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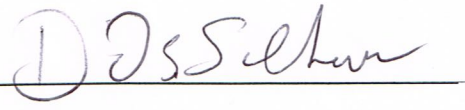
Dissertation and Abstract Approved: *  (signature)

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ABSTRACT

Title of Document: EXAMINING THE ROLE OF NEWS COVERAGE IN THE DISSEMINATION OF FDA PRESCRIPTION DRUG WARNINGS

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2017

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This thesis explores the potential role of news media coverage about U.S. Food and Drug Administration (FDA) warnings for prescription drugs in influencing patient/prescriber behavior. It extends previous literature about the impacts of the FDA warnings on antidepressants and other medication utilization in two ways. First, previous studies did not directly consider possible impacts of *news coverage* of these warnings on consumer behavior. This neglect of news coverage is surprising in light of an extensive communications literature demonstrating the broad influence of such lay information transmissions on human behavior, and despite concerns that errant or incomplete news coverage frequently yields unintended consequences (*e.g.*, stopping

medications rather than better patient monitoring) of targeted FDA recommendations. Second, this study used time-series data about four FDA warnings representing distinct therapeutic treatment classes for depression, smoking addiction, asthma and allergies, and diabetes. Using a variety of statistical models, this work found very small, though significant, evidence suggesting that news coverage surrounding FDA prescription drug warnings can have subtle impacts on down-stream doctor and consumer behavior. The results of this work should be of direct interest to those concerned with the dissemination of health communication messages and other technical news relevant to consumers.

EXAMINING THE ROLE OF NEWS COVERAGE IN THE DISSEMINATION OF FDA PRESCRIPTION DRUG WARNINGS

By

Michael Todd Abrams

Dissertation submitted to the Faculty of the Graduate School of the University of Maryland, Baltimore County, in partial fulfillment of the requirements for the degree of

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Dedication

To Janet, Bruce, M4, and Mrs. T.

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Finally, I must acknowledge the broad contribution of two principal contributors to this work:

1. Scientists who develop and evaluate biomedical approaches.
2. Journalists who deconstruct and report upon such science in a way that makes it handy and accessible for the masses.

They are the key and consummate professionals who strive daily to create and disseminate information that helps keep us healthy.

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Background/Policy Relevance

Pharmaceuticals in U.S. Health Care

As of 2008, pharmaceutical costs composed approximately 10% ($234.1 billion) of U.S. annual medical care expenditures, nearly double the 5.6% proportion ($40.3 billion) reported in 1990 (Hartman, Martin, Nuccio, & Catlin, 2010). The use of drugs in lieu of other medical interventions is often favored because ingesting or even injecting a chemical substance is simpler than surgery, talk therapy, or behavioral change alternatives (*e.g.*, diet and exercise); and economic analyses have demonstrated rates of return (based on decreased morbidity) for pharmaceutical spending on the order of 10 to 1 (Cremieux, Jarvinen, Long, & Merrigan, 2007). As the expression goes, "if you could bottle it, you'd make a fortune," and indeed since at least the mid-1980s, pharmaceutical company profits have substantially outpaced those of most other industries (U.S. Congressional Budget Office, October 2006). As a reflection of this profitability, in 2009 the top 10 drug manufacturers yielded nearly $400 billion in revenues[a]- a quantity equal to 2.6% of the U.S. Gross Domestic Product for that same year. These potential remedies and economic gains, however, do not come without risks -- risks that are monitored and mitigated by federal regulatory oversight and action.

The Food and Drug Administration's Role and History

The U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) is the principal authority responsible for management of the risks connected with the use of pharmaceutical agents in the U.S. (Szalados, 2007). Although pharmaceuticals typically offer important health benefits to consumers, they frequently prove more toxic and/or less

[a] http://money.cnn.com/magazines/fortune/global500/2009/industries/21/index.html, accessed 4/11/10.

efficacious than anticipated. It is the CDER's responsibility to approve new drugs for mass marketing and to carry out surveillance activities after such approval has been secured.

Since at least 1938, the FDA, under the Food Drug and Cosmetic Act (FDCA), has been responsible for insuring that drugs are safe before they are mass marketed. This law was precipitated by the deaths of over 100 persons who were poisoned by an antibiotic suspension in which the principal ingredients contained anti-freeze. In 1962, stronger safety and efficacy standards were created via an update of the FDCA legislation, triggered this time by reports from Europe that the tranquilizer thalidomide caused fetal death or bizarre birth defects sometimes referred to as "flipper" limbs (Hawthorne, 2005; Philipson & Sun, 2007). Today, the FDA, or more specifically CDER of the FDA, is the gate-keeper between firms working to release their products to market as quickly as possible, and consumers awaiting new and more effective remedies for disease. CDER approval is required for a drug to be sold in the U.S., and the Agency's denial prohibits such sale, or at least delays it pending further research and FDA review (Babiarz & Pisano, 2008; Hawthorne, 2005; Schacter, 2006).

Post-approval Problems

Recent post-approval (*a.k.a.*, post-marketing) adverse events have demonstrated that CDER approval, though rigorous, does not guarantee a drug's safety nor widespread benefit. Among the most visible post-marketing problems that have occurred in the past 10 years have been two which led to the eventual market withdrawal of the widely-used pain medications Vioxx and Bextra (Tong, Tong, & Tong, 2009), and others that led to a string of warnings (still in place) regarding the use of all antidepressant medications in children, adolescents, and young adults (Busch & Barry, 2009). For Vioxx and Bextra, potentially fatal cardiovascular events became widely known to the public only after these drugs had received CDER approval. When the drugs

were discontinued in 2004, they jointly accounted for over $3 billion in annual international sales (Schacter, 2006), and their withdrawal called into question the ethical behavior of the manufacturers of these drugs and the medical professionals these firms supported via grants, ghost-writing, and speaking activities (DeAngelis & Fontanarosa, 2008). For antidepressants, post-marketing data revealed that young individuals taking such drugs were at increased risk for suicidal behaviors compared to those on placebo. In October 2003, after contentious and emotional hearings, CDER issued a string of public health advisories which have since been studied extensively regarding their impact on patient and clinician behavior (Busch & Barry, 2009; Hawthorne, 2005). The Vioxx/Bextra and antidepressant warnings are frequently cited as events which demonstrate the importance of appropriate post-marketing surveillance and action by CDER. "The FDA was embarrassed in 2004 when several popular drugs it had approved (including antidepressants and Vioxx) turned out to have major adverse side effects that had been ignored by the agency," wrote Weissert and Weissert in their review of the drug safety monitoring system (Weissert & Weissert, 2006) (*pp.* 187-8).

Why is Post-approval Surveillance Necessary?

Short-comings of the approval process are not aberrations. Instead they result from regulatory action aiming to strike a balance between public safety and efficacy, and the strong desire by manufacturers and consumers to benefit from novel pharmaceuticals. Nevertheless, the CDER approval process is rigorous. Of that process, one journalist recently wrote the following:

> All the horror stories that are cited about the FDA-- the trucks pulling up to Rockville filled with bound volumes the size of phone books...tens of thousands of pages, weeks of preparation and then months of waiting for an answer-- all these are essentially true. (Hawthorne, 2005) (*p.* 94)

Without excessive sympathy for the pharmaceutical industry, it can be said that the CDER process requires petitioners with new remedies to "jump through numerous hoops" -- including years of investment in scientific study -- before they are allowed to legally market their drugs to physicians and their patients. Still, the process has at least four substantial limitations. First, pivotal trials upon which CDER review is based are constrained in duration, usually lasting well under one year from treatment initiation to completion. Although this time period may be sufficient for acute therapies, it may not be sufficient to discern the long-term impact of chronic therapies (*e.g.*, treatments for persistent mental or cardiovascular disorders). Second, sample sizes for pivotal trials may not be statistically sensitive to negative effects because of insufficient power, or because they are limited to a specified population with a defined illness and demographic profile. Such trials typically involve fewer than 3,000 participants across all treatment groupings including the placebo control group (Szalados, 2007), so a serious negative side-effect that occurs in 1 of 1,000 persons would not necessarily be discerned even as a 1 in 1,000 risk of such an effect is high and consequential to thousands for a drug used by millions of persons. Third, FDA approval of a drug is for a single indication in a narrowly-defined population, although "off-label" use for another indication is both legal and common. For example, a drug approved to treat depression in adults may be used off-label to treat anxiety disorders in children. Even in the absence of off-label use, an FDA-approved drug may eventually be consumed by thousands or millions of patients whose clinical profile is not a close match to the cases used in the efficacy trials that led to the drug's approval. The fourth major limitation of the pre-approval process is that it is dependent mainly upon data generated directly by the regulated industry, that is, by the firm petitioning for the right to market their agent. When a drug company submits a drug application to CDER, the company not only funds much of the

scientific research needed to amass evidence in support of the approval they seek, they must further pay hundreds of thousands of dollars per application to CDER which directly supports the review of their product (Philipson & Sun, 2007; Szalados, 2007; Thaul, March 13, 2007). While placing these scientific and financial responsibilities on the pharmaceutical industry has its roots in political compromise aimed at optimizing new drug releases without increasing the FDA federal budget appropriations, critics have argued these processes give industry excessive power over their regulators by financially 'coercing' the agency to expedite approvals (Thaul, March 13, 2007).

The four limitations noted above counter the notion that an FDA approval insures a drug's safety or effectiveness for the broad population that ultimately may use it. Instead, such approval indicates only that a novel drug *appears* safe and effective for a circumscribed population, or more precisely that a drug's potential benefits are perceived as greater than its potential risk, for a circumscribed population. Accordingly, the FDA has developed post-marketing surveillance and action strategies to cope with problems that occur after a drug is approved for sale. What is less certain is how consumers and clinicians respond to such post-marketing surveillance activities, including the prescription drug warnings targeted in this research.

Post-marketing Surveillance Emerges As a Federal Policy Priority

Broad legislation passed by the U.S. Congress in 2007 [(Food and Drug Administration Amendments Act (FDAAA; H.R. 3805; P.L. 110-85)] extended the so-called Prescription Drug User Fee Act (PDUFA) (Thaul, March 13, 2007) for five years. The PDUFA, first enacted in 1992, is the federal legislation under which the drug industry pays for FDA review of individual products. In addition to extending the user fee requirement, the 2007 FDAAA contained several

provisions to enhance post-marketing surveillance and action by the FDA regarding pharmaceuticals - provisions which still exist. In an undated report issued after 2007, in which the agency released an accounting of CDER's accomplishments, the division's director Janet Woodcock wrote,

> We have been tremendously successful in developing a world-class pre-market review process…. Now we are going to apply the same high standards to managing the post-marketing safety process. (U.S. Food and Drug Administration, c. 2008) (*p.*4)

This statement is a clear admission of past limitations and future goals focused upon post-marketing CDER action. In fact, the report discusses several long-standing and new initiatives related specifically to the period after a drug is approved by CDER. For example, it describes the Adverse Event Reporting System (AERS) which has both actively and passively collected post-approval reports of problems since 1969.[b] Passive reports are received from clinicians, consumers, lawyers, and others via internet or other portals. Active collection of adverse event reports (the majority of such reporting) are mandated for companies with approved agents when problems arise or if the FDA determines more aggressive surveillance is warranted. Such adverse signal detection can trigger post-marketing action by the FDA including public health advisories and early communications, safety alerts, encouragement of recalls and withdrawals, or inspections of manufacturing facilities.

Table 1 shows the comparative frequency of such actions by the CDER in 2007[c], and further stratifies those actions based on their target audience and the drug development phase (pre- or post-marketing) during which the action was undertaken. The table is first sorted by the target audience, then by frequency. As an example of different target audiences for FDA

[b] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm, accessed 4/17/2011.

[c] More recent data reports of this nature were not found.

warnings, consider that public health advisories (n=16) were directed towards the general population, whereas factory inspections (n=1,119) were typically limited to dialogues between the FDA and a single pharmaceutical firm. Table 1 shows that recalls (n=851) and safety alerts (n=102) or public advisories (n=16) are far more common than withdrawals (n=2)—thus, assuming similar trends exist today, it seems that consumer education/information strategies are more common than more aggressive, punitive regulatory strategies to protect consumers from post-marketing problems (*i.e., caveat emptor* activities heavily overshadow government injunctions). Agency withdrawals of drugs from the market seem exceedingly rare, likely because CDER instead prefers to 'encourage' voluntary action by industry. In contrast, single lot withdrawals (which are usually voluntary) occur frequently (n=851), and are both targeted and short-lived. Thus, the FDA's own reporting indicates that one of the most common and long-lasting actions CDER takes regarding post-marketing adverse events is to warn the public via "public health advisories," "early communications," or "safety alerts" (combined n= 118).

The passage of the FDAAA provisions regarding post-marketing action by the FDA empowered the agency towards increased post-marketing surveillance (Gibson & Lemmens, 2015; Parasidis, 2015; U.S. Department of Health and Human Services & Center for Drug Evaluation and Research, March 2007). However, the FDA has long been uncomfortable with its post-marketing responsibilities, perhaps because it fears the embarrassment tied to reversing previous decisions, or because its long-standing ethos is as a gate-keeper of industry innovation rather than as a monitor of actions directly tied to physician practice, or even because the CDER culture is historically that of pharmacologists (evaluating novel agents) rather than of epidemiologists (considering the broad population impact of agents that are diffused) (Carpenter, 2010). Whatever the case, the FDA's ability to communicate with clinicians and consumers

regarding post-marketing side-effects on prescription drugs has emerged since 2007 as an important and expanding area of health risk communication.

Table 1. Summary of CDER's efforts in 2007 ***(U.S. Food and Drug Administration, c. 2008).***

(Contextual notation: In 2007 CDER had over 2,600 employees responsible for these actions.)

Action category	Count	Target audience	Phase (pre- or post-marketing)	Notes
Recall and withdrawals of prescription drugs	851	Public	Post	Voluntary with FDA input. Usually a single batch (lot) issued (*e.g.*, contamination or mislabeling)
Safety Alerts	102	Public	Post	Not defined or described with examples
Public Health Advisories & Early Communications	16	Public	Post	Important information about side-effects or regulatory events
Withdrawals because of safety concerns	2	Public	Post	Voluntary. Between Jan 1st and August 1st, 2007; data not presented beyond that interval.
Adverse event reports received	482,155	FDA	Post	23,033 from consumers, the rest from manufacturers and half of those are periodic and mandatory
Public Information Act responses	3,498	Individual petitioners	Pre/Post	Enquiries from the public
Generic drug approvals	495	Drug Firm and Public	Pre	Verifies bioequivalence to existing brand name drug
New drug approvals	76	Drug Firm and Public	Pre	Not including biologic agents
Pediatric committee reviews	23	Drug Firm and Public	Pre	13 granted exclusivity; 17 labeling additions
Export certificates	7,724	Drug Firm	Post	Verifies drug complies with U.S. laws and standards
Good manufacturing practice inspections	1,119	Drug Firm	Pre/Post	Factory standards
Inspection of clinical studies	767	Drug Firm	Pre/Post	Across 28 difference countries
Advisory letters to companies regarding promotional materials	714	Drug Firm	Post	20 violation citations; 129 to provide feedback on launches
Guidance letters on direct to consumer advertisements	188	Drug Firm	Post	Not clear if this is a subset of the row above
Regulatory action letters	20	Drug Firm	Post	Reprimanding/cautioning companies promoting false or misleading claims, or unapproved uses

How is the message disseminated?

Review of FDA materials from March of 2007 (U.S. Department of Health and Human Services & Center for Drug Evaluation and Research, March 2007), just post-FDAAA enactment, shows that the agency issues safety communications that often target professionals (*e.g.*, doctors), less frequently target consumers, and occasionally target the general public. The most common form of communication seems to be product labeling or inserts, followed by letters to those doctors and patients who typically use the medication. Still, general advisories are also issued, as are press releases which presumably aim to educate a broad audience vis-à-vis mass media coverage. For example, a recent press release by the FDA warned the general public that opioid pain medications and benzodiazepines carried high risk for "extreme sleepiness…coma, and death." (http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm518697.htm, accessed 10/3/16). Other than the issuance of press releases, however, FDA dissemination material seems to rarely mention the strategies they use to spread their proceedings via the professional news outlets, despite much evidence that those outlets may be important.

Press Coverage

This section discusses the potential importance of news coverage in the dissemination of warnings on prescription drugs, but does so mostly by noting the media's relevance more generally at influencing public behavior. Whereas most persons consume some form of major news each day, be it print or broadcast media (www.pbs.org/wgbh/pages/frontline/newswar/part3/stats.html), far fewer are likely to study or even skim the lengthy and tedious literature that accompanies one of their current or prospective medications (Bandesha, Raynor, & Teale, 1996; Thrasher et al., 2015). The importance of mass

media as an influence on recipient population behavior has been richly studied and documented (Riffe, Lacy, & Fico, 1998; Severin & Tankard, 1997), and it has been noted that media coverage in the lay press specifically serves the broad public by providing a "…cognitive shortcut to make sense of complex issues." (Shih, Wijaya, & Brossard, 2008) (*p.* 142). This point was emphasized by Everett Rogers, in his text on innovation dissemination, wherein he noted the following about the press:

> Mass media channels are usually the most rapid and efficient means of informing an audience of potential adopters about the existence of an innovation…Mass media channels are all those means of transmitting messages…such as radio, television, newspapers… (Rogers, 2003) *p.*18

Furthermore, Siegel and Lotenberg specified, in their text about marketing public health, that the mass media is important because,

> What we see in newspapers, magazines, television, and on the internet-- and hear on the radio-- can influence us in two ways. First, it can tell us *what* to think about. Second, it can influence *how* to think about it. (Siegel & Lotenberg, 2007) (*p.*427)

News media more generally, of course, may influence behaviors besides those relating to health. In a text describing the potential of content analysis as a way to understand forces that impact on human behavior, Riffe and colleagues (Riffe et al., 1998) state that mass media content both reflects and influences societal attitudes. A seminal example of such effects was observed in a survey of voter responses to news media coverage during the two months leading up to the 1968 presidential election (McComb & Shaw, 1972). Content analysis of such news coverage demonstrated that voter thoughts about which issues were of greatest importance in this election correlated strongly with the news media's coverage of such issues. McComb and Shaw concluded that the media coverage actually set the agenda in the minds of undecided voters, based on their analyses that demonstrated that voter attitudes were more strongly correlated to

the prevailing media discourse than to their predilection towards one candidate over others. Specifically, these researchers found that voter responses regarding the relative importance of various issues (*i.e.*, foreign policy, law and order, financial policy, public welfare, and civil rights) among persons preferring one of three presidential tickets (*i.e.*, Nixon/Agnew, Humphrey/Muskie, or Wallace/Lemay) were more strongly correlated to news media emphasis on such issues than to the emphasis placed by their favored candidate platforms.

Other political research has used content analysis to make a causal link between media coverage and voter predilections. The text entitled, "Women for President: Media bias in eight campaigns" (Falk, 2008), studied elections dating back to the 19th century comparing female and male candidates with similar polling figures and credentials. Content analysis of the *New York Times* and of local newspaper coverage for each candidate revealed enduring patterns regarding women spanning 1872 through 1996. Those patterns included that women were more subject than men to less coverage overall and to greater coverage of personal characteristics (e.g., family and fashion) versus germane political positions. Accordingly, Falk argues that her analyses are consistent with media biases that have handicapped female candidates over men for over 100 years. She further hypothesized that the most insidious aspect of this biased coverage may be that many qualified women demurred from political involvement because of the negative press coverage. Though this argument is compelling, the work does not directly demonstrate that such news coverage was the driver of low female candidate participation, nor does it show that voters were influenced by such coverage.

Other reviews of the impact of media coverage on non-health care issues, such as national military decisions and presidential races, has further supported the contention that press coverage influences public opinion and action. Gold *et al.* (Gold, 1978) detailed how the journalistic

coverage of the 1976 presidential race between Jimmy Carter and Gerald Ford was responsible for emphasizing certain issues that ultimately had deterministic impact on the debate and the outcome of that race. One issue concerned President Ford's pardon of his predecessor Richard Nixon who resigned rather than face impeachment hearings stemming from the Watergate scandal. Gold described a scenario in which many Americans longed to move beyond Watergate, but where the news media refused to allow Ford impunity from the folly of his pardon decision. Additionally, the news media is credited by Gold for magnifying a geo-political gaffe made by President Ford in a televised debate with Carter. In that debate, Ford said that he believed much of Eastern Europe was not under Soviet military domination, an assertion that was distinctively at odds with reality. Gold did not utilize formal content and correlation analyses to demonstrate the impact these press driven issues had on the electorate, but instead argued the prominence and plausibility of a connection between these news media actions and the ultimate outcome of the 1976 presidential election.

More direct assessment of news media coverage on public opinion was carried out regarding support for the U.S.'s post-911 invasion of Saddam Hussein's Iraq (Lin, 2009). Starting with the premise that *Fox News* coverage of the war was markedly more favorable toward U.S. military action in Iraq compared to coverage by other networks (e.g., MSNBC, CNN), Lin correlated exposure to such coverage to actual public support of the U.S. action based on a random survey of news consumers in a single metropolitan region. She interviewed 261 persons to assess their news consumption habits, their support for the war, and their overall political ideology. Consistent with her a prior hypothesis, she found that exposure to *Fox News* correlated with increased support for the war whereas exposure to other networks yielded the opposite effect. These correlates were evident with adjustment for endogenous variables such as each

respondent's religiosity, their individual predilection for patriotic over more rational sentiments about national military action, and their political leanings ranging from conservative to liberal.

Randomized controlled studies have demonstrated distinct short-term, transient effects of news coverage on public opinion/perception. A seminal text entitled, "News that Matters," describes 14 randomized trials from 1980 wherein "unobtrusive" (i.e., subtle) manipulations were made to newscasts in order to test if content adjustments altered personal views about national political issues including defense, pollution, and the economy (Iyengar & Kinder, 2010). The authors specifically manipulated the ordering of the news stories or the length of each to test if these changes altered subsequent attitudes viewers had about their relative importance. Research subjects then were restricted by consent agreements to view only the experimental telecasts in lieu of the real ones issued during the period of study. That work yielded a number of significant findings consistent with the hypotheses that TV news coverage content has impacts on agenda-setting (i.e., issues people focus upon) as well as priming (i.e., issues that somewhat unconsciously come to mind over others). With regard to agenda-setting, three points emerged from the results. First, the ordinal position of the story increased its subjective importance, i.e., lead stories were subsequently viewed as more significant than those that followed. Second, vividness of the story did not affect its subjective importance. Specifically, personal vignettes that dramatized the problem did not alter the viewers' post-hoc ratings of a problem's importance. And third, personal attributes (e.g., political party, race, income) were correlated to viewers' susceptibility to the arguments proffered by the telecast. For example, stories about civil rights were more salient for black than for white viewers, and stories about Social Security were more activating for elderly viewers. Priming effects were more subconscious, but still consequential. Persons shown newscasts dominated by one issue over others were more likely to

rate a president's overall performance on that issue versus other matters. Iyengar and Kinder argue these findings support the hypothesis that our political attitudes and tendencies can be altered, at least partially, by the content of news reports on TV.

Several studies have looked at media effects with regard to scientific issues including those focused upon matters of personal or public health. One pair of researchers (Speers & Lewis, 2004) reviewed media coverage about the purported (and scientifically debunked) link between the measles, mumps, and rubella (MMR) vaccine and autism which emerged at the beginning of this millennium. They found that news reporting had the impact of "misleading" (p. 180) the public into believing that such a risk was far greater than it actually was, thereby substantially reducing MMR vaccination rates even as the risks from these infectious diseases were far greater than those posed by the vaccine. Others have also reached similar conclusions about autism/vaccine news coverage (Comis, 2015; Speers & Lewis, 2004). *Yoo et al.* (Yoo, Holland, Bhattacharya, Phelps, & Szilagyi, 2010) used U.S. Medicare Beneficiary Survey data as a representative sample of the elderly in the U.S. to observe media coverage effects regarding annual influenza vaccinations. They found that the frequency of media reports (e.g., headline counts), and more intensely the frequency of reports indicating there was shortage of such vaccinations, were both correlated with increased rates of elderly vaccinations during the study years of 2000 to 2002. The former finding suggests that simple references or reminders in the media can lead to public action, whereas the latter indicates that consumers of news act at least somewhat rationally to the information they are given -- in this case they intensify their acute consumption of a vaccine that they fear is in short supply.

Communications researchers using various forms of content analysis have observed that media coverage of health care issues is often flawed in a number of ways. The coverage may be

excessively optimistic about new technologies (Schwitzer, 2003, 2004; Wilson, Booth, Eastwood, & Watt, 2008), may promote industry perspectives over those most important to consumers (Klotz & Ceccoli, 2005; Michelle, 2006), and may over-emphasize controversy in some cases while downplaying it in others (Shih et al., 2008). Given these observations, it seems probable that news coverage can be variable in its quality with regard to FDA warnings, and that variability in such messaging/signal may relate to how effectively a warning is disseminated.

