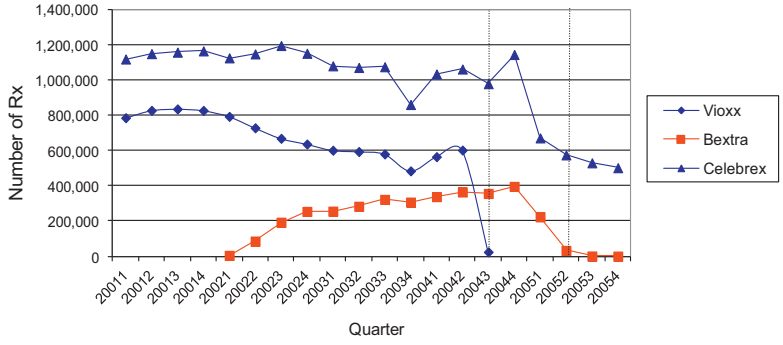


**Fig. 1.** Medicaid prescriptions for COX-2 brands.

*Source*: See notes under Table 1.

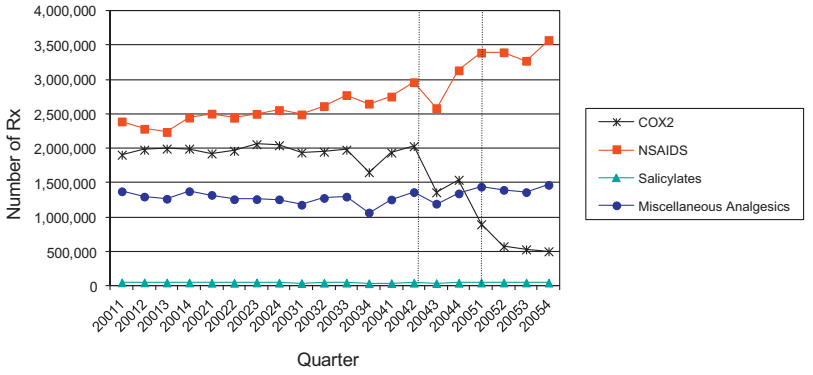


**Fig. 2.** Medicaid prescriptions for anti-inflammatory and analgesics drugs.

*Source*: See notes under Table 1.

at the time of the Bextra withdrawal. Prescriptions for Celebrex continued to decline throughout the remainder of the sample period, consistent with the interpretation that the effect is due to the stronger drug warning.

Fig. 2 shows quarterly prescription counts (including OTC drugs that appear in the SDU data) for each of the four drug classes included in our study. The graph shows a precipitous decline in the aggregate use of COX-2s after the withdrawal and warning label events, as well as a concomitant growth in the use of NSAIDs, their closest competitor drug. However, the overall increase in the number of NSAIDs prescriptions does not appear to compensate for the decline in COX-2 prescriptions. This could reflect the fact that NSAIDs are not considered perfect substitutes for COX-2s, or that NSAID growth would have been higher if not for the NSAIDs warning label that went into effect concurrently with the Bextra withdrawal in 2005. The use of Salicylates (aspirin) and Analgesics were relatively less affected by the COX-2 withdrawals. Analgesics are not a close substitute for COX-2 inhibitors, nor did they receive a warning label; hence, the lack of a strong effect of the study events on their aggregate use is not surprising. In the case of Salicylates, the total number of prescriptions in the database is small.

Quarterly Medicaid reimbursement amounts for each class over time are displayed in Fig. 3. As expected, Medicaid expenditures on COX-2s declined substantially from its peak in second quarter 2004 through the end of 2005. The figure also suggests positive competitive spillovers for the NSAIDS class, as total reimbursements increase following the Vioxx withdrawal. However, there is a distinct flattening in the NSAIDS reimbursement amounts in 2005 after they received a warning label and Bextra was withdrawn.

### 3.3. Empirical methodology

We test whether these descriptive patterns persist in more formal tests of hypotheses by estimating linear regression models of the Vioxx withdrawal effect on drug usage patterns, and reimbursement amounts in state Medicaid programs. We examine dependent variables including number of prescriptions, total dollar amount of reimbursements, and average reimbursement per prescription. The unit of observation is a drug or drug category k in state s (49) and period t (2001:1 through 2005:4).

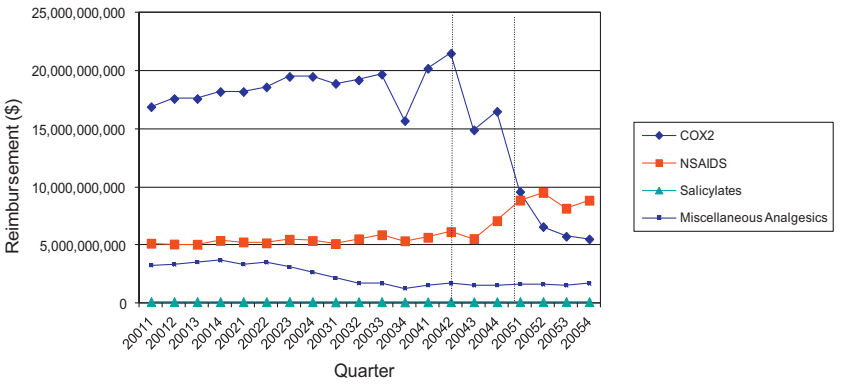


**Fig. 3.** Total Medicaid reimbursements by class.

*Source*: See note under Table 1.

In order to understand the within-class spillovers of this event, we first estimate models examining the effect of the withdrawal events on remaining brands in the COX-2 (Bextra and Celebrex) class. Because of distinct entry and exit dates of Bextra from the market, we estimate these models for each drug individually. We then combine data from each of the four classes to examine the effects of the Vioxx withdrawal on competitor drugs by class (k = COX-2, NSAIDS, Salicylates, Analgesics). Finally, we disaggregate each of the competitor classes into subclass categories of "competitors" (k = Branded Rx, Branded OTC, Generic Rx, Generic OTC), and estimate models that examine the effects of the Vioxx withdrawal on these subclasses.

We estimate the effect of the Vioxx withdrawal on our outcomes by including a withdrawal date dummy (indicated by $W_v$) set equal to 1 at the quarter of the Vioxx withdrawal and beyond, interacted with each of the drug indicators k. For ease of interpreting the interactions, we do not omit any drug as a comparison category. To avoid confounding effects of the Bextra withdrawal in the second quarter of 2005, we truncate the sample period for this analysis at 2005:1. The basic model specification is shown in Eq. (1).

$$\mathrm{Ln}(Y_{kst}) = D_k\gamma + \sum\nolimits_k \theta_k D_k W_v + X_{skt}\beta + \mu_t + \nu_s + \varepsilon_{kst}. \quad (1)$$

$Y$ represents the various alternative dependent variables mentioned above, expressed in natural logarithm form.[17] In a typical private market, supply and demand forces lead to the joint determination of the quantity and the price of a drug; however, drug reimbursements and rebate programs are negotiated mostly at the federal level in state Medicaid programs. Furthermore, Medicaid beneficiaries face very low out-of-pocket costs for the drugs relative to the reimbursement prices paid by the Medicaid program. For these reasons, the relationship between prices and quantities in a Medicaid market are of less intrinsic interest, and so we estimate reduced form models that include only exogenous state-level variables rather than specifying reimbursement and quantity equations as jointly determined.