The effects of news coverage on health issues has also been evaluated by the Cochrane Collaboration (http://www.cochrane.org/what-is-cochrane-evidence), an international consortium of scholars who create standardized reviews of health policy practice. The Cochrane Reviews, which are known for their comprehensiveness and scientific rigor, are typically based upon thorough literature searches with an emphasis on randomized clinical trial experiments or other research with high evidentiary standards. In 2002, the Cochrane Collaboration released an updated report entitled, "Mass media interventions: effects on health services utilization" (Grilli, Ramsay, & Minozzi, 2002). That report summarized a broad array of scientific evidence revealing that news media coverage directly influences health behaviors. Examples of changes in health behaviors relative to health care messaging in the news media include reductions in fat, cholesterol and salt intake (Li, Chapman, Agho, & Eastman, 2008; Reger, Wootan, Booth-Butterfield, & Smith, 1998) and the decline in the use of oral and other birth control methods in the wake of media reports regarding their potential dangers for women using such methods (Jones, Beniger, & Westoff, 1980). These researchers used newspaper or TV coverage as their main predictor variable. For the iodine salt intake study, TV coverage appeared to be especially important (Li et al., 2008). For the study on use of the birth control pill, cumulative coverage of news events surrounding risks of the pill predicted 34% of the variance in discontinuation rates

for that pharmaceutical intervention (Jones et al., 1980). Moreover, the research on the birth control pill coverage found a one to two month lag in news-related discontinuities that peaked about five months after such negative news. A similar lag to response was evident in the iodine salt intake work (Li et al, 2008).

Finally, the tobacco cessation or prevention literature is one obvious place to consider the impact of media coverage on health behaviors. Work in 2008 looked specifically at the correlation between positive, negative, or neutral smoking reduction news coverage and responses by youths regarding tobacco use based on the nationally representative *Monitoring the Future* (MTF) survey (Clegg Smith et al., 2008). "Positive cessation" coverage was defined as reports of events such as court victories against the tobacco industry or the release of new studies suggesting smoking was harmful. "Negative coverage," by contrast, reported opposing events including setbacks in tobacco control policies or scientific studies that countered or equivocated evidence regarding the adverse health impacts of tobacco use. By reviewing the content of news articles and then weighting it by geographic penetration and circulation rates, researchers discerned significant correlations between news coverage and subsequent smoking cessation behavior. For example, they reported that for each 10 additional "positive cessation" articles on smoking (tallied over a five month period in 2001-2003), there was a 7% decrease in a future month's tobacco use, after adjusting for several other explanatory variables. Additionally, separate consideration of articles that increased concern about smoking did enhance these findings, suggesting that positive rather than negative articles were most influential (Clegg Smith et al., 2008).

Are doctors influenced by lay news coverage?

Prescriptions drugs are controlled in the U.S. by physicians (or other licensed practitioners). Accordingly, the discourse presented above about press influences on health behaviors is germane to prescription seeking behaviors by patients, but incomplete without some consideration of prescription *writing* behaviors by those with such authority.

The physician-patient relationship is a central point of health care decision-making in the U.S. and most other developed nations. As noted in the textbook *Health Economics* (Phelps, 2003) (p. 31), demand for health care services are strongly impacted by physicians, and most major pharmaceutical expenditures require signed physician approval in the form of an executable prescription. Prescription medications in recent years have accounted for over 10% of all health care costs (Hartman et al., 2010)-- a figure that does not account for the other resources (e.g., doctor and nurse practitioner time) necessary to issue and attend to those prescriptions deemed necessary.[d]

Recent research on direct-to-consumer (DTC) advertising using sham patients demonstrated that physicians are influenced by patient references to such mass media messaging (Kravitz et al., 2005). The effect sizes observed in Kravitz's randomized study were substantial, suggesting that a patient presenting with major depressive disorder who referred to a TV commercial advocating psychopharmacologic treatment was three times more likely to receive a prescription for an antidepressant compared to a similar patient who did not mention a TV advertisement (76% vs. 31%). These results demonstrate the power of DTC advertising, but more precisely the power of persuasion a patient can have over their prescriber based on medical information

[d] Other major cost centers were: other professional services (10.1%), home health and nursing care (8.7%), durable and nondurable medical equipment (2.8%), administration (6.8%), public/government activities (3.0%), research (1.9%), structures and equipment (4.9%), hospital facility charges (30.7%)

obtained from the mass media. Kravitz and colleagues further found that if a person mentioned a specific brand of antidepressant to their doctor, their odds of receiving a prescription for that brand increased significantly. This brand-specific finding led the researchers to speculate that clinicians' actions were unduly influenced by the media message targeting their patients. Specifically, they wrote:

> If patients can sway physicians to prescribe drugs they would otherwise not consider, physicians may not be the stalwart intermediary that the law assumes. (p. 2000)

It is therefore plausible that physicians themselves may see an advertisement or read a newspaper article that alters their clinical decision-making.

Scholarship regarding the impact of the news media on doctor decision-making is not evident in the scientific literature. However, scholarship regarding non-bioscience influences on such decision making is evident, even as physicians can be reluctant to admit that that their clinical decisions sometimes have substantial non-scientific underpinnings (Eisenberg, 1979). Empirical studies exist which indicate that doctors are influenced by forces outside of their professional training and the realm of evidence-based medical practice. Eisenberg reports that even when underlying pathology does not differentiate between patients, clinicians are more likely to diagnose serious psychiatric conditions in persons with low versus high social standing; assign black vs. white patients ward rather than private beds; deflate the prognosis for overweight versus normal weight patients; and perform heroic measures on young versus older patients and patients without versus with a history of addiction. These socio-economic, race, weight, and age biases show that trained doctors are subject to non-scientific forces which yield or perpetuate bias—presumably news media coverage is one source of such bias.

Physicians are also influenced by their colleagues in ways that are sometimes more emotional and pedestrian rather than rational and scientific. Specifically, “contagion” effects in the use of new medications have been shown to correlate to interpersonal relationships among physicians (including friendships), and prestige (regarding clinical competence) such as may be accorded to journal authors over other clinicians -- prestige related to stronger referral and consultation arrangements. Such findings demonstrate that doctors (like most humans) make decisions at least in part based on non-scientific sourcing and ordinary influences which may well include their exposure to the news media directly or via interactions with their social network.

Though somewhat dated, perhaps one of the best bits of empirical research demonstrating that scientists pay attention to the lay press comes from Phillips and colleagues (Phillips, Kanter, Bednarczyk, & Tastad, 1991) who found that *New England Journal of Medicine* research articles described in the *New York Times* were more likely to be cited by other researchers than those not reported in the lay press. A serendipitous control set of articles was created when the *New York Times* went on strike and did not print, but did continue to generate content as a matter of journalistic record. These articles served as apt controls because they isolated issues of high impact to the *Times* staff, but that were not reported in the press, thereby useful to test the hypothesis that *New York Times* coverage merely earmarked articles of high importance. As the printed news stories had the strongest and statistically significant citation record, it was inferred that mass media exposure in a widely circulated newspaper was what mattered, not scientific impact of the article alone. This work suggests that news coverage matters even to biomedical researchers, many of whom are themselves clinicians with high influence over their peers.

Per the discourse above, media effects seem to influence the behavior of consumers of health care, and also to their agents (i.e., their licensed prescribers). But what can be said of news media as a factor in the dissemination of post-market FDA prescription drug warnings?

What is Known about the Consequences of Post-marketing Action?

Before considering how news impacts on the dissemination of prescription drug warnings, this section first addresses what is known about the impact of such warnings more generally, regardless of the dissemination vehicle.

Several commentators and researchers have indicated that post-marketing communiqués often fail to impact consumer behavior in the ways intended. In her text regarding the FDA drug oversight process, Bernice Schacter wrote that warnings do not typically change consumer or prescriber behavior, including the so-called "black box" warnings that are considered to be the "most compelling" issuances by that regulating federal agency (Schacter, 2006). Cook and colleagues (2009) created a database of all drug approvals, advisories, and committee reviews from 2003 through 2006. From that review they identified 174 post-marketing actions, including 77 new black box warnings and 11 instances of advisory committee discussions regarding such warnings. Boxed warnings[e] are those emphasized on insert materials *by placement in a text box* as a means to highlight their visibility to consumers. Cook et al., via qualitative analysis of transcripts from the 11 advisory committee meetings, found that even the experts composing these high-level advisory bodies were confused about the need and impact of boxed warnings (Cook, Gurugubelli, & Bero, 2009).

Several researchers have looked at the impact of post-market FDA warnings. While their studies have documented apparently rational changes in pharmaceutical use tied to such warnings, they have also observed negligence or unintended behaviors associated with such FDA communiqués, and they have rarely assessed the extent to which warning dissemination may be facilitated by news coverage. What follows are summaries of published studies regarding the

[e] Also referred to as a "black box warning" see: http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM107976.pdf)

impact of prescription drug warnings on the use of the drug in question. These summaries describe intended and unintended consequences of the warnings, and further note any findings or statements regarding the influence of news media coverage on the observed consequences of the warning.

Antidepressants

One of the most dramatic warnings of the 2000s was that issued in 2003 which connected the use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescent to the ironic concern that use of that therapy might increase the patient's predilection towards suicide (Hawthorne, 2005; Libby et al., 2007). Studies (reviewed below) have looked at the impact of that and related SSRI warnings from the FDA, and researchers have considered utilization indicators (e.g., counts or percentages of new users), spillover effects (e.g., use rates in populations not referenced in the warnings), and more nuanced quality of care indicators (e.g., changes in clinical oversight that are not necessarily coupled to discontinued use) as dependent variables. The apparent clinical consequences of these warnings have often been as intended, but unintended effects are also apparent. Only one study has looked specifically at *news media coverage* in response to such warnings, and that study correlated media coverage only to the warnings, not to consumer response (Barry & Busch, 2010). Still, that study concluded that the news coverage content generally was "not sufficient" as a useful source of information about the warning for the public at-large.

Regarding utilization of antidepressants among adolescents, several groups of researchers have observed that post-warning utilization rates markedly declined when compared to pre-warning rates and expected (time trended) rates. One of the first studies to review the impact of

the warning considered directly the main outcome of concern-- suicides among adolescents (Gibbons et al., 2007). Using national pharmaceutical and disease monitoring databases from the U.S. and the Netherlands, they tested for a correlation between SSRI use and suicide events via *Poisson* regression that adjusted for age and gender, and investigated time trends in SSRI use before and after the FDA and European regulators issued suicidal ideation warnings about these drugs (Gibbons et al., 2007). Not surprisingly, they observed that the warnings dampened *use* of SSRIs in both countries substantially, but they also observed that suicide rates among children and adolescents in both countries increased during the same period-- a result that regulators were certainly intending to avoid. A possible conclusion one can take from this work is that the warning may have discouraged some youths from SSRIs when the agents could have offered them benefits including saving their lives from a depression-related suicide. Supporting the protective effect of SSRIs implied by the work described above, a separate analysis of data from 26 developed countries found that per capita increases in SSRI use were correlated with declines in suicide (Ludwig, Marcotte, & Norberg, February 2007). Accordingly, these studies jointly suggest that FDA warnings may have changed consumer behavior in ways that increased rather than mitigated the target risk.

Because suicides in youth are relatively rare, other work has looked at alternative dependent variables such as SSRI utilization, or clinician monitoring of persons initiating therapy. Libby and colleagues (Libby et al., 2007) used a national managed care database which included 65,349 cases of newly diagnosed depression in youths age 5-18 years. Time-series analysis was conducted to derive expected SSRI drug use percentages for the two years after the FDA warning, based on five years of data prior to the warning. The analyses found that the observed rates of SSRI use in newly diagnosed depression cases were markedly below the expected rates

(28% versus 67%). The analyses included consideration of seasonal (i.e., monthly), gender, and physician specialty effects. Similar trends were observed across genders, but pediatricians and other primary care physicians accounted for the largest reduction in new diagnoses of depression after the warning, whereas psychiatrists continued to diagnose cases at the same rate. This latter finding is consistent with the diagnostically marginal cases (i.e., those that present to a generalist only) being disregarded or under-treated because of concerns tied to the warning, or with a decline in confidence among non-psychiatrists to pharmacologically managed new depression cases. Finally, this work noted that psychotherapy did not increase as a substitute for the marked reduction in SSRI use, though psychotherapy use did remain steady after the warning rather than decline as it had in previous years. Separate qualitative research found that primary care providers in Washington State were quite aware and concerned about the FDA warnings, but they had not adapted ways to adjust to the communications even as they noted the warnings as important barriers to treating their young patients with depression (Richardson, Lewis, Casey-Goldstein, McCauley, & Katon, 2007).

Spillover effects to adults were tested on adults using the same managed care plan data as that described above for children and adolescents. For these spillover analyses, the managed care database was used to isolate 475,838 novel cases of depression in persons between 19-89 years of age (Valuck et al., 2007). Using the same methods of Libby et al., they again found that observed percentages of SSRI use were markedly below that expected (22% versus 53%) for newly diagnosed cases of adult depression. The obvious conclusion drawn from this finding is that the warnings resulted in behavioral change in patients' outcomes or process measures which 'spilled over' to adults even though adults were not targeted by the FDA warning. No press or media coverage variables were included in this analysis, though in their discussion Valuck et al.

did speculate that "ambivalence" (p. 1204) among prescribers may have been promoted by popular press coverage surrounding the emotional hearing leading up to the warning.

The SSRI warning issued in late 2003 included a recommendation that clinicians monitor their patients for suicidal ideation via at least seven contacts during the first three months. Such clinical attention may well have provided ample safeguards to allow most youths on SSRIs to initiate or continue their medication regimen despite the warning. Accordingly, it seems logical that post-warning rates of monitoring should have increased relative to pre-warning or predicted rates based on pre-warning trends. Again, adapting the same data sources and methods described above (Libby et al., 2007; Valuck et al., 2007), Morrato and colleagues identified over 27,000 pediatric and 193,000 adult cases where SSRI treatment was initiated within 30 days of diagnosis (Morrato et al., 2008). They used time trend analyses to determine the percentage of cases where either FDA monitoring or less stringent HEDIS[f] monitoring standards (three contacts in three months) were achieved, and they found low rates of such monitoring both before and after the warning (<5% for the FDA standards, 60% for children and 40% for adults for the HEDIS standards) indicating limited direct response to the FDA warning. This work did not consider media coverage, though it did note that the warning was well-publicized and that, despite such publicity, many were confused by the precise recommendations proffered by the FDA.

A more recent analysis of the SSRI warning history and its impact was conducted which considered not only the October 2003 advisory that was the focus of most studies to date, but also four other associated warnings issued between June of 2003 and October 2004 (Busch et al., 2010). Each warning had additional details, and all except the clinically monitoring suggestion made by the FDA seem to measurably influence future medication use. The June 2003 warning

[f] The Healthcare Effectiveness Data and Information Set (HEDIS) is a set of quality or utilization measurement standards used by many public and private managed care plans. These tools are the product and property of the National Committee for Quality Assurance, a not-for-profit, industry sponsored entity.

focused on paroxetine (brand: Paxil) as the single antidepressant agent of concern. The October 2003 warning expanded the warning to seven other antidepressants, but it did so equivocally by stating that preliminary evidence was concerning, but not yet conclusive. Additionally, the October warning was the first to explicitly remind clinicians that fluoxetine (brand: Prozac) was the only medication with demonstrated effectiveness in treating pediatric depression. In March 2004, the FDA issued a warning similar to that of October 2003, but added two more specific drugs to the concern list and further required manufacturers to append warning labels to medication inserts. In September 2004, after a meta-analysis sponsored by the agency revealed a doubling in the risk of suicide among children receiving SSRIs, the FDA released public notifications that a black box (i.e., a highlighted) warning was to be added to the inserts for such pharmaceuticals. Finally, on October 15, 2004 a public health advisory was released by the FDA which, coupled with the requirement for a black box warning label on all antidepressants (including SSRIs, tricyclics, and MAO-inhibitors), explicitly called for such labeling to recommend weekly meetings between providers and their patients during the first month of new treatment (Busch et al., 2010). These five separate warning points were modeled as dummy independent variables across four separate logistic regressions with dependent binary variables as follows: i) any antidepressant use, ii) paroxetine use, iii) fluoxetine use, or iv) at least two monitoring events (in- or outpatient). All conditions were modeled as met if they occurred within 30 days of diagnosis of a new case of depression, and conditions *ii-iv* were modeled only for the subset (24%) of those cases where antidepressants were used (i.e., conditional on *i*). The odds of antidepressant use did not decline significantly until the last warning modeled (September, 2004). Declines in the odds of paroxetine conditional on antidepressant use were significant and persistent across all five post-warning intervals. Additionally, fluoxetine use

conditional on antidepressant use steadily increased after the October 2003 warning when this agent was first described in the warning as the singular one approved for pediatric use. Finally, and consistent with work previously described by Morrato and colleagues (Morrato et al., 2008), these analyses did not reveal any change in clinical attention that corresponded to any of the five warnings-- throughout the period of review, only 28-30% of those receiving antidepressants had at least two mental health visits in the first 30 days after diagnosis. These results suggest that the warnings influenced the behavior of prescribing clinicians with a sufficient level of detail to result in differential responses regarding the use of different antidepressants, but these same warnings have not resulted in the recommended increased levels of clinical vigilance the FDA advised. The authors reasonably speculate that the failure to achieve increased clinical monitoring may be partially due to cost factors or to shortages of mental health professionals. They further noted that their results are consistent with the theory that media coverage (negative or otherwise) leads to favorable responses in some cases and undesired responses in others.

A recent European study observed an intensive period of warning news coverage in the U.K. and the Netherlands, which emerged in 2003 and peaked in 2004 (Hernandez et al., 2011). These researchers reported a decline in certain SSRI use in the wake of such reports, though they stated that the observed correlations could not infer causality (Hernandez et al., 2012). No other available studies considered the correlation between news coverage and SSRI use. It is this gap in knowledge that this research aims to partially fill.

The impact of warnings on SSRIs overall have been detailed more than for any other therapeutic class. This increased scrutiny may be tied to several factors such as the fact that youths are involved, that the pharmacologic treatment of depression is quite common, or even the fact that there remains considerable societal ambivalence regarding the medical treatment of

mental disorders. Whatever the case, although the SSRI literature is relatively common regarding the impact of FDA warnings, other drug therapeutic classes have also been studied. The following sections review several such studies, grouped by therapeutic drug class.

Antipsychotics

Antipsychotic medication use has come under renewed scrutiny since the completion of the so-named "Clinical Affectiveness Trials for Intervention Effectiveness" (CATIE). Those randomized control trials matched a first generation neuroleptic medication (perfenazine) against several second generation antipsychotics (a.k.a., atypicals) which have largely supplanted use of their first-generation analogues (Lieberman et al., 2005).

Four studies have been conducted to consider two types of FDA warnings regarding the use of antipsychotic medications, especially atypicals. Three of these studies focus on warnings regarding the metabolic side-effects (e.g., diabetes and weight gain) that often accompany the use of atypical antipsychotics. The other study examines warnings regarding the off-label utilization of antipsychotics in elderly patients with dementia.

The three studies focused on the antipsychotic metabolic warnings were all conducted by a single research group, and that same group also conducted some of the SSRI warning studies described in the previous section (Morrato, Druss et al., 2010; Morrato et al., 2009; Morrato, Nicol et al., 2010). The first of these studies (Morrato et al., 2009) reviewed a commercial insurance population (n=18,876) defined as initiating atypical antipsychotics sometime between 2001 and 2006. This population was propensity score matched to a larger control population of persons with diabetes (n=56,522) based on age, sex, mental health diagnosis, and cardiovascular risk. Those matching parameters yielded over 8,000 pairs for subsequent time-series analysis that considered two tests (medical screenings) for metabolic disorders, given before and after the

American Diabetes Association (ADA) issued a statement regarding the metabolic risks associated with the ongoing use of atypical antipsychotics. The a priori hypothesis was that the ADA statement would prompt prescribers of atypicals to increase their vigilance regarding metabolic side-effects with increased screening. Their analysis did reveal slight increases in screening with time, but not tied in the expected step-wise way to the ADA statement. Additionally, after the statement was issued, rates of screening still remained low (<38% for chronic atypical users), suggesting that many clinicians and patients were not responding to the alert proffered by the ADA. The other two articles utilized fee-for-service data from three state Medicaid programs (California, Missouri, Oregon) to determine if recommendations from the FDA, ADA, and the American Psychiatric Association (APA) encouraging metabolic testing for persons using atypical antipsychotic medication were implemented (Morrato, Druss et al., 2010; Morrato, Nicol et al., 2010). A control group was composed of persons taking albuterol medication (a long-term therapy for asthma). In one experiment, interrupted time-series analyses were used adjusting for age, state of residence (geography), presence of severe mental illness, persistence of psychotropic medication use, and various inpatient and outpatient utilization indicators (Morrato, Druss et al., 2010). That report found that screening rates did not vary significantly before or after the recommendations were disseminated. Specifically, the time-series analysis found that throughout all periods, serum glucose screening was around 28% for those using atypicals and 27% for those using albuterol, and serum lipid screening was 11% for those using atypicals and 10% for those using albuterol. Neither of these screening rate differences was statistically significant. Additionally, slope coefficients reflecting time trends across three segments of the study period (23 months before, 9 months just following, and 10-25 months following the recommendations) found that rates of screening did not change

significantly within or between these three periods, except for a modest step increase of 1.7% during the warning window (9 months just following the warning) for serum lipid testing. Though these researchers did not observe what they believed to be clinically significant changes in overall prescribing behavior tied to the FDA and other warnings, they did observe very marked and statistically significant changes in the specific type of atypical used, i.e., they noticed marked drops in the use of olanzapine (brand: Zyprexa; a drug which a large clinical trial found resulted in uniquely heightened risk for metabolic side-effects) and similar increases in the use of aripriprazole (brand: Abilify) -- the latter change the authors attribute in part to the elimination of prior authorization restrictions in California during the warning period. Still, the authors concluded that while screening among atypical users *per se* did not appear to be impacted by the warning, specific drug selection (*i.e.*, less use of olanzapine) may have been. The authors did not address press coverage in their work, though they did reference the diffusion theory literature (Rogers, 2003) to contextualize their findings. In citing that literature, the authors stated that changes in drug use behavior were likely tied to the comfort level of the prescribing clinician, and that psychiatrists or other prescribers of antipsychotics may have been uncomfortable with calling for and interpreting metabolic screens. It is further plausible that mainstream press reports move prescribers and patients to feel more or less comfortable with the initiation, disruption, or heightened monitoring of a specific medication therapy.

Again using the three-state Medicaid program data noted above, but this time with a focus on youths (age 6-17 years old), a separate study reported that metabolic screening rates among children receiving atypicals was considerably higher than that among children receiving albuterol (Morrato, Nicol et al., 2010). Glucose screening occurred in 32% for children taking atypicals and only 13% for those taking albuterol. Lipid screening rates were 11% and 3%,

respectively. These rates represent results for one year after the recommendations were put forth by the ADA and APA. Accordingly, in the absence of baseline information it can only be said that rates of screening are markedly higher for atypicals than albuterol (consistent with the recommendations) but markedly below 100%, suggesting that many at-risk cases go unscreened despite the ADA and APA recommendations. Morrato and colleagues' study made no reference to press coverage as a factor regarding these results.

Finally, one study reviewed the impact of the FDA warning discouraging the use of atypicals in elderly persons with dementia (Dorsey, Rabbani, Gallagher, Conti, & Alexander, 2010). Using a nationally representative database (IMS Health's National Disease and Therapeutic Index) from 2003 to 2008, the researchers identified 13.6 million mentions of atypical use, including 0.8 million associated with a diagnosis of dementia. With these records they used interrupted time-series models that adjusted for serial autocorrelations and seasonality in order to discern marked differences between on-going use by patients with dementia and others. Specifically, before the warning was issued in April of 2005 they observed increases among those with dementia and others on the order of 16% and 34%, respectively. After the warning, declines were observed and much more so for the population with dementia (dementia versus others patients: -19% vs. -2%), and similarly so in comparisons between those below and above the age of 65. These results are consistent with an FDA warning that impacted the intended population selectively, even as some spillover effects in younger patients without dementia were also observed. Mass media influences were discussed in this study including news and direct-to-consumer (DTC) advertising impacts. The authors stated that news coverage of these warnings was extensive. They also wrote that their analyses did benefit from "adjustments in marketing and promotion" at some point, but the methods used for that correction were not delineated.

Diabetes medications

At least two recent studies considered the impact of post-marketing warnings on use of drugs that treat diabetes. One research team used commercial (BlueCross, BlueShield) plan data corresponding to 9 million enrollees to trace the usage of a drug treatment for type 2 diabetes (rosiglitazone). For this work they reviewed a subset of enrollees with medical records including pharmaceutical and physician claims (n=1.4 million) to assess cardiovascular risk associated with such usage (Starner, Schafer, Heaton, & Gleason, 2008). From May to November 2007, four FDA communications or actions targeted cardiovascular risks connected to the use of rosiglitazone. Use of rosiglitazone decreased markedly (from 97 to 41 per million enrollees) as these FDA actions unfolded during 2007, while use of this medicine's substitutes (pioglitazone and sitagliptim) increased (from 116 to 159 per million) almost completely "replacing" the decline in prescribed rosiglitazone. These patterns, in isolation, suggest a rational response to the warnings; however, review of medical claims tied to their use demonstrated that prior-to-treatment cardiovascular risk in the rosiglitazone group remained stable at about 20% through the warning period. Accordingly, the trends overall are consistent with a warning that impacts broad usage, but which do not specifically change the probability that a given drug will be avoided because of a targeted counter-indication disseminated by the FDA. The FDA actions taken throughout 2007 included the issuance of a black box warning in August that cautioned users regarding heart failure. This study included no discussion of press coverage.