$D_k$ represents dummy variable indicators for each of the k drug categories. The vector **X** represents other characteristics that determine Medicaid usage for the class. We assume relevant factors (**X**) which determine demand for, and pricing of, each drug class in a state's Medicaid program are characteristic of a state's Medicaid population and restrictions on prescription drug coverage. State-level control variables are specified as the percent of beneficiaries in managed care, percent of beneficiaries in different age categories (under 18 and over 65), and an indicator for whether the state has a Medicaid preferred drug list.[18] Since these variables may have different effects on different drugs, they are interacted with the drug category.[19] $\mu$ is a set of time fixed-effects (quarter and year), $\nu$ represents state fixed-effects, and $\varepsilon$ is a random error term. All models are estimated with standard errors that are robust to arbitrary forms of heteroskasticity, and clustered by state.

We recognize that drug class market shares and our other outcomes may trend over time due to unobservable factors, and that reactions to drug withdrawals may take some time to be realized. Therefore, in alternative model specifications, we estimate the effect of withdrawals in terms of changes in growth patterns over time, by including class- and state-specific linear time trends as controls in the models. In these models, the impact of the Vioxx withdrawal is measured in relation to underlying growth patterns for each drug category (k) in the Medicaid program nationally, and for each state's Medicaid program for any k drug categories.

We also conduct a second set of estimates to examine the incremental effect of the Bextra withdrawal on our outcomes. In this analysis we extend the sample period to 2005:4 to incorporate the periods following the Bextra withdrawal in 2005:2. We include a second withdrawal date dummy (and thus the withdrawal dates are indicated by the vector $\boldsymbol{W} = w_v, w_b$). Because the Celebrex and NSAIDs warning labels were announced at the same time as the Bextra withdrawal, the Bextra date incorporates both pieces of information. This model specification is shown in equation (2).

$$\mathrm{Ln}(Y_{kst}) = D_k\gamma + \sum\nolimits_k \theta_k D_k \boldsymbol{W} + \mathbf{X}_{skt}\beta + \mu_t + \nu_s + \varepsilon_{kst} \quad (2)$$

### 3.4. Results

#### 3.4.1. Within-class competitors

We estimate the effects of the Vioxx withdrawal on Bextra and Celebrex markets respectively through the period 2005:1, and the effects of the Vioxx and Bextra withdrawals on the market for Celebrex by extending the sample period through 2005:4. For each dependent variable we estimate a basic model that includes only the withdrawal events and quarter, year

[17] Our approach is similar to that in Freedman et al. (2012). We also estimated the models of prescription quantities using a multinomial logit demand system approach, in which the outside option is measured using the adult Medicaid population in each state (see Berry, 1994; Azoulay, 2002), and results are similar.

[18] Models were also estimated with additional age categories (distinguishing 11–18 year olds from those under age 10), percent of beneficiaries who are white, female, or high school dropouts, Medicaid maximum copayment amounts for prescription drugs, and statewide unemployment rates. Results were unchanged. Estimates were also tried with additional state Medicaid prescription policies such as fail-first requirements, tiered copayments, and prior authorization requirements (see e.g. Simon et al., 2009), but these variables tended to drop out of the estimates due to lack of sufficient variation over state and time.

[19] Because the state Medicaid characteristics variables do not vary by drug class, uninteracted versions of the variables cannot be included in the models (Mathios, 2000).

and state fixed effects; a second model which adds state-level demographic and policy variables; and a third model which adds state-specific linear time trends.

Table 3 reports the estimation results. For ease of comparison, only the estimated coefficients for the withdrawal event dummies are reported in the table.[20] We observe the signs and statistical significances of the coefficient estimates are similar in the models with and without the control variables, and adding the linear state-specific time trends reduces the estimated effects of the withdrawal events only modestly.

The results show that usage of Bextra is negatively affected by the Vioxx withdrawal, with both the number of prescriptions and total reimbursements falling dramatically. The average reimbursement per prescription also decreased moderately.[21] All of these effects are statistically significant at the 1% confidence level. Conversely, Celebrex experienced a positive spillover from the Vioxx withdrawal, with a significant rise in both the number of prescriptions and total reimbursements. Nonetheless, average reimbursement per prescription fell modestly for Celebrex just as for Bextra. These reductions in average reimbursement amounts may reflect price reductions, but could also reflect shortened prescription length or lower dosage prescriptions.

The gains for Celebrex were reversed after our second study event, in which Bextra was withdrawn from the market and Celebrex received a Black Box warning label. The declines in the number of prescriptions and total reimbursements are larger than the increases observed after the Vioxx withdrawal, reflecting the combined effects of spillovers from Bextra's withdrawal and the direct negative news associated with Celebrex's own relabeling.

### 3.4.2. Across-class competitors

Estimates of the Vioxx withdrawal effects for the four related drug classes in specifications of the form (1) are reported in Table 4. As in the previous table, three models are estimated for each dependent variable: a basic model that includes only the withdrawal events and class, quarter, year and state fixed effects; a second model adds state-level demographic and policy variables, and a third model with state-specific and class-specific linear time trends.

Estimates are reported for all three of our dependent variables – number of prescriptions, average reimbursements and total reimbursements. At the class level, estimates of total reimbursements capture the combined effects for Medicaid of changes in prescription counts, dosage, or length; changes in mix of drugs prescribed; and changes in pricing that occur after the withdrawal event. Estimates of average reimbursements reflect changes in the mix of drugs, and any changes in price, dosage or length per prescription.

The estimates suggest that the withdrawal of Vioxx resulted in positive spillover effects for the substitute drug classes of NSAIDs and Analgesics.[22] We observe a statistically significant increase in the number of NSAIDs prescriptions, total reimbursements and average reimbursement per prescription for NSAIDs after Vioxx was withdrawn. Similarly, we observe a significant increase in prescriptions for Analgesics after Vioxx was withdrawn. Total and average reimbursements for Analgesics decrease after the Vioxx withdrawal, but increase significantly relative to previous trends. Salicylates usage and reimbursements are not significantly affected by the Vioxx withdrawal event after accounting for control variables and time trends. We observe that the signs and statistical significances of the coefficient estimates are similar in the models with and without the control variables, but including linear class-specific and state-specific time trends substantially reduces the estimated effect of the Vioxx withdrawal in most cases.[23]

The results also show a reduction in prescriptions and total reimbursements for COX-2 drugs after the Vioxx withdrawal. This may be the expected result given that one drug in the class was removed from the market, and does not indicate that demand for either remaining COX-2 drug actually declined. Nonetheless, it does indicate that not all previous Vioxx users switched to the remaining in-class competitors. Once controls and time trends are accounted for, the decline in total reimbursements for COX-2 drugs closely mirrors the decline in prescriptions, leading to a nearly zero and not statistically significant effect of the withdrawal on average reimbursement per prescription for this class.[24]

Table 5 reports estimates in the form of (2), including a second withdrawal dummy variable to capture the effects the Bextra withdrawal date (and the accompanying stronger warning labels for Celebrex and the NSAIDs). The sample period for these estimates is extended through 2005:4. We report only the most fully specified models that include control variables and linear class and state time trends.

The estimated impact of the Vioxx withdrawal is not much affected by the extension of the sample period or the addition of the second event indicator. The estimated coefficients and their statistical significances are identical or very similar to

[20] Control variables were generally not statistically significant, with the exception of states with a higher percentage of beneficiaries over age 65, where average reimbursements per prescription were higher. This could reflect higher unit prices, higher doses, or longer prescription lengths.

[21] The magnitude of the estimated effects, $\exp\{\theta\} - 1$ is a 52% reduction in the number of Bextra prescriptions and a 55% reduction in total Bextra reimbursements, when control variables and time trends are included in the models. Average reimbursements fell by an estimated 6%.

[22] The estimates (calculated as $\exp\{\theta\} - 1$) suggest a nearly 9% increase in NSAIDs prescriptions, and a 16% increase in Analgesics prescriptions, after controlling for state characteristics, class, and state time trends. Combined with the nearly 11% increase in average reimbursement amount for NSAIDs and the corresponding 8% increase for Analgesics, total reimbursements increased by 20% and 25% for these two classes, respectively.

[23] In models with trends, statistically significant control variables are: the number of COX-2 prescriptions, average analgesics reimbursement per prescription, and total COX-2 and analgesics. Reimbursements are positively related to the percent of beneficiaries over age 65; total analgesics reimbursements are also positively related to the percent of beneficiaries under age 18. Average reimbursement per NSAID prescription is negatively related to state preferred drug lists. Average reimbursement per COX-2 prescription is positively related to the percent of beneficiaries in MMC (and thus not in our data).

[24] The estimates (calculated as $\exp\{\theta\} - 1$) show a 26.7% decline in COX-2 prescriptions and a 28.2% decline in total reimbursements.

**Table 3**
Estimates of effects of withdrawal events on other COX-2 drugs.

| | Ln(Number of prescriptions) | | | Ln(Average reimbursement) | | | Ln(Total reimbursement) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fixed effects only | Fixed effects + controls | Fixed effects + controls + trends | Fixed effects only | Fixed effects + controls | Fixed effects + controls + trends | Fixed effects only | Fixed effects + controls | Fixed effects + controls + trends |
| Panel A: Bextra, 2002:1–2005:1 | | | | | | | | | |
| Post-Vioxx withdrawal | −0.737*** | −0.743*** | −0.734*** | −0.059*** | −0.059*** | −0.059*** | −0.795*** | −0.802*** | −0.794*** |
| | −10.993 | −10.613 | −10.071 | −2.916 | −2.932 | −2.932 | −11.451 | −11.041 | −10.445 |
| *N* | 620 | 620 | 620 | 620 | 620 | 620 | 620 | 620 | 620 |
| $R^2$ | 0.510 | 0.510 | 0.563 | 0.088 | 0.089 | 0.089 | 0.523 | 0.523 | 0.582 |
| Panel B: Celebrex, 2001:1–2005:1 | | | | | | | | | |
| Post-Vioxx withdrawal | 0.160*** | 0.167*** | 0.149** | −0.042*** | −0.041*** | −0.039*** | 0.118** | 0.126** | 0.110* |
| | 2.933 | 2.807 | 2.570 | −4.808 | −4.616 | −4.418 | 2.128 | 2.057 | 1.849 |
| *N* | 813 | 813 | 813 | 813 | 813 | 813 | 813 | 813 | 813 |
| $R^2$ | 0.121 | 0.127 | 0.257 | 0.410 | 0.417 | 0.526 | 0.071 | 0.077 | 0.215 |
| Panel C: Celebrex, 2001:1–2005:4 | | | | | | | | | |
| Post-Vioxx withdrawal | 0.193*** | 0.194*** | 0.172*** | −0.038*** | −0.037*** | −0.034*** | 0.155** | 0.157** | 0.137** |
| | 3.046 | 2.970 | 2.661 | −4.822 | −4.532 | −4.192 | 2.460 | 2.394 | 2.112 |
| Post-bextra withdrawal | −0.200*** | −0.200*** | −0.205*** | 0.004 | 0.004 | 0.004 | −0.196*** | −0.196*** | −0.201*** |
| | −2.660 | −2.673 | −2.660 | 0.679 | 0.591 | 0.621 | −2.706 | −2.715 | −2.707 |
| *N* | 959 | 959 | 959 | 959 | 959 | 959 | 959 | 959 | 959 |
| $R^2$ | 0.236 | 0.238 | 0.335 | 0.409 | 0.414 | 0.547 | 0.187 | 0.188 | 0.295 |

All models include fixed effects for state, year, and quarter. In models that include state-level control variables these are specified as the percent of beneficiaries in managed care, percent of beneficiaries over age 65, percent of beneficiaries under age 18, and an indicator for whether the state has a Medicaid preferred drug list. Trends are specified as linear state-specific time trends and linear drug-specific time trends.

* The 10% confidence level, all two-sided tests. T-statistics are based on standard errors which are robust to heteroskedasticity and to correlation over time within a state.

** The 5% confidence level.

*** Significantly different from zero at the 1% confidence level.

**Table 4**
Estimates of effects of Vioxx withdrawal on competitor classes.

| Variable | Ln(Number of prescriptions) | | | Ln(Average reimbursement) | | | Ln(Total reimbursement) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fixed effects only | Fixed effects + controls | Fixed effects + controls + trend | Fixed effects only | Fixed effects + controls | Fixed effects + controls + trend | Fixed effects only | Fixed effects + controls | Fixed effects + controls + trend |
| Post-Vioxx* NSAIDs | 0.283*** | 0.233*** | 0.084** | 0.177*** | 0.193*** | 0.101*** | 0.460*** | 0.426*** | 0.185*** |
| | 5.696 | 4.825 | 2.026 | 8.632 | 7.690 | 5.302 | 8.077 | 7.170 | 3.764 |
| Post-Vioxx* Salicylates | 0.041 | 0.049 | 0.105 | 0.152*** | 0.099*** | −0.033 | 0.194* | 0.148 | 0.072 |
| | 0.460 | 0.488 | 1.135 | 6.551 | 3.213 | −1.556 | 1.957 | 1.421 | 0.709 |
| Post-Vioxx Analgesics | 0.187*** | 0.160** | 0.147** | −0.436*** | −0.330*** | 0.079*** | −0.248*** | −0.170** | 0.226*** |
| | 2.950 | 2.069 | 2.297 | −11.788 | −6.863 | 2.695 | −3.440 | −2.184 | 3.363 |
| Post-Vioxx* COX-2 | −0.462*** | −0.392*** | −0.313*** | 0.238*** | 0.176*** | −0.018 | −0.224*** | −0.216*** | −0.331*** |
| | −11.079 | −6.373 | −5.790 | 14.285 | 7.938 | −1.359 | −4.757 | −3.518 | −6.001 |
| *N* | 3266 | 3266 | 3266 | 3266 | 3266 | 3266 | 3266 | 3266 | 3266 |
| $R^2$ | 0.907 | 0.910 | 0.911 | 0.795 | 0.812 | 0.850 | 0.928 | 0.930 | 0.937 |

All models include indicator variables for drug class, and fixed effects for state, year, and quarter. In models that include state-level control variables these are specified as the percent of beneficiaries in managed care, percent of beneficiaries over age 65, percent of beneficiaries under age 18, and an indicator for whether the state has a Medicaid preferred drug list. All control variables are interacted with the drug class indicator variables. Trends are specified as linear state-specific time trends and linear drug-specific time trends.