A second research team, using Idaho Medicaid data, tracked prescriptions for the diabetes medication troglitazone from 1997 to 2000 (Wilkinson, Force, & Cady, 2004). Across this time span, troglitazone was the subject of four FDA warnings and was ultimately withdrawn from the market because of problems with liver toxicity. Idaho Medicaid data indicated that the first three warnings decreased only new, rather than continuing, use of troglitazone. The fourth warning

was associated with decreases in both new and continued use. These utilization findings thus appeared out of sync with the escalation of the warnings themselves, which, by the third issuance, included contraindications for drug initiation but prior to that point advocated only for increased liver function monitoring. Based on this work, the authors concluded that repeated warnings are necessary to effect changes in use, especially ongoing use (i.e., that which was initiated prior to the warnings). These researchers noted that an important barrier to more immediate responses to warnings is the fact that most practicing physicians do not have mechanisms (e.g., electronic medical records) to identify and outreach to their patients on a certain regimen of medication. Pharmacists and third-party payers thus were said to be in better positions than prescribing physicians to educate consumers about warnings, because re-fills are transacted by these entities in the absence of direct physician oversight. The authors mention mass media communication channels as having an impact on the dissemination of the troglitazone warnings, but they did not include direct analysis of that influence.

Gastrointestinal (heartburn and anti-nausea) medications

At least two reports have reviewed responses to the warnings pertaining to the drug cisapride, a treatment for heartburn. The first of these reports was the Idaho Medicaid study described above in the context of diabetes medications (Wilkinson et al., 2004). In addition to rosiglitazone, that study looked at cisapride which was the subject of FDA warnings between 1995 and 2000. Across this five-year period, six alerts were issued and cisapride was finally withdrawn from the market in 2000. The first of these alerts did not appear to alter new or continued use of cisapride, but by the second alert new prescription counts leveled-off. Both of these first two alerts involved drug-drug contraindications. The third alert presaged a decline in new prescriptions and a leveling in on-going usage. The two final alerts presaged declines in all

usage of the drug. These later alerts all included contraindications surrounding cardiovascular function. As was observed with rosiglitazone for diabetes, the serial responses to FDA alerts were interpreted as markedly lagged and non-specific. This work did not directly consider media coverage, but it did cite previous work which considered and observed the added impact of intensified third-party (i.e., not FDA) "publicity" on top of repeated "Dear Doctor" outreach letters and observed that such mass communication appeared to jointly yield the desired consumer response to an FDA warning (Weatherby, Walker, Fife, Vervaet, & Klausner, 2001).

Data from three pharmacoepidemiological sites serving the post-marketing surveillance needs of the FDA were used to assess changes in the use of cisapride after the 1998 FDA warning regarding serious cardiac side effects (Smalley et al., 2000). Annual "before and after" prescription counts showed a decline of 10% (24,840 versus 22,459). However, that aggregate decline was only accompanied by a 2% decline in contraindicated use per the cardiac warnings. These patterns were observed across two private insurance and one Medicaid population, though the Medicaid population had far higher rates of contraindicated use across both years of study (59% versus 29%). Press coverage was not addressed by this work, but the authors did comment that contraindicated use persisted despite "prominent publication of case reports" and nearly 1 million "Dear Doctor" letters (p. 3039).

Finally, the nausea medication droperidol (also used as a sedative and pre-anesthesia treatment) was the target of cardiovascular warnings in 2001 (Jacoby, Fulton, Cesta, & Heller, 2005). A survey of emergency room physicians at a national conference for these specialists reported that 97% of the respondents (80% response rate to the survey) were aware of the warning, and 81% said they changed their behavior because of it. This suggests high dissemination of a warning, though it relied on a select sample of respondents engaged in a

continuing medical education activity. It was also the case that the indication and venue of use for this medicine was constrained to emergency departments rather than as a "take home" medication. This brief report made no mention of mass media coverage.

Antibiotics

A single study looked at FDA warnings regarding the use of antibiotics (Gleason, Walters, Heaton, & Schafer, 2007). This study used administrative data from private insurance claims from the Midwestern U.S. corresponding to 1.8 million enrollees. The agent studied was telithromycin, originally approved in 2004 as a treatment for acute bacterial exacerbations of chronic bronchitis, bacterial sinusitis, and pneumonia. By 2006, warnings regarding liver toxicity and other problems emerged and eventually led to a relabeling of this medication as appropriate only for pneumonia. Simple review of prescription counts per 1 million plan members (pmm) found that the FDA warning and labeling change was associated with marked declines in overall use (940 pmm to 186 pmm), but even after the labeling change the vast majority of prescriptions (14 out of 15) were for off-label indications, i.e., ones other than pneumonia. Media coverage was not addressed, but the authors did note that the public health advisory regarding telithromycin first emerged in the wake of a scientific report in the professional journal *Annals of Internal Medicine* that documented the heightened prevalence of liver toxicity.

Montelukasts (Asthma controller medication)

Leukotriene inhibitors are a class of drugs used to control asthma. On August 28, 2009, the FDA *Medwatch* site posted an announcement directed at "pulmonology healthcare professionals" which stated that novel information was being added to the product label to caution professionals that the use of these agents may, in rare instances, result in "…agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability,

restlessness, suicidal thinking and behavior (including suicide), and tremor." (U.S. Food and Drug Administration, 2013). The announcement was not specified as a warning, nor was it directed to the general public, but it does impact medication-indication pairings that are quite common among adults and children, and thus one that is likely observable in large numbers in the Medicaid record. The most common asthma medication in the leukotriene inhibitor class at the time of the FDA announcement was a montelukast (marketed as Singulair) and it is used as prophylaxis (not alleviation of acute attacks) for asthma, exercise induced broncho constriction, and symptom relief for allergic rhinitis.

No direct post-utilization studies have been observed for this montelukast warning, but the connection between this medication has been reviewed in detail by at least one team of scientists with specific attention to suicide as a side-effect of the medication (Manalai, Woo, & Postolache, 2009). These researchers concluded that the existing data did not support suicidal concerns in use of the medication, but they also documented epidemiologic evidence supporting a link between allergies and depression and suicide. They further stated that the FDA's warning may be unnecessary, and that the warning by the FDA was "prompted" by a single highly publicized report of a completed suicide.

Varenicline (smoking cessation medication) warning

In 2009, the smoking cessation medications varenicline (Chantix) and bupropion (Zyban, Wellbutrin) were subject to an FDA warning indicating that these medications may increase the risk for negative psychological symptoms including suicidality, excessive aggression, increased anxiety, and other behavioral changes. Similar warnings dated back to 2007 for varenicline, one year after that drug was approved for use (buproprion, an antidepressant, was approved for smoking cessation in 1997). The 2009 warning involved the addition of a "black box" to the

documentation accompanying the sale of these drugs. That warning indicated the potential side-effects but also clearly stated that such symptoms may be related to nicotine withdrawal and that the warning was not intended to discourage use of these medications. Additionally, the warning reminded readers of the known and deadly consequences of prolonged smoking (cancer, cardiovascular disease) and specifically advised that the side-effects of cessation medications **"…**should always be weighed against the significant health benefits of quitting smoking." (U.S. Food and Drug Administration, 2009). Finally, the warning stated that when and if negative behavioral symptoms occurred, providers should advise their patients to stop the medication and monitor those patients until the symptoms disappear.

No study was found showing the warning impact on varenicline use, but recent analysis and discourse in the scientific literature about the warning has led to the suggestion that the warning may have been over-stated and perhaps needs to be removed or down-graded from its black box status (Gibbons & Mann, 2013; Yeh, Sarpatwari, & Kesselheim, 2016). One recent study which found no link between varenicline and neuropsychiatric symptoms noted that the drug may have been the subject of heightened adverse event reports to the FDA because of heightened media attention (Gibbons & Mann, 2013), however, no study was found which tracked that press coverage directly.

Analgesics

A single study regarding post-marketing regulation for analgesics focused upon paracetamol (acetaminophen; e.g., brand: Tylenol) (Morgan, Griffiths, & Majeed, 2007). Unlike the other studies reviewed thus far, the regulatory action was neither that of the FDA, nor was it limited to an informational intervention (e.g., a warning or public health advisory). In 1998, a federal legislative mandate introduced in the U.K. limited dispensing for paracetamol in an effort to

mitigate the risk of death by poisoning (i.e., overdose) from that drug. To control for unobservable factors resulting in temporal changes in the frequency of overdose events, this study looked not only at national statistics of deaths tied to paracetamol, but also made comparisons to analogous rates for aspirin, antidepressants, and nondrug poisonings. After adjusting the comparisons for age, the researchers found that these other drugs demonstrated similar step and slope changes in associated deaths coincident to the introduction of quantity limits which were specific only to paracetamol. These findings suggest other factors were in play besides the quantity limits, which shed considerable doubt on previous studies that concluded the regulatory action per se led to reductions in overdose deaths. Press coverage was not addressed as a potential contributing factor.

The above descriptions jointly indicated that prescription drug warnings, most introduced by the FDA, do indeed have the general impact of curtailing use in a way that is reasonably responsive to those warnings. However, these empirical reviews also show that specific responses often times are limited (impact small numbers) and even misplaced (result in unintended consequences like spillover effects). Moreover, the above reviews almost never discern how persons received (i.e., "heard about") the warnings—in particular there is only scant mention of the importance of the news media in that regard.

Public Policy Relevance

In 2008, under the authority of the FDAAA law, the FDA's Risk Communication Advisory Committee (RCAC) met for the first time. That standing 15 member committee includes experts in consumer research regarding devices, foods, and pharmaceuticals; physicians; public relations consultants; decision psychologists; and patient advocates. The Committee is appointed by the

FDA Commissioner and has an operating budget of just over $300,000 per year. Its mission is to advise the Commissioner regarding risk communication to consumers about all the products that the FDA regulates.[g] This charge includes attention to, and the encouragement of, research about the impact of risk communication activities.

Review of transcripts and other documents from the RCAC indicates the FDA's interest in direct and indirect risk communication strategies to consumers. These include communications via physicians and pharmacists, the internet, and other more traditional mass media and news coverage portals. Those transcripts further demonstrate the uncertainty that exists at the FDA regarding the boundaries and impacts of their public outreach activities.

The first meeting of February 2008 included several presentations and discussions about guidelines for press releases issued for product recalls (i.e., one time and lot specific action related to manufacturing defects or product contamination problems). Further included were discussions about other warnings or advisories such as those which are the subject of this research-- where a drug caution is issued, but the drug is not removed from the market. The presentations and discussion from that inaugural RCAC meeting in 2008 yielded the following points and questions:

- Warnings may not be perceived by the public in the way intended by the FDA. For example, a warning regarding the consumption of *Brand X* peanut butter may lead to curtailed consumption of all brands, and may further "spillover" to declining jelly consumption.

[g] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/default.htm, accessed 9/28/16.

- Despite such consumer confusion, an FDA official said that the administration relies on the mass media "to further the message, to get it out…,[h] thus the media is a recognized amplifier of press releases and direct-to-consumer or doctor communications that are implemented when a post-marketing problem becomes evident.
- Dissemination failure is common and may result from "information overload",[i] consumer neglect, or other processes that prevent consumers from being exposed to, or properly interpreting, a communication from the FDA.
- A literature review on recalls indicated that an ice cream recall may have failed to maximize public safety because news coverage rarely told consumers to discard the remaining product they had in their freezers. Confusion such as this is apparent in other relatively straight-forward food recall scenarios where many are aware of the general recall, but not of the details such as was the case with a 2006 spinach recall. That recall involved fresh spinach only, even as many consumers thought it included frozen and canned products as well.
- Hyperbolic news coverage was clearly suggested as a major force by a media consultant to the RCAC who said this:

> For the most part these (drug warnings from the 2000s) didn't reflect any major error or miscue. At best they were subtle trends or unanswered questions in the data. But they evolved into headline news.[j]

[h] Food and Drug Administration, Risk Communication Advisory Community Meeting Transcripts, February 29, 2008, p. 49
[i] *Ibid., p.* 55
[j] *Ibid, p.* 77

This comment is consistent with the concerns proffered by Barry and Busch (Barry & Busch, 2010) that news coverage regarding the SSRI warnings in the mid-2000s over-stated medication risks without reminding readers of the benefits of antidepressant treatment.

- Another communications expert noted that despite the regularity with which the general public criticizes the news media, consumers rely on these same sources of information as key guides for their consumptive behaviors.[k] This same researcher noted that there is a high level of aberrant news that can over-shadow accurate news regarding an FDA notification.

Overall, media and news coverage was a major theme of the first RCAC meeting, so much so that a veteran journalist was among the invited panelists. More recent RCAC meetings continue to involve careful consideration of the news media as it pertains to the dissemination of FDA messaging.[l]

The information presented above demonstrates the importance of post-marketing FDA activity regarding prescription medications. It also demonstrates that FDA warnings have led to changes in use of the pharmaceuticals targeted, and that lay press coverage generally influences health behaviors of both patients and physicians. Accordingly, this dissertation work aimed to determine if lay news coverage of FDA communications more specifically appeared to mediate the dissemination of FDA warnings on prescription medications.

[k] *Ibid*., *p*. 98
[l] See: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/UCM401626.pdf, accessed 9/28/16.

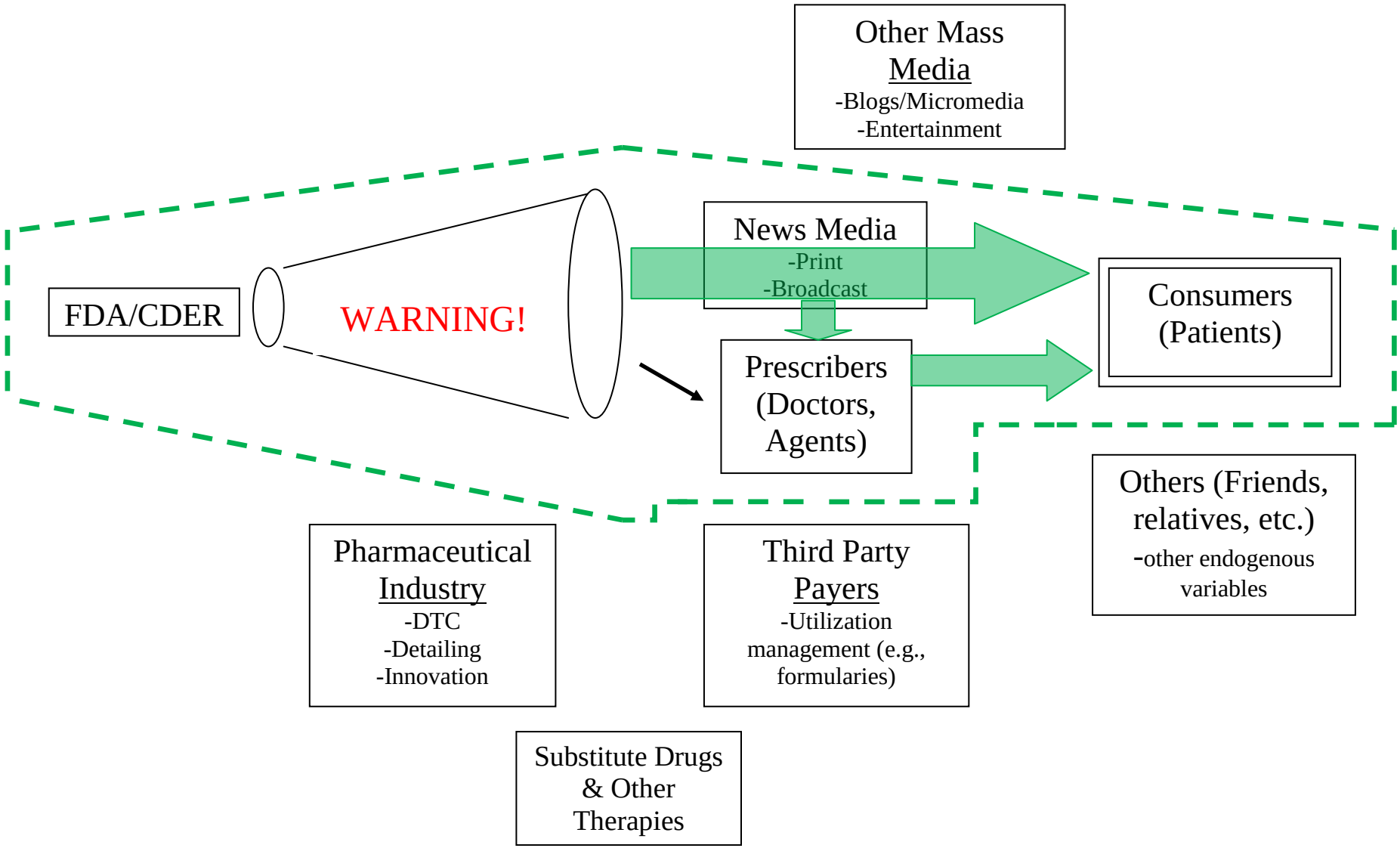
Methods

Framework/Conceptual Model

The framework for this research is depicted schematically in Figure 1 which shows a theoretical pathway from an FDA prescription drug warning to changes in prescription drug use as follows: FDA/CDER→Warning issuance→news coverage→ consumer response. The large green arrows depict a bifurcating pathway that depends on the news media influencing the patient/consumer either directly or indirectly via influencing the prescriber. It is this bifurcating pathway that was tested in this research, based on the assumption that any correlation between the news signal and consumer behavior (if it existed) would be discernible despite the likely non-news mediating influences noted in this figure. Accordingly, the power of the press to reflect and influence the full prescribing context is assumed although news signal is not the only force that impacts on the response to an FDA communication. It has been shown, for example, that pharmaceutical companies rely heavily on marketing directly to consumers (~$3 billion/year) and prescribers (~$24 billion/year) (The PEW Charitable Trusts, November 11, 2013), signal that likely works against curtailing use in response to a warning but may also be partially in sync with warnings because of post-marketing surveillance mandates by the FDA. Non-professional sources of news such as blogs and other social media outlets likely also play a role in the dissemination of warning (Kravitz et al., 2005; Wartella, Rideout, Montague, Beaudoin-Ryan, & Lauricella, 2016), though it is plausible that many "re-tweets" and "postings" are tied to professional journalism. As indicated by the small black arrow, and by FDA guidance information (U.S. Department of Health and Human Services & Center for Drug Evaluation and Research, March 2007), doctors often receive targeted mailings (e.g., pulmonologists would receive warnings about asthma drugs) directly from the FDA or a drug manufacturer regarding

emerging drug concerns and these communications may or may not be covered by the lay media. Finally, as noted at the bottom of the figure in between “pharmaceutical industry” and “third party payers” (i.e., insurance companies), the relative availability and cost of substitute therapies may influence reaction to a prescription drug warning, but that relationship is not tested here directly. It can be said that this research work, by specifically studying lay news signal to the exclusion of several other FDA warning dissemination pathways, has a focus on only some of the information flow that likely influences consumer behavior. At the same time, though, this limited review does target an information source that may be especially salient (i.e., high volume and understandable) for doctors and their patients, and particularly proximal for the latter.

Figure 1. Schematic of factors influencing consumer use of prescription drugs in the wake of an FDA warning. The green dashed line isolates the pathway under study by this dissertation research.



Hypotheses

This dissertation work explored the extent to which various components of news media coverage were predictive of consumer responses to prescription drug safety warnings made by the FDA. The guiding hypotheses were based on work reviewed in the introduction that support the theory that media coverage has at least some effect on consumer behaviors (Severin & Tankard, 1997). Moreover, given that changing or initiating a prescription requires time for patient and doctor consultation and decision-making (Kravitz & Bell, 2013), it was expected that the response to news would be a slightly time-lagged predictor of consumer behavior. It was further hypothesized that such effects would sometimes be consistent with the specific intent of the FDA warning, and at other times may have unintended consequences (Barry & Busch, 2010; Busch & Barry, 2009), with appropriateness operationalized by considering "spillover" effects from one population to another (i.e., children to adults). Finally, as was the case with smoking cessation news coverage (Clegg Smith et al., 2008), it was expected that news increasing concern about an FDA warning (INCC) would correlate with decreased use of the drug subject to that warning, whereas neutral coverage regarding that concern (NEUTRC) would promote use of the drug, based on the simple principle that most mass media exposure is 'good for business' as it highlights and normalizes the product in question.

Accordingly, three formal hypotheses were proffered for this work, one containing a corollary:

> **Hypothesis I:** Time-lagged news that INCC should correlate with dampened drug use (or prescribing processes), after simultaneous adjustment for warning, autoregressions (ARs), and (as needed) seasonal effects.

Corollary, Hypothesis IA: Significant effects supporting *Hypothesis I* should "spillover" to those not targeted by the warning.

Hypothesis II: NEUTRC news coverage should encourage drug use (or process) measures, after simultaneous adjustment for warning, ARs, and (as needed) seasonal effects.

Hypothesis III: Details about the news coverage (e.g., front page placement, quality; see text below), should intensify significant findings per *Hypotheses I and II*.

Selection of the warnings

To test these hypotheses, time-series datasets were constructed for each of four recent FDA warnings pertaining to the distinct therapeutic classes commonly used to treat depression, asthma/allergies, smoking, and diabetes. These four warnings were selected as case studies to represent different types of commonly used prescription drugs subject to FDA warning. The cases selected occurred between 2003 and 2009, during a period leading up to and just after post-marketing surveillance responsibilities of the FDA were expanded by federal legislation (FDAAA; H.R. 3805; P.L. 110-85). Two of the warnings (antidepressants, diabetes medication) were selected because published time-series surrounding the warnings for these drugs already existed in the scientific, peer-reviewed literature. The two other warnings (smoking cessation, asthma/allergy medications) were selected because they pertained to prevalent medical conditions; asthma/allergies affects >7.4% of the population, and smoking affects 17% of the population (source: U.S. Center for Disease Control and Prevention). The broad prevalence of these treatment indications were considered important because the relatively high population prevalence was presumed to correlate with widespread media coverage of available remedies.

The precise definition of a warning from the FDA regarding a prescription drug is variable, but it can generally be thought of as an official announcement that cautions physicians and consumers about the use of an otherwise approved medication. Cautions typically involve things like new side-effects of the medication alone, or drug-drug combination use adverse events which only become fully apparent after a drug has been used in a large and heterogeneous population for a considerable amount of time. Drug safety communications from the FDA typically involve dissemination on the agency's website at a portal known as *MedWatch*, as well as blast email alerts to physicians, pharmacists, and registered consumers (Kesselheim et al., 2015). The precise nature of each dissemination effort may vary from warning to warning.

The four warnings examined for this dissertation research share timing (2003-2009, spanning the passage of the FDAAA legislation), and they all convey concerns about rare but serious side-effects tied to the use of medications targeting illnesses that are relatively common in the general population, i.e., illness prevalence rates exceeding 7%. Specific aspects of each warning, including distinct features of each are detailed below.

The FDA first issued a safety warning on the antidepressant paroxetine (brand:Paxil) in June of 2003 (Busch et al., 2010). That warning became a broader public health advisory in October of 2003. The October warning emphasized the importance of monitoring patients with major depression during the initiation phase and further noted that fluoxetine was the only antidepressant with approval for use in children (Busch et al., 2010). The October 2003 warning also announced plans for an FDA advisory committee review scheduled for Feburary 2004 (www.fda.gov/safety/MedWatch). In December of 2003 the U.K. and European pharmaceutical regulatory agencies issued similar warnings (Gibbons et al., 2007). In February/March of 2004 the FDA issued a second public health advisory intensifying the caution for paroxetine and nine other antidepressants, and including adults in the warned population (www.fda.gov/safety/MedWatch). In Sepetember of 2004 the FDA reported that their advisory committee recommended the issuance of a "black box" warning label, and by the next month the FDA

required pharmaceutical manufacturers to add such warnings to all antidepressant labels (Busch et al., 2010). This October 2004 warning targeted children and adolescents only, apparently dropping the concern for adults (www.fda.gov/safety/MedWatch). It was not until December of 2006 that young adults were added to these warnings (Gibbons et al., 2007), though FDA records show the concern in adults rose to the level of a public health advisory in July of 2005. Fluoxetine (brand: Prozac) was available in generic form by 2001, and paroxetine (brand: Paxil) was available in generic form as of July 2003 (www.accessdata.fda.gov). The study period for this thesis work was thus chosen to surround the October 2003 public health advisory as a critical point in time when concern about the drug was emerging and when both of these dominant SSRI drugs were mostly available in generic forms.