* Significantly different from zero at the 10% confidence level. T-statistics are based on standard errors which are robust to heteroskedasticity and to correlation over time within a state. All are two-sided tests.

** Significantly different from zero at the 5% confidence level.

*** Significantly different from zero at the 1% confidence level.

**Table 5**
Estimates of effects of Vioxx and Bextra withdrawals on competitor classes.

| Variable | Ln(Number Rx) Fixed effects + controls + trends | Ln(Average reimbursement) Fixed effects + controls + trends | Ln(Total reimbursement) Fixed effects + controls + trends |
|---|---|---|---|
| Post-Vioxx*NSAIDs | 0.083* | 0.104*** | 0.186*** |
| | 1.924 | 5.225 | 3.716 |
| Post-Vioxx*Salicylates | 0.099 | −0.030 | 0.070 |
| | 1.057 | −1.426 | 0.677 |
| Post-Vioxx*Analgesics | 0.146** | 0.081*** | 0.226*** |
| | 2.200 | 2.814 | 3.258 |
| Post-Vioxx*COX-2 | −0.310*** | −0.014 | −0.324*** |
| | −5.239 | −1.092 | −5.392 |
| Post-Bextra*NSAIDs | −0.058 | 0.019 | −0.040 |
| | −1.464 | 0.744 | −0.874 |
| Post-Bextra*Salicylates | 0.047 | −0.070*** | −0.023 |
| | 0.917 | −3.457 | −0.407 |
| Post-Bextra*Analgesics | 0.021 | 0.107*** | 0.127*** |
| | 0.600 | 5.164 | 3.304 |
| Post-Bextra*COX-2 | −0.743*** | 0.005 | −0.738*** |
| | −9.771 | 0.518 | −10.022 |
| *N* | 3850 | 3850 | 3850 |
| $R^2$ | 0.905 | 0.860 | 0.929 |

All models include state-level control variables (percent beneficiaries in managed care, percent beneficiaries over age 65, percent beneficiaries under age 18, indicator for Medicaid preferred drug list). All models also include fixed effects for state, year, quarter and class; and class-specific and state-specific linear time trends. *T*-statistics appear below the coefficient estimates.

* Significantly different from zero at the 10% confidence level. T-statistics are based on standard errors that are robust to heteroscedasticity and to correlation of error terms over time within a state. All are two-sided tests.

** Significantly different from zero at the 5% confidence level.

*** Significantly different from zero at the 1% confidence level.

those reported in Table 4. The Bextra withdrawal (and Celebrex warning) leads to further large reductions in prescriptions and total reimbursements for the COX-2 drugs. Just as after the Vioxx withdrawal, the coefficient estimate for average reimbursements is virtually zero and is not statistically significant, suggesting no significant changes in pricing, dosage, or prescription length occurred after these events.

The effects of the Bextra withdrawal and warning labels changes on the COX-2s competitor classes are generally modest. In a reversal of the impact of the Vioxx withdrawal event, the number of NSAIDs prescriptions falls after the second event, although the estimate fails to reach statistical significance. NSAIDs reimbursements (total or average) are not significantly affected by this event. There is no effect of this second event on the number of Analgesics prescriptions, but total reimbursements and average reimbursement per prescription both increase significantly for this class. On the contrary, although there is no effect on the number of prescriptions, average reimbursement per prescription falls significantly for the Salicylates class. In combination these findings suggest that warning labels rather than spillover effects may be driving the declines for the NSAIDs class, and that consumers may be changing which drugs they use in the Analgesics and Salicylates class after these events.

To explore this hypothesis further, we estimate the impact of the two withdrawal events on within-class changes in the number of prescriptions for the NSAIDs, Analgesics, and Salicylates classes. Because of the large number of generic and OTC drugs in each of these classes, rather than examine individual brands or dosage forms we disaggregate the data for each class into four relevant subclasses: branded prescription drugs, branded OTC drugs, generic prescription drugs, and generic OTC drugs. For each class we estimate models of the specification form (2) to examine the impact of the Vioxx withdrawal and the Bextra-plus-label-changes event on the mix of products used in each class.[25] These estimates are reported in Table 6, which reports only the most fully specified models.

These estimates show statistically significant and large increases in the use of branded prescription NSAIDs and decreases in use of generic prescription NSAIDs after the Vioxx withdrawal. Thus, the observed increase in NSAIDs use after this event comes about largely from increased use of branded prescription drugs. This seems likely to account for the increase in average reimbursements per prescription observed in Table 5. For the Analgesics, we observe large and statistically

[25] The results are similar if we run the estimates using stacked data from all three classes together. Note that for the Salicylates class, the small number of prescriptions leads to observations of zero in some states and quarters. Due to the use of logarithms these observations are dropped from the estimates.

**Table 6**
Estimates of the effect of withdrawals on competitor product mix.

| Variable | NSAIDS<br>Fixed effects + controls + trends | Analgesics<br>Fixed effects + controls + trends | Salicylates<br>Fixed effects + controls + trends |
|---|---|---|---|
| Post-Vioxx* branded Rx | 0.351*** | 1.034*** | 0.172 |
| | 2.711 | 8.731 | 1.374 |
| Post-Vioxx* Branded OTC | −0.103 | 0.005 | 0.199 |
| | −0.512 | 0.038 | 1.221 |
| Post-Vioxx* generic Rx | −0.197* | −0.474*** | 0.014 |
| | −1.738 | −3.587 | 0.136 |
| Post-Vioxx* generic OTC | −0.007 | 0.109 | 0.233 |
| | −0.015 | 0.467 | 1.275 |
| Post-Bextra* branded Rx | −0.029 | 0.626*** | −0.447*** |
| | −0.232 | 5.258 | −3.192 |
| Post-Bextra* branded OTC | −0.168 | −0.115 | −0.337** |
| | −1.102 | −1.572 | −2.260 |
| Post-Bextra* generic Rx | −0.106 | −0.266*** | −0.057 |
| | −0.852 | −3.536 | −1.150 |
| Post-Bextra* generic OTC | −0.427 | −0.046 | −0.122 |
| | −0.948 | −0.219 | −0.733 |
| *N* | 3135 | 3137 | 2711 |
| $R^2$ | 0.952 | 0.975 | 0.961 |

All models include state-level control variables (percent beneficiaries in managed care, percent beneficiaries over age 65, percent beneficiaries under age 18, indicator for Medicaid preferred drug list). All models also include fixed effects for state, year, quarter and brand; and brand-specific and state-specific linear time trends. *T*-statistics appear below the coefficient estimates.

* Significantly different from zero at the 10% confidence level. *T*-statistics are based on standard errors that are robust to heteroscedasticity and to correlation of error terms over time within a state. All are two-sided tests.

** Significantly different from zero at the 5% confidence level.

*** Significantly different from zero at the 1% confidence level.

significant increases in the use of branded prescription drugs after both the Vioxx withdrawal and the Bextra withdrawal events. We also see large and significant reductions in generic Analgesic prescriptions after both events. We observe large and statistically significant declines in use of branded prescription and branded OTC products in the Salicylates class in the post-Bextra-withdrawal period. These patterns are consistent with the changes in average reimbursements per prescription observed earlier.[26]

## 4. Analysis of individual-level responses

### 4.1. Individual-level MEPS data

We use data from the Prescribed Medicines Components of the MEPS, a nationally representative survey of the U.S. civilian population sponsored by the Agency for Healthcare Research and Quality (ARHQ), to look at patterns of responses beyond what aggregated state-level data provides. Each year, the survey follows an overlapping design where new households are selected for two years of interviews. Every year, panels surveying households are beginning and ending concurrently. Thus, the yearly data includes responses from those in their first year of interviews and second year of interviews.

The Prescribed Medicines Components is an individual-event level data set. One member of the household answers the survey questions for each member of the household separately, including children. AHRQ uses the date of each office visit and filled prescription to aggregate the data up to the year level. Of particular importance for our study, each household in the MEPS is asked information about the specific drugs purchased or received since the last interview. Drugs are classified in MEPS by name and Multum class codes, allowing us to track the use of all drugs in one of the four classes of interest to our study.

[26] In other estimates not reported here (available from the authors), we confirm that similar patterns are observed when we estimate changes in the mix of drugs using percent of prescriptions within the class, rather than total number of prescriptions, as the dependent variable.

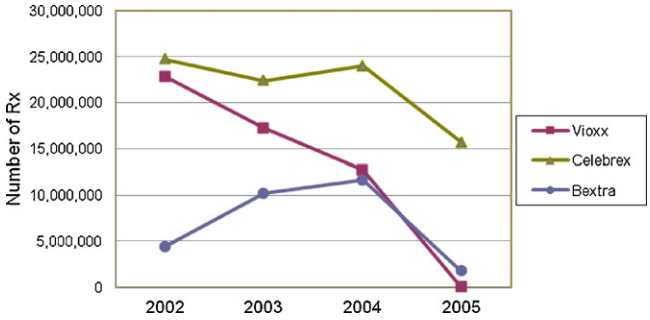


**Fig. 4.** MEPS prescriptions for COX-2 brands.
*Source*: MEPS prescription medications event files 2002–2005.

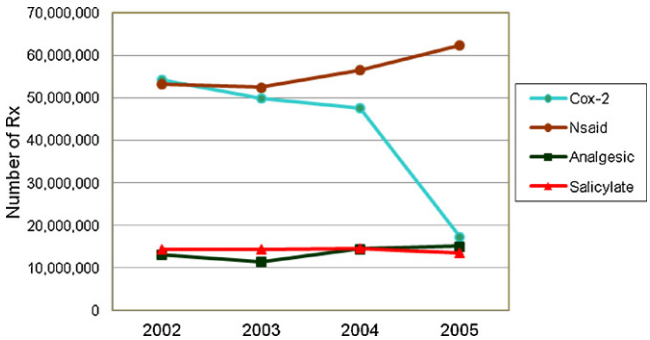


**Fig. 5.** MEPS prescriptions for COX-2 and competitor classes.
*Source*: MEPS prescription medications event files 2002–2005.

### 4.2. Trends in MEPS data

Fig. 4 displays the MEPS sample-weighted prescription totals for each drug in the COX-2 class for the years 2002–2005. The data series echoes the quarterly Medicaid data; Vioxx sales terminate in 2005, and Bextra sales are near zero for the year, confirming that the data correctly capture these events. The graph also shows a substantial decline in Celebrex sales in 2005, similar to that observed in the Medicaid data.

Fig. 5 displays MEPS sample-weighted annual prescription counts for each of the four drug classes in 2002 through 2005. Fig. 6 shows usage rates by percent of individuals in the MEPS for COX-2 and related classes over this period. Mirroring the trends seen in the quarterly Medicaid data, Fig. 5 shows a precipitous decline in the use of COX-2s in 2005, and a large increase in NSAID use. Salicylate and Analgesic usage are small in comparison, and remain relatively flat over the period. These same patterns are reflected in Fig. 6.

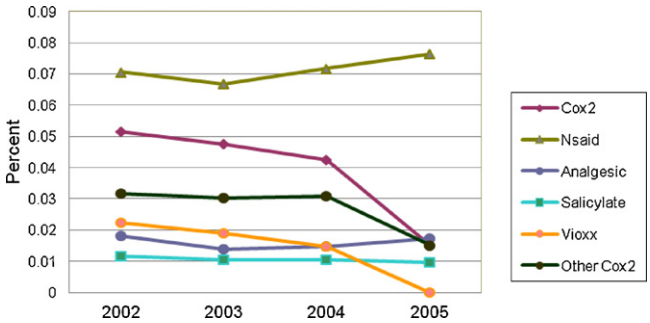


**Fig. 6.** Percent of MEPS respondents using COX-2 and competitor classes.
*Source*: MEPS prescription medications event files 2002–2005.

**Table 7**
Analysis of post-withdrawal drug use by individual Vioxx users in MEPS.

| Panel A: Vioxx users in 2004 ($N$ = 206) | | | |
|---|---|---|---|
| Use in 2004 | | Use in 2005 | |
| | Mean | | Mean |
| Cox2 user | 1.0000 | Cox2 user | 0.1249 |
| NSAID user | 0.2559 | NSAID user | 0.3044 |
| Analgesic user | 0.0561 | Analgesic user | 0.0554 |
| Salicylates user | 0.0260 | Salicylates user | 0.0397 |
| Vioxx user | 1.0000 | Vioxx user | 0.0000 |
| **Panel B: Vioxx users in 2002 ($N$ = 288)** | | | |
| Use in 2002 | | Use in 2003 | |
| | Mean | | Mean |
| Cox2 user | 1.0000 | Cox2 user | 0.4303 |
| NSAID user | 0.1631 | NSAID user | 0.1567 |
| Analgesic user | 0.0690 | Analgesic user | 0.0331 |
| Salicylates user | 0.0378 | Salicylates user | 0.0406 |
| Vioxx user | 1.0000 | Vioxx user | 0.3529 |
| **Panel C: tests of differences** | | | |
| Difference 2004–2002 | | Difference 2005–2003 | |
| | $T$-stat | | $T$-stat |
| Cox2 user | | Cox2 user | −11.39** |
| NSAID user | 2.48* | NSAID user | 6.39** |
| Analgesic user | −0.59 | Analgesic user | 5.16** |
| Salicylates user | −0.75 | Salicylates user | −0.25 |
| Vioxx user | | | |

* Significantly different from zero at the 5% confidence level.
** Significantly different from zero at the 1% confidence level.