The asthma and rhinitis drug montelukast (brand: Singulair) first became the subject of post-marketing concern for the FDA in March of 2008 when the agency requested that the adverse reaction section of the insert include concerns about "suicidal thinking and behavior." (www.fda.gov/safety/MedWatch, ucm116447). This action never rose to the level of a "black box" warning, and thus it can be considered a lower intensity warning and concern put forth by the agency compared to the others studied for this thesis work. In April 2008 feelings of "anxiousness" and actual suicides were added to the adverse reaction section of the drug insert. In January of 2009 the adverse reaction section was again expanded to add nose bleeds as a minor concern. By August of 2009 the FDA required the dissemination of a health care professional fact sheet that included the "precaution" that montelukasts and two other similar but distinct asthma/rhinitis drugs increased one's risk for the following neuropsychiatric symptons: agitation, aggression, anxiousness, dream abnormalities, hallucinations, depression, insomnia, irritability, restlessness, and suicidal ideation (including suicide) (www.fda.gov/safety/MedWatch, ucm132753). This public health advisory was directly connected to FDA safety reviews of montelukasts initiated in March of 2009. The August 2009 communication recommended provider and patient awareness, patient consultations with providers if symptoms occur, and possible discontinuance of the medication in such instances. Because this August 2009 issuance was

the most definitive and evidence-based, it was selected as the event around which news coverage effects were considered. The only other FDA warning noted at the *Medwatch* site occurred in April 2011 and it added the "possible" side effect of bruising or platelet malfunction. Singulair was on patent until 2012, i.e., through the entire study period for this thesis work.[13]

The smoking cessation drug varenicline (brand: Chantix) first was the subject of FDA post-marketing concern in November 2007 when the agency issued a communication at their *MedWatch* site (www.fda.gov/safety/MedWatch, ucm132753, ucm070765) noting the possible side-effect of aggression and erratic behavior in persons using the drug. This communication stated that the FDA had not yet reached any conclusions about causality, but it had decided to recommend vigilance regarding sudden mood changes, and drowsiness which might impair the safe operation of a motorized vehicle or other machinery. The FDA also acknowledged a recent media report regarding the death of an individual using varenicline, but the FDA communication also noted that this particular death may have instead been caused by alcohol abuse. In February of 2008 a public health advisory was issued by the agency, including a press release, which stated that "it appears likely" after reviewing safety information about Chantix that the drug is associated with the serious neuropsychiatric events listed above (www.fda.gov/safety/MedWatch, ucm132753, ucm11684). This public health advisory re-affirmed and strengthened the November communication by, for example, encouraging patients to report any history of psychiatric illness or subsequent mood or behavioral changes to their prescriber "immediately". In June/July of 2008 the *Washington Times* and ABC News reported that some veterans with post-traumatic stress disorder were participating in clinical trials of Chantix, and this participation placed them at heightened risks for neuropsychiatric symptoms including erratic behavior. In fact, the news coverage was coincident with at least one dramatic U.S. Congressional hearing.[14] In July of 2009 the FDA

[13] Merck 2008 Annual Business Briefing-Final: Eva Borattor, VP, Investory Relations, Fair Disclosure Wiver, December, 9, 2012.

[14] Ross, B; Walter, V; "'Disposable Heros': Veterans Used to Test Suicide-Linked Drugs"; June 17, 2008, abcnews.com, accessed 12/20/2016.

required manufacturers to add a "black box" warning to varenicline and buproprion (brand: Zyban), the latter an antidepressant turned smoking cessation agent, stating the neuropsychiatric concerns. That communication, also available as a podcast, noted that if any neuropsychiatric concerns emerged, patients should stop the medication and contact their prescriber immediately. The communication further noted that many of the neuropsychiatric symptoms might alternatively be the result of nicotine withdrawal. Finally, germane to this thesis research, in May of 2011 the FDA reaffirmed its conscerns about Chantix and Zyban, and noted that the drugs were yet under active safety review (Yeh et al., 2016). The "black box" warning of July 2009 was selected as the center focus of this news time-series analysis because it marked a definitive peak of the FDA's scrutiny and warning issuance activities.

Concerns about the diabetes medication rosiglitazone (brand: Avandia) first intensified by 2004 when the American Diabetes Association released a consensus statement warning practitioners that drugs in rosiglitazone's therapeutic class heightened risk of heart failure (Yeh et al., 2016). Concern for heart attack risk caused by rosiglitazone emerged strongly in May of 2007 with the publication of two separate scientific studies, one from academia, the other from industry (Starner et al., 2008). In the wake of these publications the FDA issued an "alert" stating that it was reviewing the available data, and further noting that warning materials inserted with the medication label already cautioned users about this concern (www.fda.gov/safety/MedWatch, ucm143460). In June of 2007 the FDA issued a "consumer update" which reaffirmed the points made in the May "alert" and further stated that "Concerns about possible increased chance of heart attack and heart related deaths…" were on-going and being thoroughly investigated by the agency. In the meantime, the FDA advised consumers to consult their doctors and to sign up for email or other internet alerts (www.fda.gov/safety/MedWatch, ucm049063). In July of 2007 a joint advisory committee of the FDA formally met to debate the concerns about rosiglitazone. That joint committee recommended that the agency add a "black box" warning to the drug's label. In August of

"Why Does the U.S. Department of Veterans Affairs Continue to Give a Suicide-Inducing Drug to Veterans with Post Traumatic Stress Disorder", U.S. House of Representatives Committee on Veterans Affairs, Washington, D.C., 7/9/2008.

2007 pioglitazone (a related drug) was added to the warning language by the FDA. Finally in November of 2007, via a press release and formal press conference, a "black box" warning was mandated by the FDA and that warning added the detail that co-administration of nitrates and insulin heighted risk. The press release stated that the advisory committee which met in July voted overwhelming against market withdrawal (22 to 1), even as it supported the need for the warning. The press conference included science reporters from the *New York Times*, *Washington Post*, *Wall Street Journal*, *Bloomberg News*, and *L.A. Times*, among others- and these prominent reporters all asked questions directly of CDER head Janet Woodcook (www.fda.gov/safety/MedWatch, ucm122282). News coverage was explored surrounding the November 2007 warning, but because the rosiglitazone monthly time-series dropped precipitously in May 2007 (see results), statistical analysis used that first event (related to the FDA alert noted above) as a key marker of FDA warning activity. It can finally be noted that beyond the period of study for this dissertation research, expert opinions grounded in on-going studies both within and outside of the agency remain conflicted about the necessity of the rosiglitazone warning (Dal Pan, September 10, 2010; Yeh et al., 2016).

The four FDA warnings and study periods described above all reflect serious and rare concerns about approved drugs for common diseases. Moreover, despite these novel concerns, the FDA chose to keep all four drugs on the market. However, the four warnings were also distinctive in the ways that are noted above, and especially so for the montelukast warning which unlike the other three never rose to the highest level of concern, the "black box" warning. As such, the results presented should be regarded as four case studies about news media impacts on FDA warning dissemination, rather than as more homogenous or otherwise representative sample.

Outcomes (Dependent Variables)

As just described, for selected FDA warnings were the subject of this research. For the first (antidepressants), four outcome variables were derived directly from graphs in two published,

peer-reviews articles (Libby et al., 2007; Valuck et al., 2007). Those graphs contained monthly figures on depression diagnosis by primary care physicians (PCPs) versus psychiatrists, and filled SSRI or antidepressant prescription (versus no drug use) percentages pertaining to thousands of new pediatric or adult depression cases. These data were derived from a large administrative claims database. The specific quantities isolated are described in the Table 2 below, and span the period of 49 months, with the warning month of interest (October 2003) near the center of that time span. The four outcomes for this warning were selected because they were readily available from the publications cited, and so that they would include multiple outcomes for the pediatric population and at least one for the adult population to consider spillover effects.

Table 2. Summary of the antidepressant warning (October, 2003) outcome variables.

Variable Name	Definition	Data source
child_pcpdx_pct	Percentage of new episodes of childhood depression (n=65,349), diagnosed by primary care physicians (PCPs) from a national sample spanning ~48 managed care plans and ~29 million covered lives across the age spectrum.	(Libby et al., 2007)
child_ssri_pct	Percentage of childhood depression diagnosed cases identified where an SSRI prescription was filled within 30 days of the diagnosis, from the same sample as above.	
child_pcpAD_pct	Percentage of filled childhood antidepressant prescriptions within 30 days of depression diagnosis that were prescribed by a PCP, from the same sample as above.	
adult_ pcpAD _pct	Analogous to that child_pcpAD_pct, but for adults and from the same sample as above. (n=475,838).	(Valuck et al., 2007)

For the warning on the diabetes drug rosiglitazone (Avandia), the outcome variable time-series was also taken directly from a published graph appearing in the peer-reviewed literature (Starner et al., 2008). This variable was extracted from the graph in monthly per million member units which tallied filled rosiglitazone (Avandia) prescriptions during the period of the study (17

months). These data were derived from a pharmacy claims database containing information from 9 different commercial plans (BlueCross) covering 9 million members.

For the two other warnings studied, Maryland Medicaid administrative records were used to isolate raw counts of prescription fills for varenicline (Chantix, for smoking cessation), and montelukasts (asthma/allergy) medication spanning 49 months, with the warning dates in the center of each study span. Moreover, the Medicaid eligibility records were used to isolate total populations of children and adults during the months of the study so as to provide a denominator for the monthly prescription counts. For the smoking cessation medication warning, the denominator was persons >18 years old, but for the asthma/allergy medication that denominator included all Medicaid enrollees. In July-August of 2009 (the time of these two warnings) there were approximately 840,000 total Maryland Medicaid enrollees including 370,000 persons age 18 years or greater. The Medicaid data were obtained with permission from Maryland's Department of Health and Mental Hygiene (DHMH), and with institutional review board oversight from DHMH and from University of Maryland Baltimore County (UMBC).

Main Explanatory (Independent) Variables

News Item Selection

Lexus Nexus Academic (www.lexisnexis.com) and *ProQues*t (search.proquest.com) databases were used to isolate article (major newspaper or magazine) text or broadcast (TV or radio) transcripts about each of the four general drug types subject to the warnings studied. Searches using these two databases were conducted to isolate lay and common news items surrounding each warning for at approximately 24 months pre- and post-, with specific words to capture articles that at least once mentioned the general diseases or drugs of interest (terms:

"asthma", "smoking", "depression or antidepressants", and "diabetes") and one of the words "safety" or "efficacy." This combination was used to limit articles to those that pertained to the FDA's key gate-keeping responsibilities. Major English news items were isolated including large (e.g., *New York Times*) and smaller (e.g., *Philadelphia Enquirer*) market newspaper articles, local and national TV and radio transcripts, and magazine articles including *Time*, *Newsweek*, and *The Economist*. Multiple searches were conducted to insure broad sensitivity to news signal, and the articles were "de-duplicated" by date and author to minimize the redundant inclusion of items disseminated via multiple distribution outlets.

Across all four warnings, a total of 3,295 news items were identified from the database searches. Of these, 1,019 unique items were deemed appropriate for review. Non-coded items were technical publications (e.g., market disclosure transcripts, medical journal articles or newsletters), public announcements about community events (e.g., a diabetes support group), and items in which key word mentions in the article were clearly not about the use of specific pharmacologic remedies (e.g., "a depressed stock market lower brought the valuation of technology and pharmaceutical stocks", or mentions of safety or efficacy unrelated to the use of any pharmaceutical). Inter-rater reliability for article selection from the 3,295 news items was achieved swiftly- on the first rating- with inter-rater *kappa* statistics exceeding 0.9.

Coding news items

Increase concern (INCC) or neutral regarding concern (NEUTRC)

Each of the news items isolated for this work (n=1,019) was systematically coded to discern the general attitude of the article, and to isolate specific details via full review of the text. The general attitude of the article was that it was rated as either increasing concern about the warning

in question (INCC) or neutral regarding that concern (NEUTRC). Empirically there were so few articles that were negative regarding the concern (i.e., which rebutted or cast doubt on the FDA concern) that these were clustered with the NEUTRC rated news items. It was overall quite straightforward to discern, based on a quick reading of each article, whether it heightened concern about an FDA warning or was neutral to it. Neutral news items either only mentioned the drug therapy without mention of the warning, or mentioned the warning but were otherwise equivocal about its importance to consumers (e.g., "The FDA has informed consumers that in very rare instances…, but this concern should not discourage use of the drug when a clinician determines that it represents a wise treatment option."). The general idea that positive and negative news coverage differentially influences consumer behavior is supported by previous research on smoking cessation (Clegg Smith et al., 2008).

Details about each news item (i.e., weights for the article counts)

In addition to labeling each news item as INCC or NEUTRC, each item was additionally coded along seven dimensions to discern various content attributes which were hypothesized to intensify news impact. Each of those seven attributes was used to weight the articles to create dependent variables for subsequent statistical testing (see statistical section). Appendix 1 of this dissertation is the code book used by the three raters who carried out these textual reviews.

Front page

Each news item was coded as a lead or front page article if it appeared on page 1 of a newspaper, on the cover of a magazine, or as the lead story in a broadcast. The a priori hypothesis pertaining to this coding item was simply that such "front page" coverage would increase the item's visibility thereby increasing its impact. Recent research, for example, has demonstrated that "major" news coverage defined as that appearing both on the front pages of

the *New York Times* and *L.A. Times* yield substantial stock market activity, up to 21% higher than normal, after adjusting for DOW record events, lagged stock orders, and past year return on investments (Yuan, 2015). Research considering the agenda-setting role of lay news media on health information (e.g., trans fat consumption, obesity) often captured front page versus other placement, but this information was not reported in detail nor used to consider differential responses to the article message (Barry & Busch, 2010; Barry, Jarlenski, Grob, Schlesinger, & Gollust, 2011). Accordingly, there is interest in this indicator, but an absence of testing it as a predictor of downstream consumer behavior. Despite that apparent research omission, front page coverage has long been an indication that a story is of prime importance to those who make the news, and of unique prominence to those consuming it (Karlsson, 2011; Shih et al., 2008).

Quality

Each article was rated on a scale of 0 to 5 reflecting low to high quality, respectively. The ratings were based on a scheme developed by a respected health news blog (http://www.healthnewsreview.org/) and were derived by summing across the following five sub-ratings:

i) Who is at risk? (0= no or poor description, 1= close match to the FDA warning, 0.5= intermediate)

ii) What are the risks? (0= no or poor description, 1= solid description of specific population with absolute risks clearly articulated, 0.5= intermediate description)

iii) Strength of evidence (0= no clear description, 1= description of randomized controlled trial(s) or multiple and sound observational studies, 0.5= intermediate evidence)

iv) Cost/benefits presented (0= no clear description, 1= description of both costs and benefits, 0.5= intermediate description)

v) Alternatives (0= no mention of alternatives, 1= mention of alternative drug and other therapies if they exist as well as actions to respond directly to the warning, 0.5= intermediate mention of alternatives)

Given that this quality rating is the most subjective and challenging of all coded dimensions of this research, inter-rater reliability was conducted to determine how reproducible it was between the author of this work and two hired students (one graduate student and one undergraduate). Intra-class correlation coefficients (ICC) were calculated to establish reliability between each rater and the author across three waves of ratings which included 15 to 27 articles per wave. The ICCs for the graduate student rater ranged from 0.46 to 0.60 to 0.86 across three training periods, after which point this rater was considered reliable. The ICC's for the undergraduate student required four periods to establish reliability because of a nadir in period three. Accordingly, the undergraduate rater was deemed reliable after achieving sequential ICCs of 0.68, 0.68, 0.29, and 0.75. Following the three to four periods leading to ICCs ≥ 0.75, the stability of that reliability was tracked in two separate periods by randomly selecting 1 in 10 observations for reliability testing for the graduate student, and 1 in 5 observations for the undergraduate. Post-rating reliability for the graduate student ultimately demonstrated an ICC= 0.83, and for the undergraduate it was 0.71. Since the graduate student rated nearly twice the number of articles as the undergraduate, it can be said that in the aggregate post-rating reliability for the quality indicator (a value ranging from 0 to 5) was reproducible with and ICC exceeding 0.75 (i.e., >75% of a perfectly/completely reliable rating process).

Length

To assess the sheer volume of coverage surrounding the targeted pharmaceuticals, word counts per article were tallied and then clustered into one of six levels ranging from 1 (word count ≤ 85) to 6 (word count >4,186). These six levels were empirically derived based on the five cut points (5th, 25th, 50th, 75th, and 95th percentiles) of word count across all the articles reviewed. Other researchers have considered word count as an indicator of coverage amounts, though they have not necessarily considered its impact on health behaviors (Busch & Barry, 2009; Shih et al., 2008). Outside of health issues, research on stock trading suggests that increased counts of positive or negative words in newspaper articles about a specific company led to associated stock valuation changes subsequent to such news media coverage (Azuma, Okada, & Hamuro, 2014). Journalist commentators have recently debated the extent to which news coverage tends to be too long or too short, but there appears to be agreement that length is an attribute that influences the quality and dissemination of a report (Buttry, January 29, 2013; MacMillan, January 1, 2010).

FDA mention

The FDA has a unique reputation as the supreme gate-keeper for pharmaceuticals entering the U.S. market, and more recently as an important source of information on medications after they are approved for sale. The FDA not only issues warnings to clinicians and doctors, it further has the authority and responsibility to sanction companies for poor manufacturing or marketing practices regarding the appropriate and safe distribution and sale of drugs which have previously been approved (Carpenter, 2010). Because of the FDA's enormous regulatory power and influential ethos as a trusted source of practical biomedical information, in this study articles about each warning were coded as mentioning the FDA or otherwise, and the a priori hypothesis was that FDA mention would increase the extent to which the article altered consumer behavior,

positively or negatively, depending upon whether the article concern was rated as generally INCC or was NEUTRC about the warning.

Anecdotal valence

A common criticism of health journalism is that it tends to sensationalize findings by over-stating the efficacy of new medications (Schwitzer, 2003, 2004) or the dangers of well-established ones (Comis, 2015). Communications researchers have stated that a published study is a "prime candidate" for lay news coverage if it has "…novelty, negativity, controversy, and potential for widespread impact" (Anderson, Brossard, & Scheufele, 2012). The prioritization of these sensational attributes lends itself to hyperbolic reporting. Moreover, this dramatic journalistic framing (e.g., focused on unethical behavior, uncertainty, conflict, and competition) has been observed to increase reader/public engagement and action in response (Nisbet & Huge, 2006).

As a simple proxy for dramatic framing, this thesis coded each news item as low, medium, or high valence based on content review. Colorful stories about individuals experiencing dramatic side effects (e.g., near death, violence, catastrophic illness) to the drug subject to the warning were rated as having higher anecdotal variance, whereas stories with population-based data were considered to be low anecdotal valence. Intermediate valence stories were those with both anecdotal and more scientific reporting to balance against that anecdote. This three level variable (integers 1 to 3) was ultimately used to test if increasing valence correlated with increased responses to each warning.

FDA warning mention

Lay news coverage of medications may or may not refer to the official pronouncement of an FDA warning. In the present study, this variable was simply coded using a binary flag variable

(1 or 0) recording if the warning was mentioned or not. The a priori hypothesis was of an interaction between warning and concern, such that mention of the FDA warning would yield decreases in aggregate use of the medication for articles that INCC about the warning whereas the opposite effect who hold for articles that were NEUTRC. Mention of the FDA *warning* differs from mention of the FDA per se, because news coverage of drugs often mentions the FDA's general regulatory authority over the approval or surveillance process without mentioning specific drug warnings issued by that agency.

Radio/TV (Broadcast) placement

Each article was coded to denote if the placement was broadcast via TV or radio, or only via print media (digital or paper). This variable is an important indicator of the broadest dissemination to the public in terms of the volume of consumers who attend to the news, in part because TV and radio consumption is a more passive form of information intake than reading, but also because TV and radio still are dominant sources of news among the majority of Americans. A recent Pew Research Center study found that 57% of U.S. adults obtained news about the U.S. Presidential election from TV (not including late night comedy), 44% from radio, 48% from news websites, and 36% from print newspapers (Gottfried, Barthel, Shearer, & Mitchell, 2016). Accordingly, despite the continued relevance of print media and the expansion of digital news, non-interactive video and audio broadcast media remain a dominant mode through which most Americans consume news. This information leads to the final a priori hypothesis that FDA warning news signal originating from TV or radio will be more influential than signal originating from print media.

Statistical model

The primary statistical models used for this study tested whether or not each outcome was related to INCC news coverage surrounding the respective warning, after adjusting for the warning itself. Equation 1 shows the form of that model which included a 1st order autoregressive term (AR1) pertaining to the error-- an adjustment that is important for time-series analysis because adjacent points are not randomly selected (Hagihara, Tarumi, & Abe, 2007; Studenmund, 2006; UCLA: Statistical Consulting Group, 2016; Wooldridge, 2006). The news variable was an accumulation (sum) of news signal from the first time point in the study onwards, and both it and the warning flag was lagged 1 month (t-1) to reflect the signal just prior to the modeled month for each time t. This lag was used to allow time for the warning to disseminate and a recorded prescription event to occur. The decision to use an accumulation of signal is based on the likelihood that news signal stays in a recipient's mind for more than just the month in which it appears in print (sensitivity analysis described below will test a very limited news signal 'half-life').

Though three seasonal flags are included in Equation 1, with winter as the referent, they will only be included in antidepressant, asthma, and smoking cessation models treatment activities because those diseases/treatments have know seasonal variation (Chandra & Chaloupka, 2003; Gardarsdottir, Egberts, van Dijk, & Heerdink, 2010), and the final models will only include seasonal adjusters if an *F-test* deems them jointly significant ($p<.05$) (Studenmund, 2006).

Equation 1. $$Y_t = \beta_0 + \beta_1 * (\text{warning flag})_{t-1} + \beta_2 * (\text{INCC\_SUM\_NEWS})_{t-1} + \{\beta_3 * \text{Spring}_t + \beta_6 * \text{Summer}_t + \beta_7 * \text{Fall}_t\} + v_t$$

Where…

t= month

t-1= 1 month lag (i.e., the month before)

time=1 in the first month of the study and n+1 in each subsequent month

warning flag= a flag of 1 after the warning was issued, or 0 before it was issued

INCC_SUM_NEWS= accumulation of news i.e., the sum of news signal from the beginning of the study.

{**Quarterly seasonal dummies** included if joint *F-test* is significant}

$\mathbf{v_t} = -\Phi * v_{t-1} + \epsilon_t$ (where $\boldsymbol{\epsilon_t}$ is the residual error with an assumed mean of 0 and standard deviation of σ^2).

The communications research identified and reviewed for this thesis work mainly looked for instantaneous or immediate (i.e., near term and short-lived) down-stream effects of news exposure on consumer behavior (Ishii et al., 2013; Severin & Tankard, 2001; Siegel & Lotenberg, 2007). However, given that the FDA warnings studied here are about innate (to the medication) side-effect concerns which do not change after the warning has been issued, it is expected that dissemination of the warning will "stick" after its issuance by influencing doctor and patient vigilance moving forward. Accordingly, the independent variables regarding news coverage was generated as an accumulation of signal from one month to the next- spanning the duration of the study (17 to 49 months, depending upon the warning).

To carry out these analyses, SAS 9.3 AUTOREG or REG functions were used (SAS/ETS(R) 9.22 User's Guide, date accessed 3/4/16). For the news variables and warning effects, a 1-tailed *p*-value of 0.1 was assumed as the threshold point for significance because the direction of the significant effect was predicted, i.e., the warning and INCC news were expected to decrease pharmaceutical use, and NEUTRC news was expected to increase such use. For other effects including the seasonality and AR terms, a two-tailed *p*-value threshold of .05 was assumed.

Sensitivity Analysis

Beyond the primary models described above, the follow additional models were used to test the robustness of the findings using alterations in the explanatory variables as follows:

1. Five month accumulation of the news coverage independent variable, rather than ongoing accumulation, to consider if the news signal appears to have transient 'half-life', rather than an ongoing influence across the period of study. Previous research on smoking cessation showed significant effects with a five month accumulation of news coverage (Clegg Smith et al., 2008).
2. The inclusion of the NEUTRC term, to determine any separate influence of such neutral news coverage.
3. 2nd order autoregressive errors were test (AR2)
4. Lagged dependent (outcome) variables instead of AR terms, as a way to directly model the impact of the 'baseline' level in that outcome.
5. Weighted news coverage variables (e.g., front page counts), in lieu of INCC news counts generally, to determine if such details intensify new signal correlations to the outcomes.

Results

This section gives results for each outcome beginning with the four pertaining to the antidepressant warning, followed by that for the asthma, smoking cessation, and diabetes medication warnings. Each sub-section begins with a brief restatement of the warning and the data sources used to create the dependent variable(s). Then, a summary table of all outcome and independent variables is presented with monthly mean values, followed by a time-series graph that plots the course of the outcome variable and the overall INCC and NEUTRC time courses. Finally, additional tables separately present the results for the INCC (and NEUTRC) analysis in isolation (per Equation 1), followed by a separate table and text for the weighted news variables (e.g., front page counts) sensitivity tests. Each sub-section concludes with a summary statement about all the statistical findings, and the close of this entire results section presents a summary across all four warnings.

Antidepressant warning

In October 2003, the FDA issued a warning about suicidal ideation among children and adolescents initiating antidepressants. Four distinct outcomes (presented individually below) derived from two published articles were used as dependent variables to test the impact of news coverage surrounding this warning on both youth and adult antidepressant prescribing and use (Libby et al., 2007; Valuck et al., 2007).

Table 3 provides summary statistics for all of the antidepressant outcome and predictor variables, by month, for the antidepressant warning analysis. For example, the table shows the following about the *monthly averages* of outcomes and news media predictor variables during the 50 month study period for the SSRI warning: 59% of new childhood depression cases resulted in an SSRI prescription (range 29-66%), 5.6 INCC articles appeared per month, and 0.98

of these INCC articles were lead or front page stories, and 6.1 quality units were attached to each monthly cluster of INCC articles (sum of units which range from 0-5 per article).