### 4.3. Empirical methodology

We construct a longitudinal dataset of individuals who are observed in the MEPS in both 2002 and 2003 and individuals who are observed in both 2004 and 2005. Our dataset has one observation per individual per year. These data are then utilized to determine the changes in drug usage in the aftermath of the Vioxx withdrawal at the end of 2004, and the withdrawal and warning label events that occurred for the remaining COX-2 drugs and the NSAIDs in 2005. Because the MEPS data are reported annually without monthly indicators of the interview, we cannot separately examine these two events.

We examine the drug usage in year 2005 of those individuals who reported using Vioxx in 2004 to observe the effect of the withdrawal events. We use the sample of individuals who report using Vioxx in 2002 as a control group, examining reported usage of COX-2 and related classes by these individuals in 2003. The control group is used because not all Vioxx users will remain on Vioxx for extended periods of time, and even in the absence of the negative information, some users will report discontinued use in subsequent years. This comparison allows us to discern whether usage patterns following the withdrawal events differ from those in normal years.[27] We also examine separately the usage patterns in the MEPS for individuals ages 65 and over.

The withdrawal and the related changes in warning labels may also have affected drug choice among new users of pain relief drugs. Our longitudinal MEPS sample can also be used to examine this latter question. We examine the usage of COX-2s and related classes of drugs in year 2005 of those individuals who did not report using these drugs in 2004. We examine this using both a narrow measure – individuals who did not use any COX-2 drugs, and a broad measure – individuals who did not use COX-2s or any drugs in the related classes. As in the analysis of continuation use, we use as a control group the sample of individuals who did not use the drugs in 2002 and separately examine the usage patterns for all adult individuals and those ages 65 and over.

[27] We also examined continuing versus new usage of non-withdrawn drugs in the second year, and whether usage changes varied with education. We did not observe noticeable difference in patterns by either of these covariates.

**Table 8**
Analysis of post-withdrawal drug use by Vioxx users over age 65 in MEPS.

| Panel A: Vioxx users in 2004 [$N = 64$] | | | |
|---|---|---|---|
| Use in 2004 | | Use in 2005 | |
| | Mean | | Mean |
| Cox2 user | 1.0000 | Cox2 user | 0.1250 |
| NSAID user | 0.2640 | NSAID user | 0.2340 |
| Analgesic user | 0.0950 | Analgesic user | 0.1120 |
| Salicylates user | 0.0270 | Salicylates user | 0.0510 |
| Vioxx user | 1.0000 | Vioxx user | 0.0000 |
| **Panel B: Vioxx users in 2002 ($N = 76$)** | | | |
| Use in 2002 | | Use in 2003 | |
| | Mean | | Mean |
| Cox2 user | 1.0000 | Cox2 user | 0.5830 |
| NSAID user | 0.1430 | NSAID user | 0.0710 |
| Analgesic user | 0.0550 | Analgesic user | 0.0580 |
| Salicylates user | 0.1170 | Salicylates user | 0.1090 |
| Vioxx user | 1.0000 | Vioxx user | 0.5080 |
| **Panel C: Tests of differences** | | | |
| Difference 2004–2002 | | Difference 2005–2003 | |
| | *T*-stat | | *T*-stat |
| Cox2 user | | Cox2 user | −6.67*** |
| NSAID user | 1.76* | NSAID user | 5.37*** |
| Analgesic user | 0.88 | Analgesic user | 3.48*** |
| Salicylates user | −2.12** | Salicylates user | −4.13*** |
| Vioxx user | | | |

* Significantly different from zero at the 10% confidence level.
** Significantly different from zero at the 5% confidence level.
*** Significantly different from zero at the 1% confidence level.

### 4.4. Results

Table 7 compares patterns in drug usage over 2004–2005 for all MEPS 2004 COX-2 users to the patterns over 2002–2003 for all MEPS 2002 COX-2 users. Panel A shows 2004–2005 use, Panel B shows 2002–2003 use, and Panel C shows results of *T*-tests for differences in usage of each drug across years 2002–2004 and years 2003–2005.

The table shows that among the 206 Vioxx users in 2004, 25.59% also used NSAIDS during the year, 5.61% used Analgesics and 2.60% used Salicylates. When examining these individuals' drug use in 2005, we observe a sharp decrease in COX-2 use from 2004 to 2005. Only 12.49% of Vioxx users in 2004 report using any COX-2 drug in 2005. We see an increase in use of NSAIDs in 2005, with 30.44% of individuals reporting their use in 2005. This suggests a switch from COX-2 use to NSAIDs use. Similarly, we observe an increase in reported use of Salicylates in 2005, with 4.06% of those who used Vioxx in 2004 reporting Salicylates use in 2005. There is virtually no change in Analgesics use among this group from 2004 to 2005.

The data reveal very different patterns of use in 2002 and 2003. In 2002, Vioxx users reported less concurrent use of drugs in related classes than those in 2004: only 16.31% report using NSAIDS, 6.90% report using Analgesics and 3.78% report using Salicylates. We also observe much greater continuation use of COX-2 drugs in 2003, with 43.03% of Vioxx users continuing COX-2 use and 35.29% of them specifically continuing with Vioxx. Also in contrast to 2005, we do not observe an increase in NSAIDS and we observe a much smaller increase in Salicylates use in 2003. Analgesic use in 2003 actually declines compared to 2002.

*T*-tests in Panel C reveal that the only statistically significant difference in use of competitor drug classes among Vioxx users in 2004 versus 2002 is an increased use of NSAIDS in 2004 as compared with 2002. Because the data are annual and Vioxx was withdrawn in the third quarter of 2004, some of the use of related drug classes may have occurred as a result of discontinuing the use of Vioxx or other COX-2 drugs. Comparing 2005 drug usage patterns among 2004 Vioxx users to 2003 usage among 2002 Vioxx users confirms, however, that usage patterns are significantly different in the latter post-withdrawal period. Vioxx users in 2004 are significantly less likely to use a COX-2 drug in 2005 than Vioxx users in the earlier period; users are also significantly more likely to use NSAIDs and Analgesics than the earlier Vioxx users.