Child_pcpdx_pct (percent of new childhood cases diagnosed by a primary care physician)

At the top of Table 3, the data show that across the 50 months studied, 38% (standard deviation= 3.5%) of new depression cases in children were diagnosed by primary care physicians (PCP). The remainder of this section aims to consider if this PCP new case detection percentage varied with news coverage of the antidepressant FDA warning.

Table 3. Summary statistics for the antidepressant (SSRI) drug warning

Variable	By month			
	Mean	St. dev.	Min	Max
OUTCOMES				
child_pcpdx_pct (%)	38	3.5	32	47
child_ssri_pct (%)	59	6.9	29	66
child_pcpAD_pct (%)	41	3.5	32	50
adult_pcpAD_pct (%)	59	2.4	54	63
PREDICTORS				
INCC (count)	5.6	8.6	0	38
INCC_FRONT (count)	0.98	2.2	0	8.9
INCC_QUAL (cumulative score)	6.1	12	0	67
INCC_LENGTH (cumulative score)	18	28	0	113
INCC_FDA_MENTION (count)	4.7	7.7	0	37
INCC_VAL (cumulative score)	8.4	14	0	73
INCC_FDA_WARN (count)	2.9	5.4	0	28
INCC_BROADCAST (count)	2.2	4.6	0	25.0
NEUTRC (count)	6.2	3.7	0	18
NEUTRC_FRONT (count)	0.93	0.94	0	4.0
NEUTRC_QUAL (cumulative score)	1.5	2.4	0	12
NEUTRC_LENGTH (cumulative score)	23	13	0	72
NEUTRC_FDA_MENTION (count)	2.6	2.0	0	8.0
NEUTRC_VAL (cumulative score)	10	6.6	0	34
NEUTRC_FDA_WARN (count)	0.32	0.68	0	3.0
NEUTRC_BROADCAST (count)	2.1	2.5	0	10

Pcpdx_ pcp= new cases diagnosed by a primary care physician
ssri= selective serotonin reuptake inhibitors
pcpAD= news cased where a PCP prescription for antidepressants was filled
adult_pcp_pct= as per pcpAD, but for adults

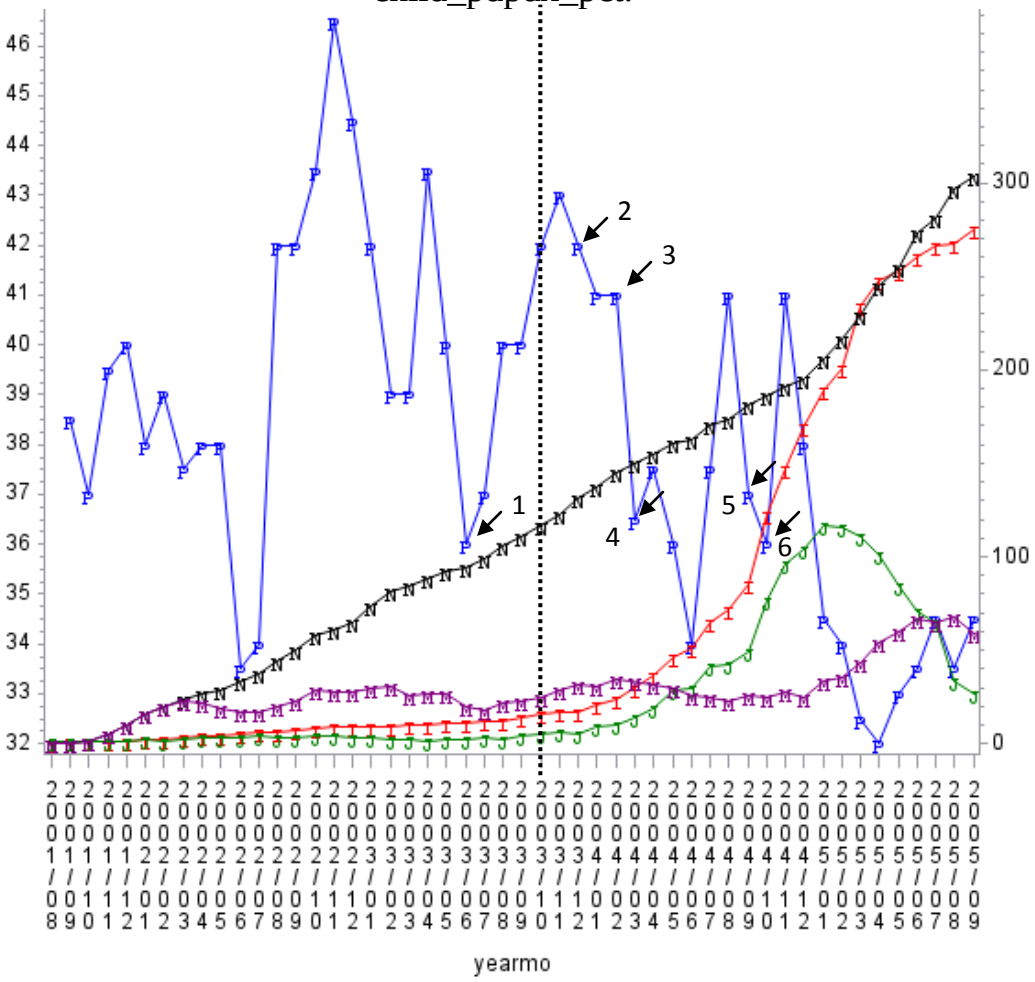
INCC= article increases concern about the warning
NEUTRC = article is neutral regarding concern (or decreases concern) about the warning

Outcomes sources: (Libby et al., 2007; Valuck et al., 2007)

Predictor source: Author's analysis of 588 news items from 26 months before to 24 months after the warning, corresponding to a total of 133 (117 NEUTRC) articles that appeared in the months before and 455 (192 NEUTRC) articles that appeared on or after the warning month.

Figure 2 depicts the *cumulative* 1 month lagged time-series of news articles which INCC about the antidepressant warning or were NEUTRC, juxtaposed to the monthly percent of new cases of childhood depression diagnosed by a PCP (child_pdpdx_pct). The figure shows that that the time trend of the dependent variable child_pdpdx_pct was reasonably stationary with periodic peaks and valleys, though some end-of-series downward trending is evident after the warning, consistent with observations of previous research. Neutral coverage of antidepressant medication moved steadily upward with time for the entire period, but coverage that increased concern escalated more markedly about 6 months after the first major warning month (October 2003), but well before the actual black box warning was enacted in October of 2004. Additionally, at least five FDA announcements occurred after the October 2003 warning which likely contributed to the signal doctors and consumers received during that period even as the warning is modeled only as a binary event before or after October 2003.

Figure 2. Time-series for the antidepressant warning news versus child_pdpdx_pct.



'P' blue= child_pcpdx_pct (percent of new childhood depression cases diagnosed by a primary care physician)
'I' red= cumulative counts of articles that INCREASE concern about the warning, lagged 1 month.
'N' black= cumulative counts of articles that are NEUTRAL regarding concern about the warning, lagged 1 month
'J' green = 5 month moving sums of I
'M' purple= 5 month moving sums of N
The *left* Y-axis shows the percentage for the **'P'(blue plot).**
The *right* Y-axis shows the article counts for the I, N, J, and M plots.
The dashed line marks the October 2003 FDA warning month (The first full warning on the issue)
The numbered arrows identify other events surrounding the FDA warning of interest as follows:

1. June 2003: initial FDA safety warning based on data obtained by agency, and focused on paroxetine
2. December 2003: Eurpoean regulators issue warnings to their constituents, including "Dear Doctor" letters
3. February 2004: FDA public health advisory (still not "black box") expanded further
4. March 2004: FDA warning expanded to 10 antidepressants (still not "black box")
5. September 2004: FDA advisory committee recommends "black box" warning
6. October 2004: "Black box" warning implemented

yearmo= Year/Month (X-axis)

Table 4a gives the statistical results for all the general (i.e., new item counts not weighted by things like front page placement) INCC models, as well as for several sensitivity models. A conditional test for inclusion of the seasonal quarterly variables was non-significant (F=.96, p=.42) and thus seasonal adjusters were not included in any of the models presented. Model 1A *AIC* determined to be among the best fits, reveals that for each additional INCC item there was an average decline in child_pcpdx_pct of .025 after adjusting for a non-significant warning term, and a highly significant first order AR. The five month moving sum did not yield a significant result (Model 1B, p=.15), pointing to the cumulating sum as the more predictive variable. The NEUTRC coefficient estimate was not significant and its inclusion did not change the significance and general magnitude of the INCC estimate. Substituting the lagged DV variable for the AR1 term did reduce the INCC to marginal non-significance (p=.10). Because it was counter-intuitive that the warning term was sometimes positive, models 1F and 1G were run. They show that the warning term in isolation was in the expected direction, and that dropping the warning term (1G) gave results consistent with model 1A. Jointly these last two regressions are consistent with the expected co-linearity of the warning per se and warning news coverage variables.

Table 4b gives the results of the weighted INCC (e.g., front page count) regressions building upon model 1A. AR1 coefficients were all consistent with model 1A. All the weighted INCC coefficients were significant, but the front page effect was the strongest, demonstrating that for each additional lead or front page INCC news item the child_pcpdx_pct declined an average of .13 after adjusting for the non-significant warning effect, but with adjustment for the AR1. Other effects were only slightly larger than the general INCC effect even after multiplying the non-binary indicators (i.e., quality- range from 0 to 5, length- range from 1 to 6, valence- range from

1 to 3) by a factor to calculate the an intermediate item effect (i.e., multipliers of 2.5, 3.5, and 2, respectively).

Overall then, the results summarized in Tables 4a and 4b offer support for *HYPOTHESIS I* (INCC coverage decreases PCP diagnostic percentage), do not support *HYPOTHESIS II* (NEUTRC does not increase the DV), and provide limited support for *HYPOTHESIS III* based on the intensified INCC effects for front page, broadcast, and perhaps quality weighted INCC coverage. However, the news coverage effects are quite small, and not confirmed if the lagged DV is used as adjuster in lieu of the AR terms. Additionally, the results demonstrate no significant or consistent warning effect, though it is notable that the warning evolved over more than 12 months from a advisory to a "black box" warning that first targeted a single antidepressant an then added on essentially nearly all drugs in that therapeutic class.

Table 4a. Regression results predicting child_pcpdx_pct

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
1A	IV: *full* accumulation of INCC	.58, 226	.44 (.80)	-.025 (.013)*	-.54 (<.0001)*	Season excluded as joint F=.96 (p=.42)
1B	IV: *5 month* accumulation of INCC	.55, 230	-.59 (.75)	-.039 (.15)	-.60 (<.0001)	5 month INCC not significant
1C	Model 1A with NEUTRC term	.59, 228	-.47 (.82)	-.034 (.043)*	-.52 (.0002)*	NEUTRC is not significant
1D	Model 1A, but AR2	.61, 226	.21 (.89)	-.024 (.0054)*	-.67 (<.0001)*	AR2 is not significant
1E	Model 1A, but no AR and lagged DV	.58, 222	-.31 (.74)	-.010 (.10)	--	OLS, Lagged DV β=.55, p<.0001
1F	Warning only	.53, 230	-1.8 (.29)	--	-.66 (<.0001)*	Warning still not significant
1G	Model 1A, but drop warning	.58, 224	--	-.023 (.0026)*	-.54 (<.0001)*	Consistent with 1A

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
DV= dependent variable (outcome)
*significant effect per set *p*-value threshold
OLS= ordinary least squared regression use

Table 4b. Weighted-independent-variable regression results predicting child_pcpdx_pct

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
1A-F	Model 1A, but IV: front page counts	.59, 226	.44 (.79)	-.13 (.0094)*	-.54 (<.0001)*	> INCC general effect
1A-Q	Model 1A, but IV: quality unit counts	.58, 226	.67 (.70)	-.022 (.012)*	-.54 (<.0001)*	-.022x2.5[a]= .055 > INCC general effect
1A-L	Model 1A, but IV: length unit counts	.58. 226	.43 (.78)	-.0076 (.013)*	-.54 (<.0001)*	-.0076x3.5[b]=.027 ~ INCC general effect
1A-FD	Model 1A, but IV: FDA mention counts	.59, 226	.48 (.78)	-.029 (.013)*	-.54 (<.0001)*	~ INCC general effect
1A-V	Model 1A, but IV: valence unit counts	58. 226	.38 (.82)	-.017 (.014)*	-.55 (<.0001)*	-.017x2[c]=.034 ~ INCC general effects
1A-W	Model 1A, but IV: warning mention counts	.58, 227	.22 (.90)	-.042 (.018)*	-.54 (<.0001)*	~ INCC general effect

1A-B	Model 1A, but IV: broadcast counts	59, 226	.18 (.91)	-.062 (.0091)*	-.53 (<.0001)*	> INCC general effect

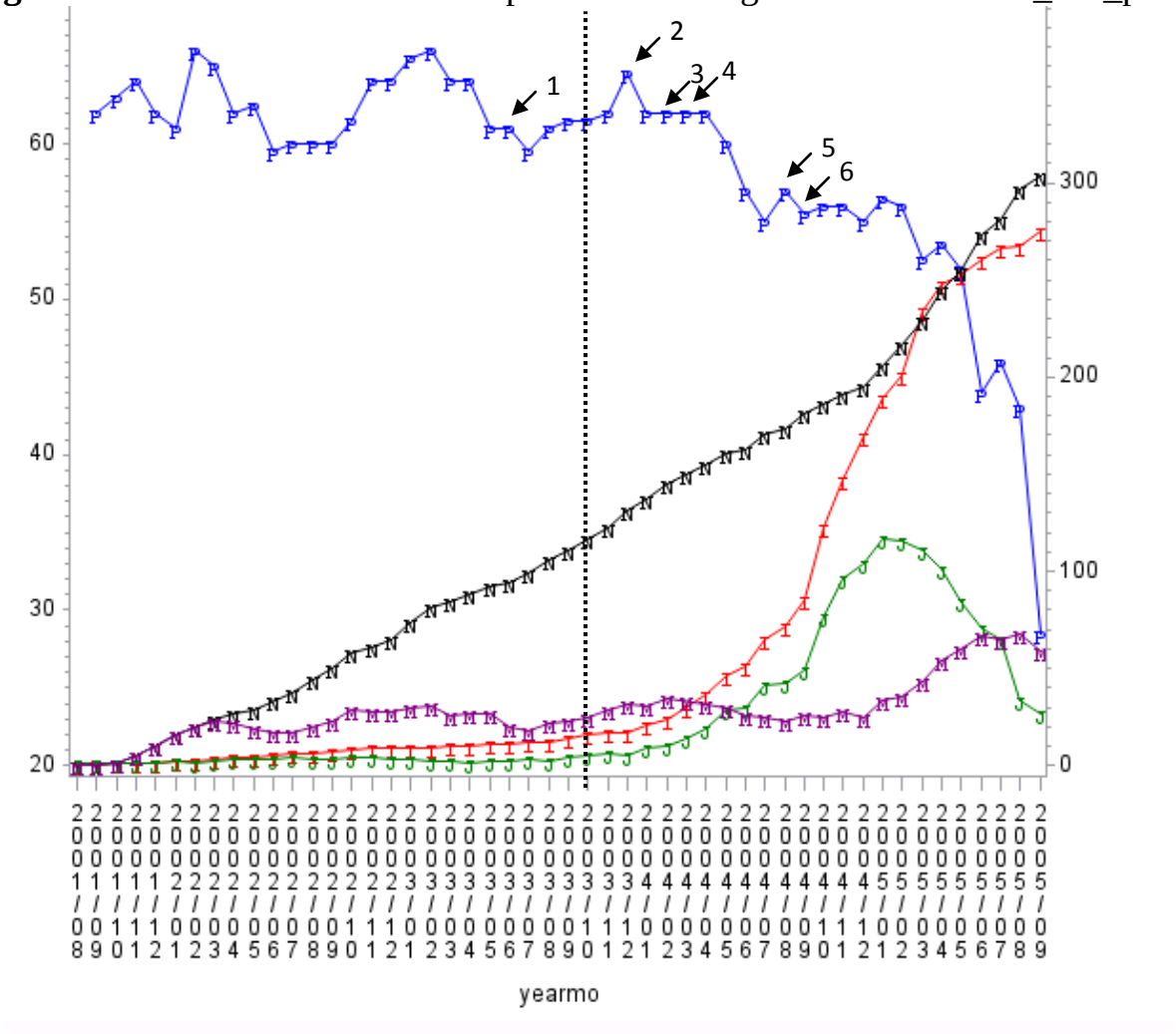
Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
*significant effect per set *p*-value threshold
[a] This multiplier of 2.5 is used to represent an intermediate quality item (range of quality rating is 0 to 5)
[b] This multiplier of 3.5 is used to represent an intermediate length item (range of length rating is 1 to 6)
[a] This multiplier of 2 is used to represent an intermediate valence item (range of valence rating is 1 to 3)

Child_ssri_pct (percent of new childhood cases filling an SSRI prescription)

Referring back to Table 3, it can be seen that the average proportion of new child depression cases filling an SSRI prescription within 30 days of diagnosis was 59% (standard deviation= 6.9%). This section aims to test the extent to which this percentage changed with differing news coverage surrounding the FDA antidepressant warning.

Figure 3 shows the time-series of the percent of new pediatric depression cases resulting in an SSRI prescription (Child_ssri_pct) juxtaposed to the news coverage variables regarding antidepressant use (same as those appearing in Figure 2). Here the DV is clearly trending downward after the warning, thereby supporting the inclusion of the warning interruption term in the regression model. Note that previous research from which the trend used here was obtained showed that SSRI prescription rates dropped markedly from expectation after the October 2003 FDA warning (Libby et al., 2007). Also note that though SSRIs are subset of all antidepressants, they are by far the dominant form of such pharmacological treatment, particularly in children. Further note that unlike the other antidepressant variables studied in this dissertation, this variable is not conditional upon PCP prescribing, instead it reflects a filled prescription written by any provider.

Figure 3. Time-series for the antidepressant warning news versus child_ssri_pct.



'P' blue= child_ssri_pct (percent of new childhood depression cases where an SSRI prescription was filled within 30 days of diagnosis)
'I' red= cumulative counts of articles that INCREASE concern about the warning, lagged 1 month.
'N' black= cumulative counts of articles that are NEUTRAL regarding concern about the warning. Lagged 1 month
'J' green = 5 month moving sums of I
'M' purple= 5 month moving sums of N
The *left* Y-axis shows the percentage for the 'P'(blue plot).
The *right* Y-axis shows the article counts for the I, N, J, and M plots.
The dashed line marks the October 2003 FDA warning month (The first full warning on the issue)
The numbered arrows identify other events surrounding the FDA warning of interest as follows:

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4. March 2004: FDA warnng expanded to 10 antidepressants (still not "black box")
5. September 2004: FDA advisory committee recommends "black box" warning
6. October 2004: "Black box" warning implemented

yearmo= Year/Month (X-axis)

Table 5a gives the statistical results for all the general (i.e., news item counts not weighted by factors like front page placement) INCC models, as well as for several sensitivity models. A conditional test for inclusion of the seasonal quarterly variables was non-significant (F=1.5, p=.23) and thus seasonal adjusters were not included in any of the models presented. Model 2A was determined by *AIC* to be among the best fitting models (excluding the lagged DV model), and reveals that for each additional INCC item there was an average decline in child_ssri_pct of .084 after adjusting for a non-significant warning term, and a highly significant first order AR. The five month moving sum did not yield a significant result (Model 2B, p=.19). The NEUTRC coefficient estimate was not significant, but its addition did not change the INCC coefficient to non-significance (Model C, p=.18). The second order AR term was not significant. Substituting the lagged DV variable for the AR1 term yielded a highly significant result for that lagged DV (β=.98, p<.0001), and it reduced the INCC effect to non-significance (p=.14). This latter result corresponds to a model that is dominated by a single factor thereby leaving little variance to consider against other variables. Because the positive warning term is non-significant, Model 2F was run to test its isolated effect. The warning coefficient remained non-significant and slightly positive, suggesting the AR1 term accounted for the decline that is otherwise evident in the raw time series (see Figure 3). Model 2G confirms the INCC coefficient estimate observed per Model 1A in the absence of the warning term. Note that though the binary warning term is non-significant, several of the later warning events do occur at time points which suggest their effects may contribute both to the mounting news signal and the declining SSRI use.

Table 5b gives the results of the weighted INCC (e.g., front page count) regressions building upon model 2A. AR1 coefficients were all consistent with Model 2A. All the weighted INCC coefficients were significant, but the front page effect was the strongest demonstrating that for

each additional lead or front page INCC news item the child_ssri_pct declined an average of .37 after adjusting for the non-significant warning effect, but with adjustment for the AR1. Other weighted effects which appear more intensified than the general INCC effect, but less so than the front page effect, were those for warning mention counts broadcast counts, and article quality, in that order.

Overall then, the results summarized in Tables 5a and 5b offer support for *HYPOTHESIS I* (INCC coverage decreases SSRI prescriptions), do not support *HYPOTHESIS II* (NEUTRC does not increase the DV), and further support *HYPOTHESIS III* based on the intensified INCC effects for front page, broadcast, FDA mention and quality weighted INCC coverage. However, the news coverage effects are small, and not confirmed if the lagged DV is used as an adjuster in lieu of the AR terms, or if the NEUTRC variable is added to the regression. Additionally, as was the case with the child_pcpdx_pct dependent variable, the results demonstrate no significant or consistent warning effect, though after October 2003 other European and FDA communications occur which likely contribute to news signal and SSRI declines.

Table 5a. Regression results predicting child_ssri_pct

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
2A	IV: *full* accumulation of INCC	.83, 248	.91 (.74)	-.084 (.0010)*	-.77 (<.0001)*	Season excluded as joint F=1.5 (p=.23)
2B	IV: *5 month* accumulation of INCC	.82, 255	.07 (.98)	.072 (.19)	-.98 (<.0001)*	5 month INCC not significant
2C	Model 2A with NEUTRC term	.83, 248	2.4 (.43)	-.048 (.18)	-.79 (<.0001)*	NEUTRC is not significant, and INCC became not significant
2D	Model 2A, but AR2	.84, 249	.77 (.78)	-.084 (.0017)*	-.93 (.0001)*	AR2 is not significant
2E	Model 2A, but no AR and lagged DV	.85, 237	.44 (.69)	-.015 (.14)	--	OLS, Lagged DV β=.98, p<.0001, INCC became not significant
2F	Warning only	.81, 255	.10 (.97)	--	-.98(<.0001)*	Warning not significant or negative with AR1
2G	Model 2A, but no warning	.83, 246	--	-.081 (.0009)*	-.78 (<.0001)*	Consistent with 2A

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
DV= dependent variable (outcome)
*significant effect per set p-value threshold
OLS= ordinary least squared regression use

Table 5b. Weighted-independent-variable regression results predicting child_ssri_pct

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
2A-F	Model 2A, but IV: front page counts	.81, 254	-.27 (.93)	-.37 (.0034)*	-.80 (<.0001)*	> INCC general effect
2A-Q	Model 2A, but IV: quality unit counts	.82, 251	.60 (.83)	-.067 (.0030)*	-.80 (<.0001)*	-.067x2.5[a]= -.17 > INCC general effect
2A-L	Model 2A, but IV: length unit counts	.83, 249	.81 (.77)	-.025 (.0011)*	-.77 (<.0001)*	-.025x3.5[b]=.088 ~ INCC general effect
2A-FD	Model 2A, but IV: FDA mention counts	.83, 250	.62 (.82)	-.093 (.0014)*	-.77 (<.0001)*	~ INCC general effect
2A-V	Model 2A, but IV: valence unit counts	.84, 247	.88 (.74)	-.057 (.0005)*	-.76 (<.0001)*	-.057x2[c]= .11 ~ INCC general effects

2A-W	Model 2A, but IV: warning mention counts	.83, 250	.50 (.86)	-.15 (.0014)*	-.79 (<.0001)*	> INCC general effect
2A-B	Model 2A, but IV: broadcast counts	.84, 247	.33 (.90)	-.21 (.0002)*	-.75 (<.0001)*	> INCC general effect

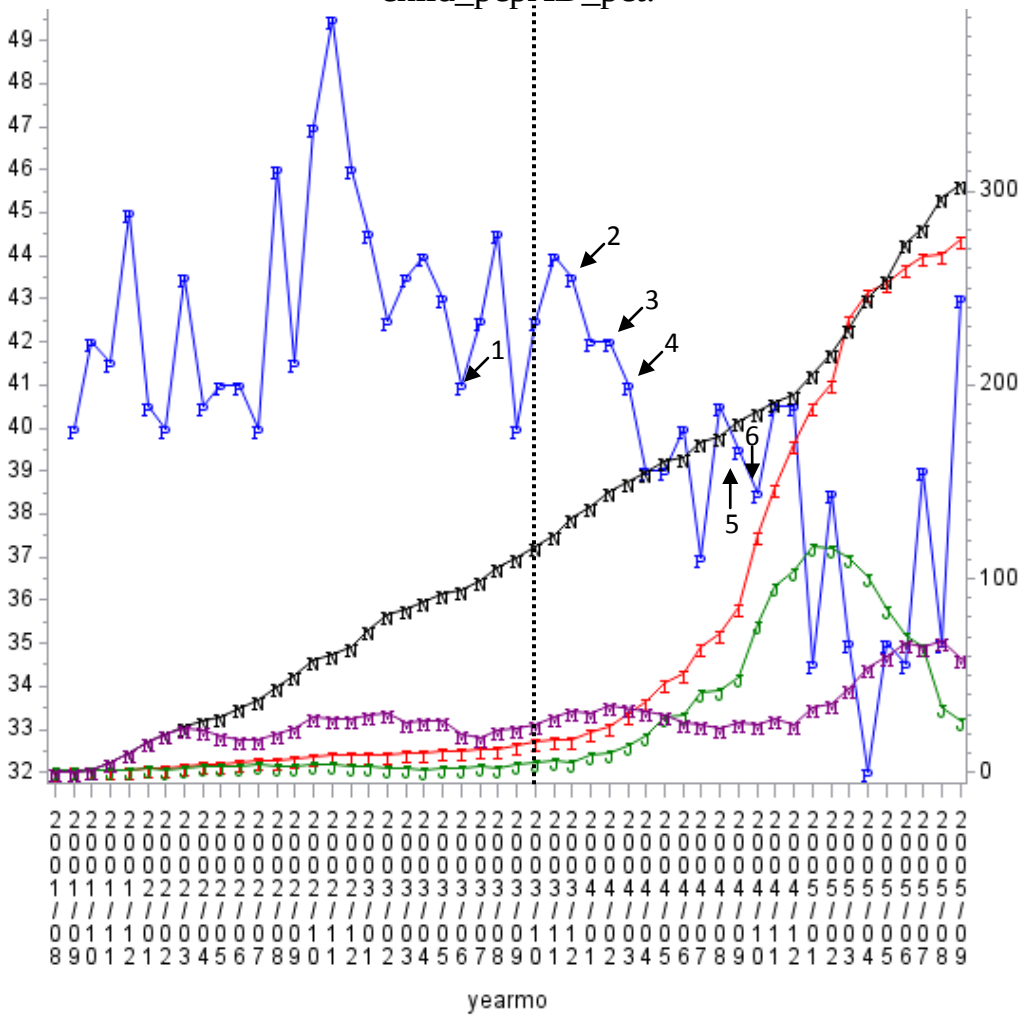
Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
*significant effect per set *p*-value threshold
[a] This multiplier of 2.5 is used to represent an intermediate quality item (range of quality rating is 0 to 5)
[b] This multiplier of 3.5 is used to represent an intermediate length item (range of lenght rating is 1 to 6)
[c] This multiplier of 2 is used to represent an intermediate valence item (range of valence rating is 1 to 3)

Child_pcpAD_pct (percent of new childhood cases filling an antidepressant prescription written by a PCP)

Referring back to Table 3, it can be seen that the average proportion of new child depression cases which resulted in a PCP written and filled antidepressant prescription within 30 days of diagnosis was 41% (standard deviation= 3.5%). This section aims to test the extent to which this percentage changed with differing news coverage surrounding the FDA antidepressant warning.