Table 8 displays this same set of comparisons for COX-2 users in the MEPS who are over age 65. The results are generally similar for the Vioxx users of all ages, but with a few notable differences. First, in 2002–2003 we observe a much higher rate of continual use of COX-2 drugs, and of Vioxx in particular, among elderly Vioxx use in 2002. Fully 58.3% continued use of one of the COX-2s in 2003, and 50.8% specifically continued the use of Vioxx. Examination of the 2004–2005 drug use patterns for the 2004 COX-2 users in this older age group reveals that only 12.5% of COX-2 users in 2004 continued their

**Table 9**
Analysis of post-withdrawal starts of pain-relievers by adults in MEPS.

| Panel A: Non-users in 2004 | | | |
|---|---|---|---|
| No use of COX-2s in 2004 ($N = 6609$) | | No use of Any Class in 2004 [$N = 5377$] | |
| Use in 2005 | | Use in 2005 | |
| | Mean | | Mean |
| Cox2 user | 0.0053 | Cox2 user | 0.0038 |
| NSAID user | 0.1063 | NSAID user | 0.0594 |
| Analgesic user | 0.0208 | Analgesic user | 0.0106 |
| Salicylates user | 0.0150 | Salicylates user | 0.0033 |
| Vioxx user | 0.0000 | Vioxx user | 0.0000 |
| **Panel B: Non-users in 2002** | | | |
| No use of COX-2s in 2002 ($N = 6644$) | | No use of Any Class in 2002 ($N = 5471$) | |
| Use in 2003 | | Use in 2003 | |
| | Mean | | Mean |
| Cox2 user | 0.0354 | Cox2 user | 0.0332 |
| NSAID user | 0.0916 | NSAID user | 0.0528 |
| Analgesic user | 0.0151 | Analgesic user | 0.0074 |
| Salicylates user | 0.0168 | Salicylates user | 0.0039 |
| Vioxx user | 0.0134 | Vioxx user | 0.0132 |
| **Panel C: Tests of differences** | | | |
| No use of COX-2s in prior year | | No use of any class in prior year | |
| Difference 2005–2003 | | Difference 2005–2003 | |
| | *T*-stat | | *T*-stat |
| Cox2 user | −12.33*** | Cox2 user | −11.45*** |
| NSAID user | 2.84*** | NSAID user | 1.50 |
| Analgesic user | 2.46** | Analgesic user | 1.73* |
| Salicylates user | −0.80 | Salicylates user | −0.51 |

* Significantly different from zero at the 10% confidence level.
** Significantly different from zero at the 5% confidence level.
*** Significantly different from zero at the 1% confidence level.

usage in 2005. As in the all-ages sample, COX-2 users in this age group were more likely to use NSAIDs in 2004 than in 2002, with 26.4% reporting NSAIDs use. This percentage remained about the same in 2005, with 23.4% reporting NSAIDs use.

Another difference is that use of NSAIDs other than Vioxx declined dramatically for this group between 2002 and 2003, from 14.3% in 2002 to 7.1 in 2003. This suggests that COX-2 drugs were being substituted for the other NSAIDs, consistent with the greater risks of NSAIDs among this age group. There are also notable differences in analgesic use in this age group over time and relative to the all-ages sample. Analgesics use is much higher among COX-2 users over age 65 in the later time period: 9.5% reported analgesics use in 2004, and 11.2% reported their use in 2005. This pattern is consistent with a return to earlier therapeutic approaches among the elderly (Griffin, 2000).

Salicylates use among elderly COX-2 users also declined in the 2004–2005 time period. In 2004, only 3.3% of elderly COX-2 users reported salicylates use, while 11.7% of reported their use in 2002, and 10.9% reported use in 2003. Recall that the stronger warning labels on NSAIDs did not occur until 2005, and that these labels did not apply to the Salicylates. However, the risks of gastrointestinal bleeding were being discussed by the FDA as early as 2003, and the stronger warning labels were initially recommended for aspirin as well as for the NSAIDs. The decline in use of Salicylates by 2004 may be in response to these discussions, and could be viewed as an anticipatory response to stronger warning labels. In 2005, 5.8% of the elderly sample reported using salicylates; this is still much lower than in 2002–2003, but represents an increase over 2004. This uptick could signal a switch away from NSAIDs toward aspirin as a result of the stronger NSAIDs warning.

Table 9 reports the results of analyzing new starts of COX-2 and related drug classes in 2005 compared with 2003, and Table 10 reports results of this analysis for individuals over age 65. The left-hand columns in each table compare new starts for individuals who did not use any COX-2 drugs in the previous year; the right-hand columns compare new starts for individuals who did not use COX-2s or any related classes of drugs in the previous year.

Comparing the left-hand columns in Panel A and B of Table 9 shows that new starts of COX-2 drugs in our MEPS sample were dramatically lower in 2005 than in 2003. Among individuals who did not use COX-2s in the previous year, 3.5% began using COX-2s in 2003 while only 0.5% began new use of COX-2s in 2005. This difference is statistically significant at the 1% confidence level, as shown in Panel C. Conversely, those who did not use COX-2s in the previous year were more likely to begin using NSAIDs (10.6%) or Analgesics (2.1%) in 2005 when compared with new starts of NSAIDs (9.2%) and Analgesics

**Table 10**
Analysis of post-withdrawal starts of pain-relievers by adults over Age 65.

| Panel A: Non-users in 2004 | | | |
|---|---|---|---|
| No use of COX-2s in 2004 [$N = 1188$] | | No use of any class in 2004 [$N = 940$] | |
| Use in 2005 | | Use in 2005 | |
| | Mean | | Mean |
| Cox2 user | 0.0065 | Cox2 user | 0.0054 |
| NSAID user | 0.1100 | NSAID user | 0.0499 |
| Analgesic user | 0.0256 | Analgesic user | 0.0122 |
| Salicylates user | 0.0428 | Salicylates user | 0.0054 |
| Vioxx user | 0.0000 | Vioxx user | 0.0000 |
| **Panel B: Non-users in 2002** | | | |
| No use of COX-2s in 2002 ($N = 1113$) | | No use of any class in 2002 ($N = 890$) | |
| Use in 2003 | | Use in 2003 | |
| | Mean | | Mean |
| Cox2 user | 0.0559 | Cox2 user | 0.0497 |
| NSAID user | 0.0839 | NSAID user | 0.0392 |
| Analgesic user | 0.0147 | Analgesic user | 0.0019 |
| Salicylates user | 0.0433 | Salicylates user | 0.0091 |
| Vioxx user | 0.0167 | Vioxx user | 0.0135 |
| **Panel C: Tests of differences** | | | |
| No use of COX-2s in prior year | | No use of any class in prior year | |
| Difference 2005–2003 | | Difference 2005–2003 | |
| | *T*-stat | | *T*-stat |
| Cox2 user | −6.84*** | Cox2 user | −5.78*** |
| NSAID user | 2.13** | NSAID user | 1.11 |
| Analgesic user | 1.87* | Analgesic user | 2.66*** |
| Salicylates user | −0.05 | Salicylates user | −0.93 |

* Significantly different from zero at the 10% confidence level.
** Significantly different from zero at the 5% confidence level.
*** Significantly different from zero at the 1% confidence level.

(1.5%) in 2003. These differences are also statistically significant, and suggest a switch in take-up away from COX-2s as a result of the withdrawal events. There are no significant differences in new starts of Salicylates in 2005 as compared with 2003.

Results reported in the right-hand columns of Table 9 provide the comparisons of new starts for individuals who previously did not use drugs in any of the competitor classes. Sample sizes are slightly smaller, but patterns of new usage and comparisons of 2005–2003 are similar. One difference is that usage of NSAIDs and Analgesics occurs at a smaller rate in this sample, as would be expected among a sample that did not use any painkilling drugs in the previous year. As a result, while the direction of change is the same – new starts of NSAIDs and Analgesics are higher in 2005 than in 2003 – differences for these drug classes are not statistically significant, or are only marginally so.

Analysis of new starts for those ages 65 and over, displayed in Table 10, produces similar findings. Among the elderly who did not use COX-2 drugs in the previous year, 5.6% started use in 2003 but only 0.65% took them up in 2005. This difference is statistically significant at the 1% confidence level. The data similarly show a shift toward other competitor classes in 2005 compared to 2003. Among this sample 11.0% of previous non-users of COX-2s began NSAID use in 2005, compared with only 8.4% in 2003. 2.6% started new Analgesic use in 2005, whereas only 1.5% of the sample displays new starts of Analgesics in 2003. These differences are statistically significant, although only at the 10% confidence level for Analgesics. These findings confirm a shift away from new usage of COX-2 drugs, with substitution toward competitor classes, in the aftermath of the withdrawal events.

Analysis of new starts among the elderly who did not use any drugs from the competitor classes in the previous year (right-hand columns of Table 10) reveals one important difference for this age group relative to the full sample of adults. Among the elderly, new starts of Analgesics are significantly higher in 2005 compared with 2003, while starts of NSAIDs show no significant increase relative to 2003. In magnitude, the elderly in this sample are 184% more likely to start using Analgesics in 2005 as compared with 2003 and 27% more likely to start using NSAIDs. This compares with a 45% increase in Analgesics starts and a 12.5% increase in NSAIDs starts for the general adult population in the MEPS. These results suggest a much greater switch toward Analgesics among the elderly, consistent with the greater risks of NSAIDs for this age group.

Evaluated together, changes in drug usage patterns in the MEPS suggest a strong positive spillover effect for the NSAID class as a result of the withdrawal events. In the over 65 group, the data also suggests a greater relative use of Analgesic drugs among (former) Vioxx users in 2005 than was seen among the Vioxx users in 2002. The retreat from both the COX-2 drugs and NSAIDs (and aspirin, among the elderly) seems likely to reflect concerns about side-effects. Moreover, the differences in usage pattern changes for the elderly versus the full sample are consistent with long-term use of these drugs among the elderly and the greater risk of gastrointestinal side-effects among this age group.

The shifts in usage patterns between drugs and drug categories do not appear to be inappropriate responses to the withdrawal and warning events. However, the data also show an overall decline in usage of the drugs in these categories. Summing across all four classes of drugs, we observe that 66% of those who used Vioxx in 2002 report use of one or more drugs in related classes in 2003; in 2005 this drops to under 53% (Table 7). Among the elderly these changes are even more pronounced. While 82% of elderly Vioxx users in 2002 reported use of one or more drugs in related classes in 2003, only 52% reported such use in 2005 (Table 8). Similarly, 9.7% of adults who did not use any drugs from these classes in 2002 started use of one or more of the drugs in 2003. In 2005, new use dropped to 7.8% among adults who had no usage in 2004 (Table 9). Comparable statistics for the elderly are 9.1% in 2003 versus 6.7% in 2005 (Table 10). Thus, consumers switched away from the COX-2 drugs after the Vioxx withdrawal, but the declines in use were not completely absorbed by shifts into related drug classes.

## 5. Conclusion

Using state-level data from the Medicaid SDU database and individual-level data from the MEPs, this paper has evaluated the effect of the Vioxx withdrawal in 2004 on consumers' use of drugs in these classes. The results suggest a positive spillover effect for the NSAIDs class as a result of the Vioxx withdrawal. In aggregate Medicaid data, the number of prescriptions and the market share of these drugs increased, as did the average reimbursement per prescription. In individual data, former Vioxx users were much more likely to shift to an NSAID than to another drug in the COX-2 class. In the aggregate data we can also observe responses to the Bextra withdrawal and subsequent FDA warning labels for Celebrex and the NSAIDs, and these events reduced the aggregate market share of both the COX-2 drugs and the NSAIDs.

The data also show a greater relative use of Analgesic drugs after the Vioxx withdrawal, both in the aggregate data and among former Vioxx users over age 65. In the aggregate data we observe a shift toward branded prescription and OTC Analgesics, and away from generics. This shift, along with the increased market share, leads to higher aggregate reimbursement levels and higher average reimbursements per prescription for the Analgesics class. Nonetheless, since the average reimbursement per prescription for the COX-2 drugs is nearly ten times as high as for NSAIDs and Analgesics, and four times that of Salicylates, total reimbursement costs for the Medicaid programs declined substantially after the withdrawals (Table 1). Medicaid reimbursements for these drug classes peaked in 2001 at over $1 billion, declined to $800–$900 million in 2002 through 2004, and dropped precipitously to $477 million in 2005. To put the relative cost of the COX-2 drugs for Medicaid programs in perspective, their share of prescriptions in these classes fell from 34.6% in 2001 to 11.4% in 2005; but as a result of this decline their share of total reimbursements fell from 65.7% to 54%.

The implications of changes in drug usage for patient wellbeing or aggregate social welfare cannot be determined with precision. However, the informational context of the withdrawal and labeling events highlights a risk-benefit trade-off, suggesting most patients may switch their usage to other drug classes. These shifts in drug usage represent what may be viewed as an appropriate response to the events. However, to the extent that patients quit using any anti-inflammatory drug, or switch to drugs (such as analgesics) which are not close substitutes for the withdrawn drugs, there are likely to be negative effects on health and wellbeing (Garthwaite, 2012). Both the state-level data and individual-level data also show declines in the overall usage of drugs in these categories after the withdrawal events. In the four classes combined, state Medicaid programs reimbursed nearly 23 million prescriptions each year in 2001–2003 and 23.6 million prescriptions in 2004; prescriptions declined to just under 22 million in 2005. The same patterns of usage declines in 2005 are observed for individual users in the MEPS data. This suggests that some consumers may have responded to the withdrawal events in ways that lessened the health benefits they received from these kinds of drugs.

The negative side effects of the COX-2 drugs received a great deal of attention from the FDA and were highly publicized in the media, which may make it difficult to generalize to other cases of drug withdrawals or warnings. In particular, the withdrawal of Vioxx received extensive media coverage nationally and internationally, and was the subject of Congressional hearings. Most withdrawn drugs represent a small portion of their respective markets (Wysowski and Swartz, 2005) and so may not receive extensive media attention. The large numbers of users of COX-2 drugs made our in-depth analysis of the effects of the withdrawals and surrounding events possible. However, it also led to extensive media attention, so the effects of these events may differ from those affecting drugs that are less widely used.

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