Figure 4 shows the time-series of the percent on new pediatric depression cases resulting in any filled antidepressant prescription made by a PCP (child_pcpAD_pct). As was the case with earlier time-series plots, this graph includes an overlay of the INCC and NEUTRC news coverage article counts. The trend for child_pcpAD_pct appears somewhat stationary before the warning, but does decline after the warning, thus supporting the importance of including a warning term in the model. It is also noticeable that several European or FDA warnings happen after the initial October 2003 warning, and these warnings may contribute to the on-going decline in the DV observed.

Figure 4. Time-series for the antidepressant warning news versus child_pcpAD_pct.



'P' blue= child_pcpAD_pct (percent of new childhood depression cases diagnosed by a PCP where any AD prescription was filled within 30 days of diagnosis)
'I' red= cumulative counts of articles that INCREASE concern about the warning, lagged 1 month.
'N' black= cumulative counts of articles that are NEUTRAL regarding concern about the warning. Lagged 1 month
'J' green = 5 month moving sums of I
'M' purple= 5 month moving sums of N
The *left* Y-axis shows the percentage for the 'P'(blue plot).
The *right* Y-axis shows the article counts for the I, N, J, and M plots.
The dashed line marks the October 2003 FDA warning month (The first full warning on the issue)
The numbered arrows identify other events surrounding the FDA warning of interest as follows:

1. June 2003: initial FDA safety warning based on data obtained by agency, and focused on paroxetine
2. December 2003: Eurpoean regulators issue warnings to their constituents, including "Dear Doctor" letters
3. February 2004: FDA public health advisory (still not "black box") expanded further
4. March 2004: FDA warning expanded to 10 antidepressants (still not "black box")
5. September 2004: FDA advisory committee recommends "black box" warning
6. October 2004: "Black box" warning implemented

yearmo= Year/Month (X-axis)

Tables 6a gives the statistical results for the general (i.e., news item counts not weighted by things like front page placement) INCC models predicting child_pcpAD_pct. A conditional test for inclusion of the seasonal quarterly variables was non-significant (F=1.4, p=.26) and thus seasonal adjusters were not included in any of the models presented. All the tabulated models demonstrated consistency in non-significant warning and the AR coefficients, and in a significant and negative INCC coefficient which ranging from -.020 to -.054. In contrast to the outcomes reviewed thus far, the child_pcpAD_pct regressions demonstrated larger and more significant effects pertaining to the short-duration (five month) accumulation of the news signal (Model 3B) rather than the full accumulation form. The NEUTRC concern effect was not significant (Model 3C). The best model (based on the lowest *AIC*) was that which included the lagged DV in lieu of the AR term (Model 3D). That model showed that for each additional INCC news item (per five month accumulations) the child_pcpAD_pct declined an average of .041 (p= .0071) after adjusting for the warning and lagged DV, the latter of which was nearly significant (β= .27, p< .054). Because Model 3D presented as the best fit of the regressions, and because it was also consistent with the other models in Table 6a, it was used as the base model testing the weighted INCC variables presented in Table 6b.

Table 6b gives the results of the weighted INCC (e.g., front page count) regressions based directly on the regression form used in Model 3D. All seven of the models demonstrate fairly consistent and non-significant warning coefficients, and lagged DV coefficient effects. The five month INCC news variable was also significant and negative across all seven weighted forms of that variable, but only the front page and the broadcast counts presented as higher in magnitude than the general INCC effect. Specifically, and for example, Model 3D-F shows that for each additional front page or lead INCC news item, there was a decline in child_pcpAD_pct

averaging .14 (p= .018) after adjusting for the warning and lagged DV effects. This decline is more than 3 times that observed in Model 3D in Table 6 (the general effect).

Overall then, the results summarized in Tables 6a and 6b offer support for *HYPOTHESIS I* (INCC coverage decreases the percentage of filled antidepressant prescription which were written by PCPs), do not support *HYPOTHESIS II* (NEUTRC does not increase the DV), and further provide limited support for *HYPOTHESIS III* based on the intensified INCC effects for front page and broadcast. These findings are significant and appear strongest in models that include five month accumulations of news as the key explanatory variable and the lagged DV as an additional "right-hand" side variable.

Table 6a. Regression results predicting child_pcpAD_pct

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
3A	IV: *full* accumulation of INCC	.51, 233	-1.2 (.32)	-.020 (.0054)*	-.21 (.19)	Season excluded as joint F=1.4 (p=.26)
3B	IV: *5 month* accumulation of INCC	.52, 232	-1.0 (.42)	-.054 (.0030)*	-.23 (.12)	Stronger fit than 3A
3C	Model 3B with NEUTRC term	.53, 233	-.55 (.69)	-.052 (.0041)*	-.23 (.13)	NEUTRC is not significant
3D	Model 3B, but no AR and lagged DV	.55, 225	-.86 (.55)	-.041 (.0071)*	--	OLS, Lagged DV β=.27, p< .054, lowest *AIC*

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
DV= dependent variable (outcome)
*significant effect per set p-value threshold
OLS= ordinary least squared regression use

Table 6b. Weighted-independent-variable regression results predicting child_pcpAD_pct

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	Lagged DV *β (p)*	Notes
3D-F	Model 3D, but IV: front page counts	.53, 227	-1.3 (.19)	-.14 (.018)*	.35 (.012)*	> INCC general effect
3D-Q	Model 3D, but IV: quality unit counts	.51, 230	-1.2 (.29)	-.023 (.070)*	.37 (.0079)*	-.023x2.5[a]= -.058 ~ INCC general effect
3D-L	Model 3D, but IV: length unit counts	.55, 225	-.88 (.38)	-.013 (.0062)*	.27 (.0055)*	-.013x3.5[b]= -.046 ~ INCC general effect
3D-FD	Model 3D, but IV: FDA mention counts	.54, 226	-.92 (.37)	-.043 (.011)*	.30 (.030)*	~ INCC general effect
3D-V	Model 3D, but IV: valence unit counts	.56, 224	-.88 (.37)	-.030 (.0044)*	.24 (.092)*	-.030x2[c]= .060 ~ INCC general effects
3D-W	Model 3D, but IV: warning mention counts	.51, 229	-1.2 (.24)	-.048 (.054)*	.35 (.013)*	~ INCC general effects
3D-B	Model 3D, but IV: broadcast counts	.58, 222	-1.1 (.25)	-.10 (.0014)*	.20 (.17)	> INCC general effect

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month

AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
*significant effect per set *p*-value threshold
[a] This multiplier of 2.5 is used to represent an intermediate quality item (range of quality rating is 0 to 5)
[b] This multiplier of 3.5 is used to represent an intermediate length item (range of length rating is 1 to 6)
[c] This multiplier of 2 is used to represent an intermediate valence item (range of valence rating is 1 to 3)

Adult_pcpAD_pct ("spillover" effects to adults)

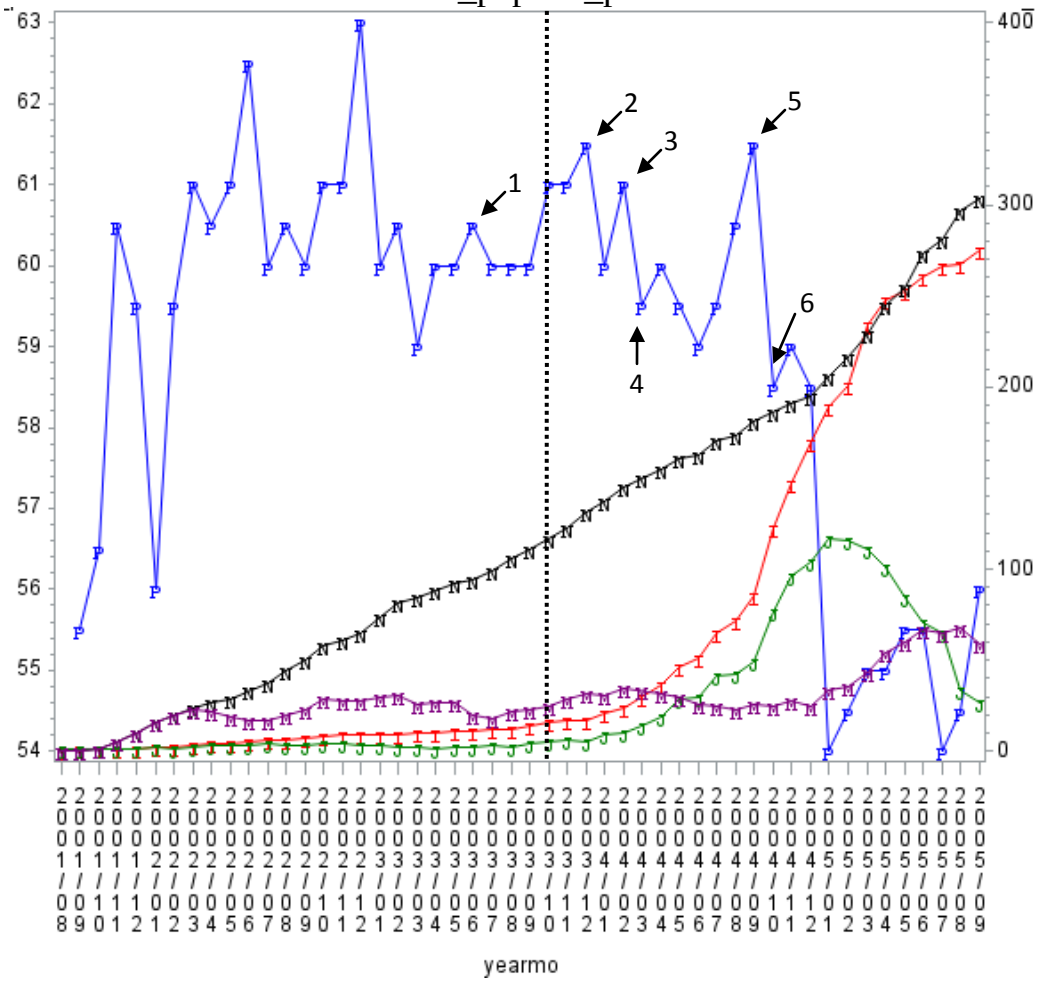
Referring back to Table 3 it can be seen that the average proportion of new adult depression cases which resulted in a PCP written filled antidepressant prescription within 30 days of diagnosis was 59% (standard deviation= 2.4%). This section aims to test the extent to which this percentage changed with differing news coverage surrounding the FDA antidepressant warning.

As described in the background section of this work, sometimes FDA communications directed at one group "spillover" and impact another group, and this occurred with the antidepressant warning which originally was directed at children and adolescents, but which also curtailed use of these drugs by adults (Valuck et al., 2007). Accordingly, this section reports the results which tested whether the news-to-adult_pcpAD_pct effect described above "spillover" to adults. Stated another way, these results answer the following question: For news coverage that influenced PCP pediatric use of antidepressants surrounding the FDA warning, did that same coverage similarly impact PCP adult use of these drugs? The adult_pcpAD_pct outcome variable was specifically selected for this "spillover" analysis because its analogous child variable demonstrated the most robust significant results of the three outcomes tested (i.e., child_pcp_pct, child_ssri_pct, child_pcpAD_pct), including INCC news significance with the inclusion of a lagged dependent variable.

Figure 5 shows the times-series plots for the adult_pcpAD_pct and for the news coverage surrounding the antidepressant warning of October 2003. Note that the time-series for the adult_pcpAD_pct variable is reasonably stationary though there is a noticeable, slight decline near the end. The time course of adult_pcpAD_pct is similar to that for the child_pcpAD_pct (Figure 4), but the adult series is a bit smoother and always higher than the child series. Based on

that comparison of alone, the correlation to INCC should be similar for the adult and child outcomes. The next section tests that expectation, but only for a limited set of variables tested for children: the general news effect (to consider various forms of the model), the front page effect (because it had the largest β coefficient of the child focused regressions), and the quality effect (to look at this relatively complex variable as well). As seen with the other antidepressant time-series, it is noticeable that several European of FDA warning activities come after the first warning and it is possible that they, per se, yield the reductions in adult diagnoses (presumed related to drug use) which this research generally attributes to news coverage of those and related events.

Figure 5. Time-series for the antidepressant warning news versus adult_pcpAD_pct.



'P' blue= adult_pcpAD_pct (percent of new adult depression cases diagnosed by a PCP where any AD prescription was filled within 30 days of diagnosis)
'I' red= cumulative counts of articles that INCREASE concern about the warning, lagged 1 month.
'N' black= cumulative counts of articles that are NEUTRAL regarding concern about the warning. Lagged 1 month
'J' green = 5 month moving sums of I
'M' purple= 5 month moving sums of N
The *left* Y-axis shows the percentage for the 'P '(blue plot).
The *right* Y-axis shows the article counts for the I, N J, and M plots.
The dashed line marks the October 2003 FDA warning month.
The numbered arrows identify other events surrounding the FDA warning of interest as follows:

1. June 2003: initial FDA safety warning based on data obtained by agency, and focused on paroxetine
2. December 2003: Eurpoean regulators issue warnings to their constituents, including "Dear Doctor" letters
3. February 2004: FDA public health advisory (still not "black box") expanded further
4. March 2004: FDA warning expanded to 10 antidepressants (still not "black box")
5. September 2004: FDA advisory committee recommends "black box" warning
6. October 2004: "Black box" warning implemented

yearmo= Year/Month (X-axis)

Tables 7a and 7b demonstrate results which are mostly analogous to those seen in Tables 6a and 6b, thereby supporting the expectation that news mediated warning responses "spillover" to adults. Specifically, and for example, the last row of Table 7a shows that for each additional INCC news item (five months sums), the adult_pcpAD_pct declined by .025 (p=.0036), after adjusting for the warning and for a lag of the dependent variable. The five month sum (Model 4B) was the basis for most models in Table 7a because it is consistent with Model 4A and parallel to the analyses done for the child_pcpAD_pct measure. Unlike for the child analysis, however, for adults the full accumulation is actually a superior fit (*AIC*=176 versus 181), suggesting that the observed effects may be more persistent in adults.

Table 7a further shows that a negative and significant INCC coefficient is evident across the different forms of the regression presented, and Table 7b shows that front page coverage markedly intensifies the INCC effect, whereas the quality rating does not- just as was the case for the child measure. Significant AR1 terms are evident in the adult_pcpAD_pct which were not observed in the child_pcpAD_pct. This inconsistency perhaps indicates that status quo prescription fill rates are generally more stable in adults than in children.

Overall then, the results summarized for adult_pcpAD_pct support *HYPOTHESIS I* (that INCC news yields decreased antidepressant use), refute *HYPOTHESIS II* (that NEUTRC news yields opposite direction effects), and support *HYPOTHESIS III* (that details about the INCC news intensifies the *HYPOTHESIS I* observed effect). Additionally, these results are consistent with a news coverage mediated "spillover" effect from children to adults, i.e., consistent with *HYPOTHESIS IA.*

Table 7a. Regression results predicting adult_pcpAD_pct

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
4A	IV: *full* accumulation of INCC	.68, 176	.99 (.27)	-.023 (< .0001)*	-.43 (.0029)*	Season excluded as joint *F*=.04 (*p*=.99); AR significant contrasts child measure (Model 3A)
4B	IV: *5 month* accumulation of INCC	.65, 181	.23 (.85)	-.043 (.026)*	-.69 (< .0001)*	Selected for models below to be consistent with Table 6a
4C	Model 4B with NEUTRC term	.66, 182	.65 (.61)	-.042 (.022)*	-.65 (< .0001)*	NEUTRC is not significant
4D	Model 4B, but AR2	.66, 183	.25 (.84)	-.043 (.041)*	-.65 (.0001)*	AR2 is not significant
4E	Model 4B, but no AR, and with a lagged DV	.70, 167	.10 (.85)	-.025 (.0036)*	--	OLS; Lagged DV *β*=.57, *p*< .0001, contrasts child Model 3D slightly; lowest *AIC*
4F	Warning only	.61, 184	-.86 (.50)	--	-.77 (< .0001)*	
4G	Model 4B, but no warning	.65, 179	--	-.042 (.015)*	-.69 (< .0001)*	Consistent with 4B

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
DV= dependent variable (outcome)
*significant effect per set *p*-value threshold
OLS= ordinary least squared regression use

Table 7b. Weighted-independent-variable regression results predicting adult_pcpAD_pct

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	Lagged DV *β (p)*	Notes
4E-F	Model 4E, but IV: front page counts	.71, 167	-.19 (.70)	-.096 (.0040)*	.60 (< .0001)*	> INCC general effect
4E-Q	Model 4E, but IV: quality unit counts	.68, 171	-.081 (.89)	-.016 (.024)*	.66 (< .0001)*	-.016x2.5[a]= -.040 ~INCC general effect

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
IV= Key independent variable, INCC
*significant effect per set *p*-value threshold
[a] This multiplier of 2.5 is used to represent an intermediate quality item (range of quality rating is 0 to 5)
[b] This multiplier of 3.5 is used to represent an intermediate length item (range of lenght rating is 1 to 6)
[c] This multiplier of 2 is used to represent an intermediate valence item (range of valence rating is 1 to 3)

Montelukast (asthma/allergy controller medication) warning

In August of 2009 the FDA posted a warning to health professionals that leukotriene inhibitor use carry increased risk for neuropsychiatric symptoms including depression, restlessness, tremor, and suicide. The below results pertain to news coverage regarding asthma medications generally surrounding that FDA communication, with the dependent variable being montelukast filled prescription counts per 1,000 Maryland Medicaid program enrollees during that same period (see methods).

Table 8 gives summary statistics for the raw counts of filled montelukast prescriptions, and for the counts of news coverage. The top entry in that table shows that across the 50 months studied there was an average of 6884.4 filled montelukast prescriptions in Maryland Medicaid (standard deviation= 890.7 prescriptions). This section aims to test the extent to which this amount (adjusted for the monthly Medicaid population) changed with differing news coverage surrounding the FDA montelukast warning. Additionally, it can be seen that INCC news coverage was relatively low each month, but with a high coefficient of variation (mean=.41 items, standard deviation= 1.1 items), while NEUTRC coverage was substantially higher (mean=1.7, standard deviation=1.6). The aim of this section is to determine the extent to which the various news coverage appears to correlate with changes in the outcome variable.

Figure 6 shows the time-series of the number of filled montelukast prescriptions per 1,000 Maryland Medicaid enrollees and of the news coverage associated with asthma medication more generally during the period. The figure shows that the montelukast time-series is reasonably stationary, though slightly downward sloping, and that it ranges from just over 10 to just under 7 prescriptions per 1,000 Medicaid participants. INCC article counts reached just over 20 and

NEUTRC sums reached just over 80 at the close of the 50 month study period. Comparing Table 8 to Table 3 reveals that news coverage surrounding the antidepressant suicidality warning was far greater than analogous news coverage surrounding the montelukast advisory. For example, per Table 8 the mean number of INCC articles in a given month for the asthma drug warning was .41, while per Table 3 the mean number of analogous articles for the antidepressant warning was 5.6, more than 10 times higher. Moreover, whereas the 50 months of study yielded 114 asthma related news items in total, that same time period yielded 588 news items pertaining to antidepressants.

Figure 6 also shows that that at least five other FDA actions occurred during the time-series study, beyond the August 2009 warning that was explicitly modeled in the regression analysis. These other FDA actions pertained to adverse events that were often relatively mild (e.g., nose bleeds, bruising) or inchoate, while the August 2009 warning which, though it never reached the level of a "black box" warning, contained the most extensive list of neuropsychiatric concerns proffered by the FDA. Finally and still, it can be said that this particular FDA warning was the least serious of the four studied for this dissertation research in terms of the likelihood of the concern, and also in terms of the way the FDA framed and disseminated it.

Table 8. Summary statistics for the asthma/allergy drug warning

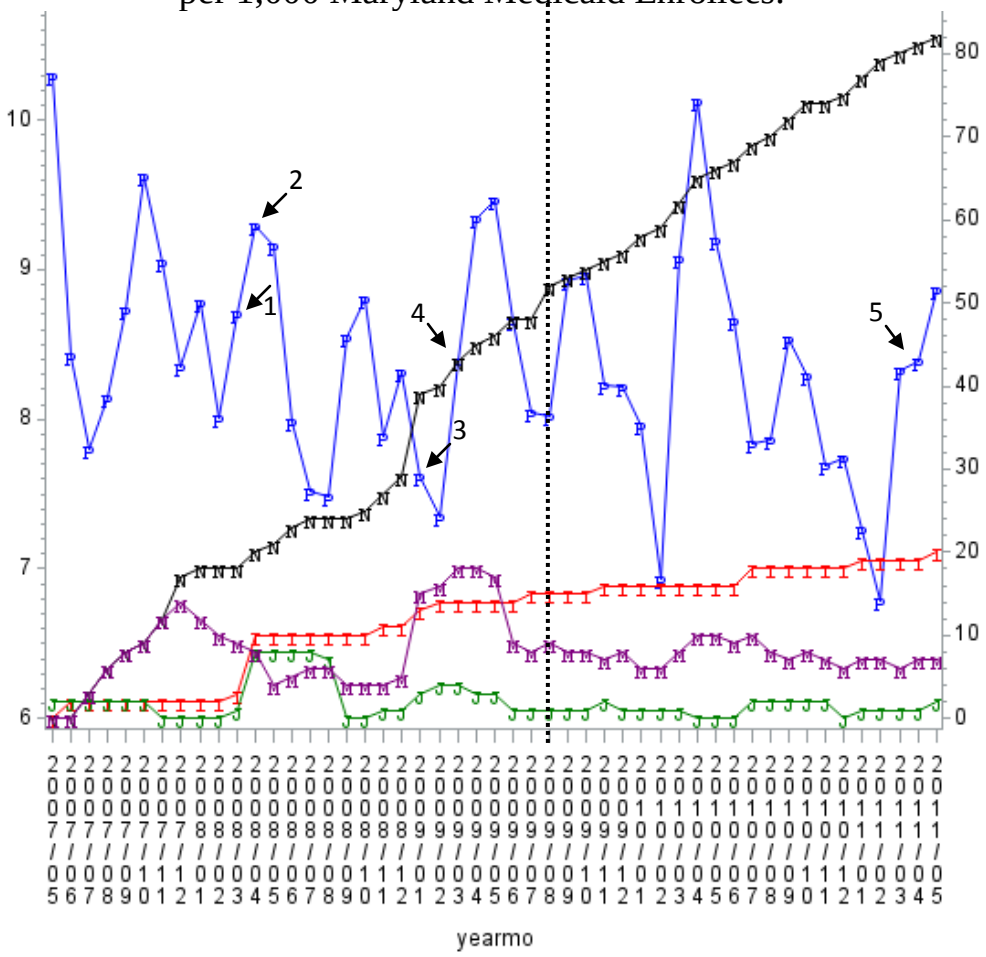
Variable	By month			
	Mean	St. dev.	Min	Max
OUTCOMES				
montelukast_rx_cnt (count)	6848.4	890.7	5461.0	9015.0
PREDICTORS				
INCC (count)	0.41	1.1	0.0	7.0
INCC_FRONT (count)	0.020	0.14	0.0	1.0
INCC_QUAL (cumulative score)	0.48	2.1	0.0	15
INCC_LENGTH (cumulative score)	1.1	2.7	0.0	14
INCC_FDA_MENTION (count)	0.37	1.1	0.0	7.0
INCC_VAL (cumulative score)	0.51	1.3	0.0	7.0
INCC_FDA_WARN (count)	0.29	1.1	0.0	7.0
INCC_BROADCAST (count)	0.12	0.73	0.0	5.0
NEUTRC (count)	1.7	1.6	0.0	10
NEUTRC_FRONT (count)	0.22	0.51	0.0	2.0
NEUTRC_QUAL (cumulative score)	0.32	0.56	0.0	3.0
NEUTRC_LENGTH (cumulative score)	6.2	5.3	0.0	26
NEUTRC_FDA_MENTION (count)	0.71	1.2	0.0	7.0
NEUTRC_VAL (cumulative score)	2.8	2.8	0.0	17
NEUTRC_FDA_WARN (count)	0.020	0.14	0.0	1.0
NEUTRC_BROADCAST (count)	0.12	0.36	0.0	2.0

rx_cnt= fill prescription count
INCC= article increases concern about the warning
NEUTRC= article is neutral regarding concern (or decreases concern) about the warning

Outcomes source: Maryland Medicaid pharmacy claims derived by author with permissions from Maryland's Department of Health and Mental Hygiene.

Predictor source: Author's analysis of 114 news items from 27 months before to 23 months after the warning, corresponding to a total of 67 (52 NEUTRC) articles that appeared in the months before and 47 (38 NEUTRC) articles that appeared on or after the warning month.

Figure 6. Time-series for the Montelukast warning news versus that drug's count per 1,000 Maryland Medicaid Enrollees.



'P' blue= Montelukast filled prescription counts per 1,000 Maryland Medicaid enrollees.
'I' red= cumulative counts of articles that INCREASE concern about the warning, lagged 1 month.
'N' black= cumulative counts of articles that are NEUTRAL regarding concern about the warning. Lagged 1 month
'J' green = 5 month moving sums of I
'M' purple= 5 month moving sums of N
The *left* Y-axis shows the percentage for the 'P '(blue plot).
The *right* Y-axis shows the article counts for the I, N J, and M plots.
The dashed line marks the August 2009 FDA warning month ("black box" status never reached).
The numbered arrows identify other events surrounding the FDA warning of interest as follows:

1. March 2008: FDA warning section of the insert was modified to include "suicidal thinking and behavior" as a rare, but possible side-effect (note that this and other similar concerns never rose to the level of "black box" warning).
2. April 2008: FDA warning, feelings of "anxiousness" added to concern.
3. January 2009: FDA warning, nose bleeds added to concern
4. March 2009: FDA warning, safety review announced
5. April 2011: FDA warning, "possible" side-effect of bruising or other platelet malfunction added to label.

yearmo= Year/Month (X-axis)

Tables 9a and 9b show the regression results for the montelukast time-series analyses. Table 9a gives the statistical results for all the general (i.e., news item counts not weighted by things like front page placement) INCC models, as well as for several sensitivity models. A conditional test for inclusion of the seasonal quarterly variables was significant (F=13, p< .0001) and thus seasonal adjusters were included in the models presented. Comparing the *AIC* and INCC *p*-values between Models 5A and 5B suggests that the accumulation of INCC news (5A) is slightly superior, though both show significant and negative effects of INCC news on filled montelukast prescriptions. None of the models demonstrated a significant AR (p>.15), but the lagged DV was significant per Model 5D (β=.30, p<.0023). All the models revealed a fairly consistent estimate for the INCC effect, and 3 of 4 (except with the inclusion of the non-significant NEUTRC) were significant (p<.064). Per Model 5D, the INCC estimate indicates that for each additional news item that increased concern about the warning, the counts of filled montelukast prescriptions dropped by .03 per 1,000 (i.e., 3 per 100,000) after adjusting for the non-significant warning term and the highly significant lagged DV term.

Because the positive warning coefficients are counter-intuitive, Models 5E and 5F were constructed to test the impact of the warning absent news coverage and vice-versa. These models show that the warning term was negative, but non-significant in isolation, and that the INCC term remained consistent with Model 1A, findings that are also consistent with co-linearity between these two parameters and with the warning term demonstrating considerable instability as a predictor.

Table 9b gives the results of the weighted INCC (e.g., front page count) regressions building upon Model 5D. Lagged DV coefficients were all consistent with each other and only slightly different than Model 5D. Four of seven weighted INCC coefficients were significant, but they

generally did not exceed the general INCC effect in magnitude (Model 5D coefficient), with the possible exception of the FDA warning mention which seemed slightly more influential (β= -.044, p= .045) than the general effect of -.034. Note the article counts for this warning were quite limited, so much so that there was only one front page article and thus the regression for that indicator could not be run.

Overall then, the results summarized in Tables 4a and 4b offer support for *HYPOTHESIS I* (INCC coverage yields decreased montelukast prescription fills in Maryland Medicaid), did not support *HYPOTHESIS II* (NEUTRC did not yield increases in the DV), and provide limited support for *HYPOTHESIS III* based on the intensified INCC effects for INCC coverage which actually mentions the FDA warning.

Table 9a. Regression results predicting montelukast filled prescription counts per 1,000 Maryland Medicaid enrollees

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
5A	IV: *full* accumulation of INCC	.60, 72	.19 (.48)	-.047 (.041)*	-.21 (.20)	Seasons significant (F=13, p< .0001) and thus included in all models
5B	IV: *5 month* accumulation of INCC	.59, 73	-.33 (.09)*	-.078 (.064)*	-.22 (.19)	Warning not consistent with 5A. 5A superior because of *AIC* and INC *p*.
5C	Model 5A with NEUTRC term	.60, 74	.21 (.57)	-.043 (.36)	-.22 (.20)	NEUTRC is not significant and also makes INCC not signficant
5D	Model 5A, but no AR and lagged DV	.63, 63	.12 (.54)	-.033 (.064)*	--	Lagged DV β=.30, p<.0023; lowest *AIC*
5E	Warning only	.56, 74	-.22 (.29)	--	-.31 (.058)	
5F	Model 4A, but no warning	.63, 73	--	-.043 (.052)*	-23 (.15)	Consistent with 5A

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
DV= dependent variable (outcome)
*significant effect per set *p*-value threshold
OLS= ordinary least squared regression use

Table 9b. Weighted-independent-variable regression results predicting montelukast filled prescription counts per 1,000 Maryland Medicaid enrollees

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	Lagged DV *β (p)*	Notes
5D-F	Model 5D, but IV: front page counts	n/a	n/a	n/a	n/a	Just 1 front page article in series, so regression not valid
5D-Q	Model 5D, but IV: quality unit counts	.66, 64	.031 (.86)	-.017 (.12)	.30 (.0018)*	-.017x2.5[a]= -.042 ~INCC general effect
5D-L	Model 5D, but IV: length unit counts	.67, 62	.15 (.47)	-.015 (.051)*	.29 (.0024)*	-.015x3.5[b]= -.052 ~INCC general effect
5D-FD	Model 5D, but IV: FDA mention counts	.67, 63	.090 (.63)	-.035 (.066)*	.29 (.0024)*	~ INCC general effect
5D-V	Model 5D, but IV: valence unit counts	.67, 62	.14 (.48)	-.028 (.052)*	.29 (.0025)*	-.028x2.0[c]= -.056 ~INCC general effect
5D-W	Model 5D, but IV: warning mention counts	.67, 62	.15 (.46)	-.044 (.045)*	.29 (.0028)*	> INCC general effect

5D-B	Model 5D, but IV: broadcast counts	.65, 64	-.048 (.76)	-.045 (.18)	.31 (.0013)*	INCC not significant

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
IV= Key independent variable, INCC
*significant effect per set *p*-value threshold
[a] This multiplier of 2.5 is used to represent an intermediate quality item (range of quality rating is 0 to 5)
[b] This multiplier of 3.5 is used to represent an intermediate length item (range of length rating is 1 to 6)
[c] This multiplier of 2 is used to represent an intermediate valence item (range of valence rating is 1 to 3)

Varenicline (smoking cessation medication) warning

In July of 2009, the FDA issued a "black box" warning that smoking cessation medications including varenicline (brand: Chantix) increased one's risk for negative psychological symptoms including excessive aggression, anxiety and suicide. The results below pertain to news coverage regarding smoking cessation medications which surrounded that FDA warning, with the dependent variable being varenicline filled prescription counts per 1,000 adult Maryland Medicaid program enrollees.

Table 10 gives the raw counts of varenicline prescriptions among Maryland Medicaid enrollees and further provides quantification regarding the news coverage surrounding the warning study period. The detailed "predictor" tallies stratify the news coverage into those articles that INCC or are NEUTRC and further stratify them into the detailed sub-categories of news coverage (e.g., front page, quality, etc.). It can be seen from the table that across the 49 months of study, Maryland Medicaid had an average of 285.5 claims for varenicline prescription (standard deviation= 64.2). The aim of this section is to determine if the rate of such claims (per adult Medicaid enrollee) changed in response to news coverage surrounding and FDA about this medication.

Table 10. Summary statistics for the smoking cessation drug warning

Variable	By month			
	Mean	St. dev.	Min	Max
OUTCOMES				
varenicline_rx_cnt (count)	285.8	64.2	110.0	425.0
PREDICTORS				
INCC (count)	0.61	1.3	0.0	7.0
INCC_FRONT (count)	0.082	0.28	0.0	1.0
INCC_QUAL (cumulative score)	0.78	2.0	0.0	12
INCC_LENGTH (cumulative score)	1.8	3.4	0.0	17
INCC_FDA_MENTION (count)	0.53	1.2	0.0	6.0
INCC_VAL (cumulative score)	1.0	2.0	0.0	9.0
INCC_FDA_WARN (count)	0.39	1.1	0.0	5.0
INCC_BROADCAST (count)	0.22	0.71	0.0	4.0
NEUTRC (count)	0.43	0.54	0.0	2
NEUTRC_FRONT (count)	0.041	0.20	0.0	1.0
NEUTRC QUAL (cumulative score)	0.14	0.32	0.0	1.5
NEUTRC_LENGTH (cumulative score)	1.6	2.0	0.0	6.0
NEUTRC_FDA_MENTION (count)	0.18	0.39	0.0	1.0
NEUTRC_VAL (cumulative score)	0.55	0.82	0.0	3.0
NEUTRC_FDA_WARN (count)	0.20	0.14	0.0	1.0
NEUTRC_BROADCAST (count)	0.20	0.14	0.0	1.0

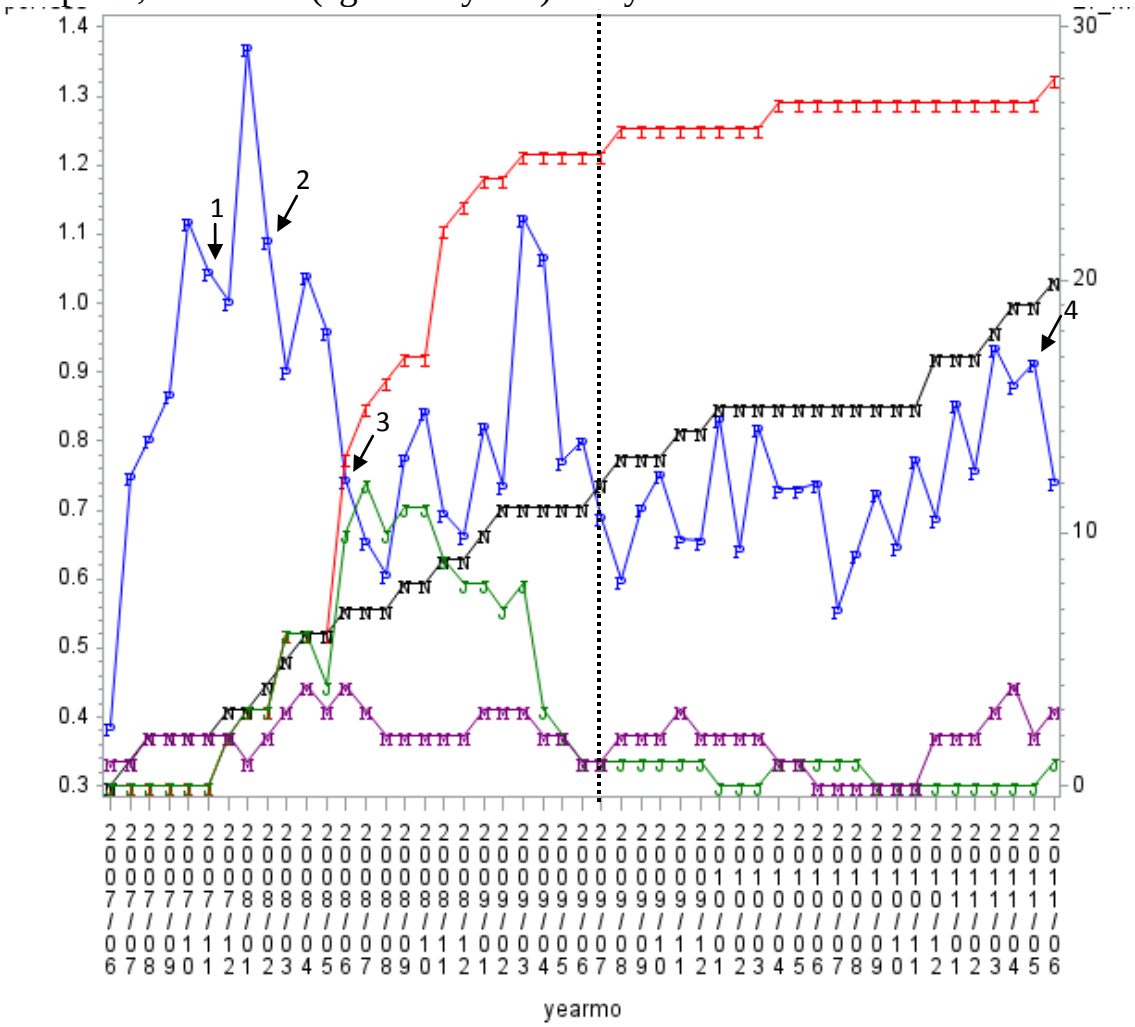
rx_cnt= filled prescription count
INCC= article increases concern about the warning
NEUTRC= article is neutral regarding concern (or decreases concern) about the warning

Outcomes source: Maryland Medicaid pharmacy claims derived by author with permissions from Maryland's Department of Health and Mental Hygiene.

Predictor source: Author's analysis of 49 news items from 25 months before and 24 months after the warning, corresponding to a total of 37 (12 NEUTRC) articles that appeared in the months before and 12 (8 NEUTRC) articles that appeared on or after the warning month.

Figure 7 shows the time-series associated with the varenicline warning overlaid with the time-series for the INCC and NEUTRC cumulative sums and 5 month rolling sums of the respective news coverage. The dependent variable (varenicline drug counts per 1,000 Medicaid engaged adults) demonstrates a reasonably stable time-series, though there is a suggestion of increased variability prior to the warning month of focus for this thesis work (July 2009). The five month cumulative time series demonstrate that there was very little news coverage after that warning month, suggesting that much of the coverage was likely tied to concerns characterized in the news media prior to that point in time. Figure 7 also shows that four other warning events surrounded the July 2009 "black box" warning. Most notably, dramatic coverage by media outlets and U.S. Congressional hearings appeared in June/July of 2008, but such events likely would have resulted in news coverage even as it also coincided with FDA action that may have more directly reached manufacturers and providers and subsequently influenced prescription behavior.

Figure 7. Time-series for the Varenicline warning news versus that drug's count per 1,000 adults (age > 18 years) Maryland Medicaid Enrollees.



'P' blue= Varenicline filled prescription counts per 1,000 Maryland Medicaid enrollees age > 18 years.
'I' red= cumulative counts of articles that INCREASE concern about the warning, lagged 1 month.
'N' black= cumulative counts of articles that are NEUTRAL regarding concern about the warning. Lagged 1 month
'J' green = 5 month moving sums of I
'M' purple= 5 month moving sums of N
The *left* Y-axis shows the percentage for the 'P '(blue plot).
The *right* Y-axis shows the article counts for the I, N J, and M plots.
The dashed line marks the July 2009 FDA warning month.
The numbered arrows identify other events surrounding the FDA warning of interest as follows:

1. November 2007: FDA issued a communication suggesting the possibility of aggression and erratic behavior as side-effects.
2. February 2008: FDA public health advisory said that "it appears likely" that neuropsychiatric events are related to varenicline use.
3. June/July 2008: Dramatic reports by ABC News and the *Washington Times* that veterans with PTSD were being subject to trials with a drug that increases suicide risk (varenicline). U.S. Congressional hearings.
4. May 2011: FDA reaffirmed above warnings and noted that both vareniciline and bupropion remained under FDA scrutiny.

yearmo= Year/Month (X-axis)

Tables 11a and 11b shows the regression results for the varenicline time-series analysis. Table 11a gives the statistical result for all the general (i.e., news item counts not weighted by things like front page placement) INCC models, as well as for several sensitivity models. A conditional test for inclusion of the seasonal quarterly variables was significant (F=7.1, p< .0006) and thus seasonal adjusters were included in the models presented. All of the models presented in Table 11a demonstrated significant, albeit small, INCC effects along with negative warning effects which are significant in three of four models. The full accumulation model (6A) was used to construct the 6C and 6D sensitivity models based on the slightly lower *AIC* (-284) versus the five month accumulation model (6B). Model 6C demonstrates a significant NEUTRC effect, and Model 6D shows that this effect is not consistent when the lagged DV is substituted for the AR term. Model 6C is used as the form to explore the weighted news coverage variable effects (see next section) and that model suggests small news effects in the following two directions: for each INCC news item, the number of varenicline prescriptions in Medicaid declined and average of .071 per 1,000 enrollees, and NEUTRC coverage appear to offset that effect by an average of .027 per 1,000. Both of these effects were jointly evident with adjustment for the warning and first order autoregression error terms.

Table 11b presents the results for the weighted news variables (e.g., front page counts). The form used was the same as that used for Model 6D, which included lagged DV and NEUTRC (i.e., the most complete model considered and the one with the lowest *AIC* in Table 11a). None of the results of Table 11b reveal any significant effects pertaining to the INCC or NEUTRC variables that seem larger in magnitude than those observed in Model 6D, with one exception. The NEUTRC effect was significant in Model 6D-FD, suggesting that for each added neutral news item about smoking cessation medications, the number of varenicline prescriptions

increased an average of .043 per 1,000 Maryland Medicaid enrollees after adjusting for the other parameters in the model. This is, like the INCC effects, a very small attributable change, but one that is significant and appears to intensify (i.e., increase) slightly the effects seen in Model 6C.

Overall then, the results summarized in Tables 11a and 11b offer quite *limited* support for the three hypotheses of this work. The support is limited because the effects are small (<10 per 1 million members per news item), they are not consistent across different specifications for the NEUTRC variable, and they only support intensifying weighted variable effects for the NEUTRC news coverage that mentions the FDA.

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Table 11a. Regression results for predicting varenicline filled prescription counts per 1,000 Maryland Medicaid enrollees >18 years of age.

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
6A	IV: *full* accumulation of INCC	.57, -284	-.033 (.52)	-.0084 (.0021)*	-.77 (.64)	Seasons significant (F=7, p< .0006) and thus included in all models
6B	IV: *5 month* accumulation of INCC	.53, -280	-.22 (<.0001)*	-.017 (.017)*	-1.2 (.46)	*AIC* higher than 6A
6C	Model 6A with NEUTRC term	.60, -286	-.15 (.060)*	-.017 (.0020)*	-.039 (.98)	NEUTRC was significant: β=.027, p< .065
6D	Model 6C, but no AR and lagged DV	.61, -288	-.11 (.19)	-.014 (.015)*	--	OLS; NEUTRC and Lagged DV both not significant, lowest *AIC*

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
DV= dependent variable (outcome)
*significant effect per set *p*-value threshold
OLS= ordinary least squared regression use

Table 11b. Weighted-independent-variable regression results predicting varenicline filled prescription counts per 1,000 adult Maryland Medicaid enrollees

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	Lagged DV *β (p)*	Notes
6D-F	Model 6D, but IV: front page counts	.61, -288.	-.0057 (.20)	-.0069 (.78)	.18 (.12)	Only 1 NEUTRC item and that effect not significant; Only 5 INCC items
6D-Q	Model 6D, but IV: quality unit counts	.62, -288	-.098 (.22)	-.0073 (.0021)*	.16 (.18)	NEUTRC is not significant; -.0073x2.5[a]= -.018 ~ INCC general effect
6D-L	Model 6D, but IV: length unit counts	.60, -286	-.065 (.39)	-.0039 (.051)*	.19 (.13)	NEUTRC is not significant; -.0039 x3.5[b]= -.014 ~ INCC general effect
6D-FD	Model 6D, but IV: FDA mention counts	.63, -289	-.17 (.081)*	-.011 (.0007)*	.14 (.23)	NEUTRC: β= .043, p= .086, NEUTRC supports *HYPOTHESIS III*, but INCC finding does not (versus 6D)
6D-V	Model 6D, but IV: valence unit counts	.61, -288	-.075 (.24)	-.0090 (.018)*	.15 (.23)	NEUTRC is not significant; -.0090x2[c]= .018 ~ INCC general effects
6D-W	Model 6D, but IV: warning mention counts	.61, -289	-.020 (.64)	-.012 (.0013)*	.19 (.091)	No NEUTRC articles were evident, so that term excluded.

6D-B	Model 6D, but IV: broadcast counts	.60, -286	-.034 (.44)	-.018 (.0053)*	-20 (.15)	NEUTRC is not significant, just one NEUTRC

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
IV= Key independent variable, INCC
*significant effect per set *p*-value threshold
[a] This multiplier of 2.5 is used to represent an intermediate quality item (range of quality rating is 0 to 5)
[b] This multiplier of 3.5 is used to represent an intermediate length item (range of length rating is 1 to 6)
[c] This multiplier of 2 is used to represent an intermediate valence item (range of valence rating is 1 to 3)

Rosiglitazone (diabetes medication) warning

In May of 2007 the FDA issued an advisory that the diabetes medication rosiglitazone (Avandia) carried a risk of heart failure. By November of 2007 that advisory had been intensified via two black box warning updates for this medication. The outcome time-series used to analyze the impact of news surrounding this FDA action were by-month filled prescription rates (average per day fills within the month) derived from administrative claims pertaining to 1.4 million BlueCross enrollees (Starner et al., 2008).

Table 12 shows that across the 17 months (a shorter duration than the other time-series studied in this dissertation), there was an average of 60.1 rosiglitazone prescriptions per day (standard deviation= 26). The table further shows the news signal for a 49 month period surrounding this warning. For example, Table 12 shows that the average number of INCC news items per month was 1.4 (standard deviation= 27) while the average number of NEUTRC items was 3.4 (standard deviation= 1.4). The aim of this section is to determine if there was any correlation between these per month daily prescription rates and the news coverage surrounding the FDA warnings pertaining to rosiglitazone.

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Table 12. Summary statistics for the diabetes drug warning

Variable	By month			
	Mean	St. dev.	Min	Max
OUTCOMES				
ros_claims_pd_pmm (daily prescription fills per million members)	60.1	26	31.8	99.1
PREDICTORS				
INCC (count)	1.4	2.7	0.0	14
INCC_FRONT (count)	0.10	0.37	0.0	2.0
INCC_QUAL (cumulative score)	1.9	4.9	0.0	28
INCC_LENGTH (cumulative score)	4.63	9.2	0.0	49
INCC_FDA_MENTION (count)	1.3	2.5	0.0	13
INCC_VAL (cumulative score)	1.5	2.8	0.0	14
INCC_FDA_WARN (count)	0.82	1.8	0.0	10
INCC_BROADCAST (count)	0.040	0.20	0.0	1.0
NEUTRC (count)	3.4	1.4	1.0	7.0
NEUTRC_FRONT (count)	0.72	0.8	0.0	2.5
NEUTRC_QUAL (cumulative score)	0.65	0.77	0.0	3.0
NEUTRC_LENGTH (cumulative score)	12.1	5.25	4.0	24
NEUTRC_FDA_MENTION (count)	1.5	1.1	0.0	5.0
NEUTRC_VAL (cumulative score)	5.4	2.64	1.0	11
NEUTRC_FDA_WARN (count)	0.020	0.14	0.0	1.0
NEUTRC_BROADCAST (count)	0.37	0.97	0.0	6.0

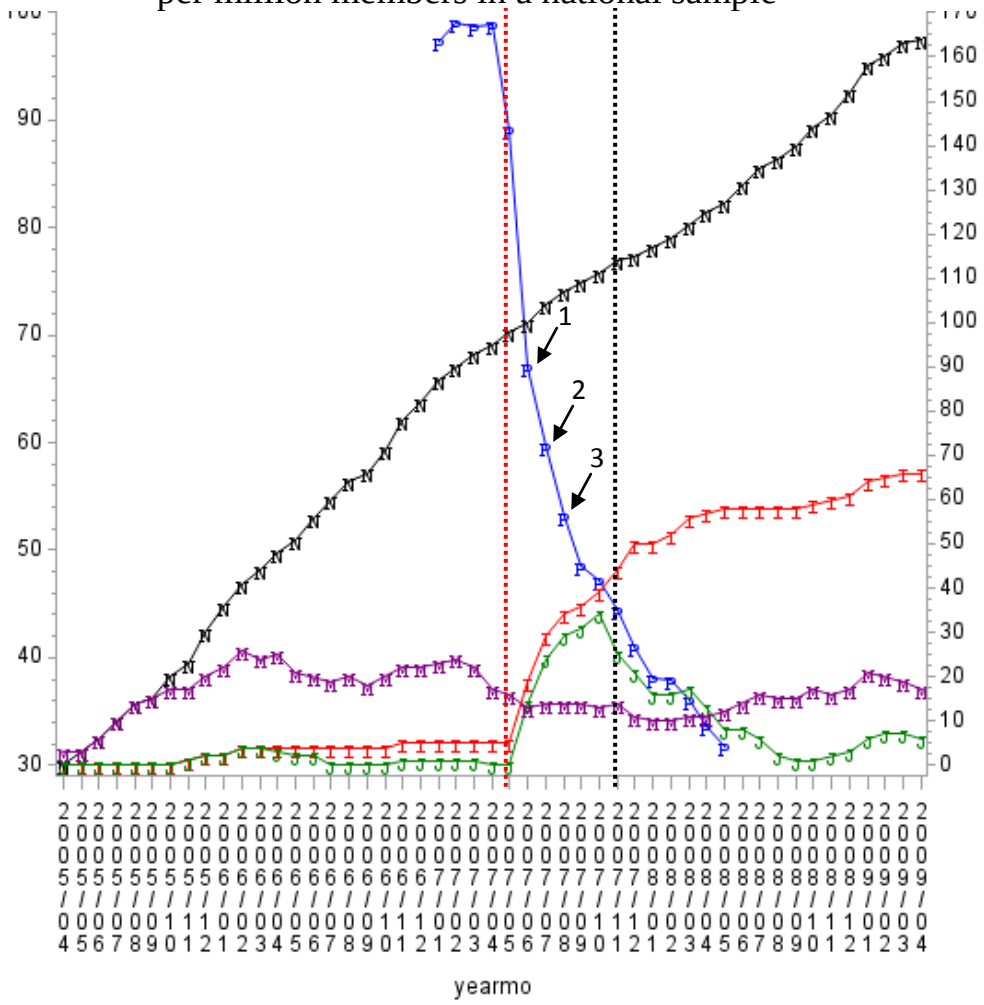
ros=rosiglitazone
INCC= article increases concern about the warning
NEUTRC= article is neutral regarding concern (or decreases concern) about the warning

Outcome source: (Starner et al., 2008)

Predictor source: Author's analysis of 234 news items from 25 months before to 24 months after the warning, corresponding to a total of 103 (98 NEUTRC) articles appear in the months before and 131 (68 NEUTRC) article appearing on or after the warning month.

Figure 8 shows the times-series for rosiglitazone prescriptions and for the news coverage surrounding the warning for this medication. The DV trajectory is clearly non-stationary with a steep decline from April 2007 to May 2008, the termination of the series. As such, the randomness assumption (Hill, Griffiths, & Lim, 2011) of the time-series model is violated even with the addition of the interruption term used to represent the FDA warning. Despite this concern, a limited number of AR models were conducted, similar to others in this research. Having noted that, it can be seen from Figure 8 that there is a progressive and evenly spread series of actions by the FDA which occur during the period of the decline. The assumption of this thesis work is generally that the first warning is a key trigger point for the decline in rosiglitazone observed, and that subsequent (to that first warning) FDA activities likely were covered by the news media.

Figure 8. Time-series for the rosiglitazone warning news versus that drug's count per million members in a national sample



'P' blue= Rosiglitazone filled prescription counts per million members…
'I' red= cumulative counts of articles that INCREASE concern about the warning, lagged 1 month.
'N' black= cumulative counts of articles that are NEUTRAL regarding concern about the warning. Lagged 1 month
'J' green = 5 month moving sums of I
'M' purple= 5 month moving sums of N
The *left* Y-axis shows the percentage for the 'P '(blue plot).
The *right* Y-axis shows the article counts for the I, N J, and M plots.
The **dashed black line** marks the November 2007 FDA warning month, the dashed red line is placed to mark the month of an advisory issued by the FDA, rather than the more severe issuance of the black box warning which came in November.

1. June 2007: FDA consumer update issued re-affirming May "alert" and noting that further investigation regarding the concern was on-going.
2. July 2007: FDA advisory committee met and recommended a "black box" warning be added.
3. August 2007: pioglitazone added to the FDA warning, but warning not yet a "black box"..

yearmo= Year/Month (X-axis)

Tables 13a and 13b show the regression results pertaining to the rosiglitazone warning. Seasonal effects were not significant and thus were dropped from the models presented (F=.86, p=.49). All four models in Table 13a confirm the presence of a significant warning term which can be interpreted as follows: the average decline in per day rosiglitazone prescription counts per million members was 18 to 20, after adjusting for the other parameters in these models. These four models also demonstrate that AR and lagged DV terms were not significant except for the five month accumulation Model 7B which, by *AIC* and absence of INCC significance, seems inferior to the others. Comparing Models 7A and 7B indicates that full accumulation of the INCC news signal is the form that not only best fits the data, but which also supports the hypothesized decline in the outcome relating to such news. This finding is further consistent across Models 7C and 7D which, respectively, do not support significant NEUTRC or lagged DV effects. Model 7D is thus used moving forward as it has the lowest *AIC* of those tested, and because it also accounts for the status quo via inclusion of the lagged DV, even as that variable is not a significant correlate of the outcome. The results of this model suggest that for each additional INCC news item the average decline in daily rosiglitazone prescriptions is .60 per million BlueCross insure members, after adjusting for the warning effect and for the lagged DV.

The results presented in Table 13b review all the models where the INCC variable has been weighted by additional details (e.g., front page placement), and it found only one of seven effects (Model 7D-Q) to be significant and of a magnitude greater than the general INCC effects described in Table 13a. Only the quality ratings appeared to intensify the impact of the news coverage. Specifically, the INCC coefficient from Model 7D-Q can be interpreted as follows: for each additional INCC item quality unit in a given month (note that the range is from 0-5, with 5 being the highest quality score based on a review of item details and accuracy), the number of

rosiglitazone prescriptions declined an average of .64 per day per million insures. Given that an intermediate quality news item was one with 2.5 quality units, then the average quality effect translates to an intermediate effect of .64*2.5= 1.6, markedly above the general effect observed in Model 7D (.60).

Accordingly, the results from Tables 13a and 13b support *HYPOTHESIS I* (that INCC coverage corresponds to decreased rosiglitazone prescriptions), do not support *HYPOTHESIS II* (that NEUTRC coverage alters rosiglitazone prescriptions), and in only one of seven instances (quality) supports *HYPOTHESIS III* (that details of the news coverage intensifies general coverage effects).

Table 13a. Regression results for rosiglitazone filled prescription average counts per day per 1 million members.

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	AR *β (p)*	Notes
7A	IV: *full* accumulation of INCC	.99, 86	-19 (< .0001)*	-.86 (<.0001)*	.085 (.80)	Season excluded as joint *F*=.86 (*p*=.49)
7B	IV: *5 month* accumulation of INCC	.98, 106	-20 (.0053)*	-.16 (<.59)	-.98 (<.0001)*	5 month INCC not significant
7C	Model 7A with NEUTRC term	.99, 83	-21 (< .0001)*	-.57 (.0040)*	.11 (.74)	NEUTRC is not significant
7D	Model 7A, but no AR and lagged DV	.99, 81	-18 (< .0001)*	-.60 (.029)*	--	OLS, Lagged DV is not significant

Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month
AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
DV= dependent variable (outcome)
*significant effect per set *p*-value threshold
OLS= ordinary least squared regression use

Table 13b. Weighted-independent-variable regression results predicting rosiglitazone filled prescription

Model	Description	R^2, *AIC*	Warning *β (p)*	INCC *β (p)*	Lagged DV *β (p)*	Notes
7D-F	Model 7D, but IV: front page counts	.99, 84	-29 (.0018)*	4.8 (.15)	.83 (<.0001)*	INCC not significant
7D-Q	Model 7D, but IV: quality unit counts	.99, 82	-9.7 (.10)	-.64 (.057)*	.0054 (.98)	-.64x2.5[a]= -1.6 > INCC general effect
7D-L	Model 7D, but IV: length unit counts	.99, 81	-18 (< .0001)*	-.16 (.030)*	.26 (.15)	-.16x3.5[b]=.56 ~ INCC general effect
7D-FD	Model 7D, but IV: FDA mention counts	.99, 81	-17 (.0001)*	-.72 (.030)*	.17 (.43)	~ INCC general effect
7D-V	Model 7D, but IV: valence unit counts	.99, 81	-19 (< .0001)*	-.47 (.031)*	.28 (.12)	-..47x2[c]= .94 ~ INCC general effects
7D-W	Model 7D, but IV: warning mention counts	.99, 82	-16 (.0005)*	-1.0 (.044)*	.19 (.39)	~ INCC general effect
7D-B	Model 7D, but IV: broadcast counts	n/a	n/a	n/a	n/a	Only 2 INCC broadcast items occurred

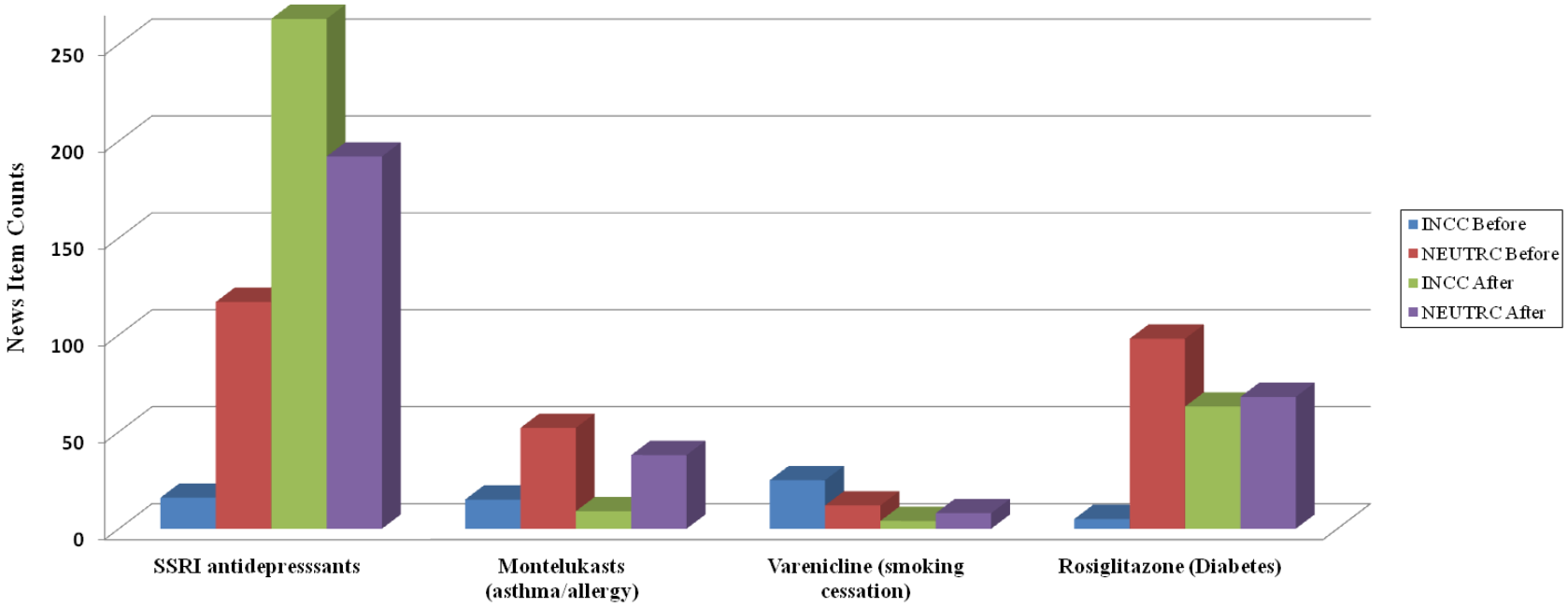
Warning= a flag if previous month was after the warning
INCC= news coverage that increases concern about warning up to t-1 month

AR= Autoregressive error term, AR1 is first order, etc.
IV= Key independent variable, INCC
DV= dependent variable (outcome)
*significant effect per set *p*-value threshold
[a] This multiplier of 2.5 is used to represent an intermediate quality item (range of quality rating is 0 to 5)
[b] This multiplier of 3.5 is used to represent an intermediate length item (range of length rating is 1 to 6)
[c] This multiplier of 2 is used to represent an intermediate valence item (range of valence rating is 1 to 3)

Summary of findings across all four warnings

This section summarizes the findings across all four warnings. Figure 9 shows the news coverage profiles pertaining to each of the four drugs studied before and after their specific FDA warnings occurred. Though the study was not designed to test whether different warnings yielded different *amounts* of news coverage, the figure clearly demonstrates that antidepressants received substantially more news coverage than did the three other medication classes, and that the diabetes medication coverage was markedly greater than the small amount of coverage focused on the two remaining therapies. The *patterns* of news coverage for each drug category were also distinct. The substantial antidepressant coverage was principally NEUTRC before the warning, and then INCC coverage became dominant after the warning. The asthma drug coverage was mostly NEUTRC before and after the warning. The smoking cessation drug coverage was exceptionally rare, with a mode pertaining to INCC coverage before the warning. Finally the diabetes drug news coverage was substantial for NEUTRC before and after the warning, and for INCC only after the warning, with a mode value pertaining to the NEUTRC coverage before the warning. Accordingly, the four warnings studied differed not only regarding their respective therapeutic class, FDA and other warning signals and events surrounding them (see "Selection of the warnings" section of the methods), they also demonstrated different levels and patterns of pertinent news coverage based on relatively standardized *Lexis Nexis Academic* and *ProQues*t database searches, all based on general disease references, the mention of some medical treatment, and the mention of the terms "safety" or "efficacy."

Figure 9. News coverage surrounding four distinct FDA Warnings



INCC= news item increases concern about the FDA warning

NEUTRC= news item is neutral regarding or decreases concern about the FDA warning

Before= item occurred in months before the warning

After= item occurred in the month of or months after the warning

Table 14 presents the finding across the four drug warnings in one exhibit. Overall the aim of this exhibit is to note the general pattern of significant results that either support the hypotheses of this work that news coverage is correlated to subsequent prescription use behavior, or which clarifies the results more broadly (significant or otherwise).

General patterns that can be observed from Table 14 are as follows:

1. Significant and negative general INCC effects are evident across all the warnings studied, thus consistently supporting HYPOTHESIS I. However, these effects are all small, i.e., much less than 1.0 unit per news item. It should be noted that the units differ, especially as they pertain to the denominator of the report ratio. More specifically, the antidepressant warnings all pertain to percents with *new* depression cases as the denominator. This *incidence* correction factor is markedly different from the denominators for the three other warnings, which are based on general populations of Medicaid enrollees for the asthma and smoking cessation drug warnings, and on a large population of BlueCross commercial plan enrollees for the diabetes drug warning. As such, the range of the magnitude of the significant INCC findings is from -.025 *per 100 new depression cases* to -.014 *per 1,000 adult Maryland Medicaid enrollees*. These units are not directly comparable, though they do all support the hypothesis that INCC news coverage results in decreased prescription activity generally.
2. The adult_pcpAD_pct results were the test of HYPOTHESIS IA (i.e., “spillover” effects). The results support that hypothesis, though the analogous child effect seemed more transient because a five month INCC sum yielded a better fit than an accumulating sum for the child measure, but not for the adult measure.

3. Several INCC weighted effects were stronger than the general effects, offering partial support to HYPOTHESIS III. The results in this regard were mixed, several times supporting the importance of front page placement as a factor intensifying consumer response to news, but only occasionally revealing quality, FDA mention, or broadcast (TV or radio) signals as intensifying the effects. Moreover, the front page effect appears isolated to the antidepressant warning.
4. Only a single warning (smoking cessation) demonstrated a significant NEUTRC effect of news coverage on prescription use, after adjusting for the INCC coverage. That effect was small, like the INCC effects observed. This limited finding suggests similarly limited support for HYPOTHESIS II.
5. The warning flag per se, was often not significant (except for the rosiglitazone warning) and sometimes was even positive, a counter-intuitive finding suggesting that a simple time-interruption[15] term was not generally influential on subsequent prescription use when compared against an accumulation of news signal about the warning. Still, most INCC effects were significant when the warning was included in the model, and most warning flags were negative (and usually significant) in the absence of the news coverage confirming that these two variables were correlated.
6. Most of the significant INCC findings reported were robust to either the inclusion of a first order autoregressive term (AR1), or to a lagged dependent variable, thereby offering some accounting for unobserved time-variant effects and for the "status quo" prescribing behaviors. Higher order autoregressive terms were either unnecessary or had limited

[15] Time-series plots did suggest that all warnings had distinctive features and drawn-out time courses, demonstrating two points relevant to the data interpretation: 1) all warnings were not equal in duration, frequency, intensity, and qualitatively, and 2) warning signals and events to the public were not single "point in time" occurrences.

additional impact on the models. Exceptions to these general findings were that both the Child_pcpdx_pct and the Child_ssri_pct variables did not show significant INCC effects when their lagged terms were included as ‘right-hand’ side variables.

Table 14. Summary of findings across all studied FDA warnings and dependent variables (DVs).

Warning	DV	INCC *β (p)*	INCC weighted *β (p)*	NEUTRC	Notations
Anti-depressants	Child_pcpdx_pct	-.025 (.013)	-.13 (.0094) per front page item -.022 (.012) per quality unit -.062 (.0091) per broadcast item	ns	ns with significant lagged DV inclusion; Warning ns
	Child_ssri_pct	-.084 (.0010)	-.37 (.0034) per front page item -.067 (.0030) per quality unit -.15 (.0014) per warning mention item -.21 (.0002) per broadcast item	ns	ns with significant lagged DV inclusion; Warning ns
	Child_pcpAD_pct	-.041 (.0071)	-.14 (.018) per front page item -.10 (.0014) per broadcast item	ns	Five month accumulation of DV used; Significant lagged DV included; Warning ns
	Adult_pcpAD_pct	-.025 (.0036)	-.096 (.0040) per front page item	ns	Five month accumulation of DV used, but full accumulation slightly superior; Significant lagged DV included; Warning ns
Asthma	Montelukast Rx (per month per 1,000 enrollees in Maryland Medicaid)	-.033 (.064)	-.044 (.045) per FDA mention item	ns	Significant lagged DV included; Significant seasonal variable included; Warning ns
Smoking	Varenicline Rx (per month per 1,000 enrollees in Maryland Medicaid)	-.014 (.015)	[.043 (.086) per NEUTRC FDA mention item]	β=.027, p< .065 (with AR1)	In full model (6D) both NEUTRC and lagged DV ns; Warning ns
Diabetes	Rosiglitazone Rx (per day per 10^6 enrollees in a large commercial population)	-.60 (.029)	-.64 (.057) per quality unit	ns	Significant season variable, and ns lagged DV included; Warning significant

INCC= news coverage that increases concern regarding the warning
NEUTRC= news coverage that does not increase concern regarding the warning, i.e., is mainly neutral regarding that concern
ns= not significant

Child_pcpdx_pct = percent of children with a new case of depression who were diagnosed by a primary care provider
Child_ssri_pct = percent of new pediatric depression cases resulting in an SSRI prescription
Child_pcpAD_pct = per of new pediatric depression cases resulting in a filled antidepressant prescription made by a primary care physician
Adult_pcpAD_pct = as above, but for new adult cases
Montelukast Rx= montelukast prescription fills per 1,000 Maryland Medicaid enrollees
Varenicline Rx= varenicline filled prescriptions per 10,000 Maryland Medicaid enrollees >18 years of age
Rosiglitazone Rx= rosiglitazone filled prescriptions per day per million enrollees
AR1= first order autoregressive error term
DV= Dependent variable

Discussion

Summary of findings

The aim of this research was to determine if there were effects between time-lagged lay news coverage surrounding select FDA prescription drug warnings and the use of the corresponding pharmaceutical agent. The research findings showed subtle but significant effects of such news coverage on outcomes related to prescription drug use directly or diagnoses made by primary care or other physicians. These effects were evident across four distinct therapeutic classes (treatments for: depression, asthma/allergies, smoking, or diabetes). For all but two of the seven outcomes (child_pcpdx_pct and child_ssri_pct), these effects remained significant after adjustment by autoregression terms or lagged dependent variables[16], the latter of which is especially strong evidence of true significance because lagged dependent variable inclusion often eclipses the significance of other explanatory variables (Achen, November 2, 2001). More specifically, the significant effects observed across warnings generally revealed that news coverage which increased concern about a warning (INCC) preceded significant declines in use of the drug subject to that warning. By contrast, there was almost no evidence that neutral coverage about the drugs subject to the warning (NEUTRC) had any impact on offsetting the INCC warning coverage. NEUTRC coverage mentioned or discussed the pharmacologic treatment, but did not increase concern or even mention the warning. Finally, there was some albeit limited, evidence that different *details* about the INCC coverage (i.e., front page, lead, TV or radio placement, and FDA mention) intensified the impact of the warning on some outcomes. Spillover effects (from children to adults) of news coverage on the antidepressant warning were

[16] For child_pcpdx_pct and child_ssri_pct the AR1 models were significant, but the lagged dependent variable models were not, though they marginally so (*p*-value range: .10 to .14).

also supported by this research. In summary, the findings show that news coverage of FDA warnings does appear to at least subtly influence how consumers and doctors respond to those warnings across four distinct therapeutic classes. The next section considers the magnitude of the observed effects.

Magnitude of the Observed Effects

Among the results presented (summarized across warnings in Table 14) it may be challenging to determine if the magnitude of the significant effects were substantial. Accordingly, two *post hoc* indicators were computed to convert the main findings into more absolute and standardized units. Column C of Table 15 restates the INCC result from each model *n*A, (i.e., Models 1A to 7A, the AR1 regression models). Column D lists the absolute number of INCC news items which appeared for each warning over the course of the full study period. Column E is the product of Columns C and D, and thus it shows the total change (in terms of the absolute magnitude for the entire study period) for each outcome per the statistically significant regression coefficients. For example, the first row of Table 15 shows that child diagnoses made by a primary care physician (child_pcpdx_pct) declined by 7% over the study period, based on the average effect calculated for a one-month period. Over the 50 months studied, that is arguably a substantial impact. That aggregated effect is especially high (-23%) for the child_ssri_pct outcome, perhaps because SSRIs were the dominant form of the antidepressants and were the original target of the FDA warning. The absolute magnitude for the asthma, smoking, and diabetes drugs are reported in prescription fills per million members (pmm), so these magnitudes are not directly comparable to the percent of incident cases studied for the antidepressant cases. Still, two of three of these non-antidepressant warning outcomes (for asthma and diabetes drugs) demonstrated significant INCC effects corresponding to declines in

prescription use which exceeded 1,000 prescriptions pmm over the 50 months studied- perhaps a substantial amount, but perhaps trivial given the volume each drug generated over that same time period. Importantly, "members" in these calculations include individuals in the general population, and thus this number is not limited to those individuals with the disease targeted by the warning, nor to those with incident (i.e., newly diagnosed) morbidity. Finally, Table 15 provides elasticity calculations $\{\beta^{*}(\textit{mean INCC} \div \textit{mean outcome})\}$[17] for each outcome regression to consider the percent change in that outcome for each 1% change in the INCC news item count. The elasticities observed generally suggest that the findings were modest, revealing elasticities well below |.5| for all outcomes, and below |.1| for the antidepressant and montelukast warnings.

The utility of Table 15 is that it indicates that the significant effects observed in the current study might be considered marked for all but the varenicline warning if one considers just the "estimate of accumulated effect", but the effects become somewhat more modest (especially for the antidepressants and asthma/allergy warning) if the elasticity is considered. Specifically, Table 15 (Column F), for example, shows that at the mean values of the dependent and main explanatory variables, a 1% increase in antidepressant warning INCC coverage led to a decline in the outcomes ranging from -.029 to -.094% (note that antidepressant outcome is itself a percent). The somewhat higher elasticities for varenicline and rosiglitazone suggest that use of those drugs may have been more sensitive to news coverage (though the varenicline usage was already quite low). Rosiglitazone's heightened elasticity to news coverage may in part stem from the fact that this warning was supported by strong and well-publicized evidence of

[17] This is equivalent to the equation: (dy/dx)*(*mean* x)/ (*mean* y)

heightened risk compared to the concerns regarding the other three drug warnings studied (Dal Pan, September 10, 2010).

Table 15. Indicators of the Magnitude of the General INCC Effects Observed (per Models *n*A)

Column A	Column B	Column C	Column D	Column E	Column F
Warning	Variable	Average INCC news effect (*p*)	Total Count of INCC items	Estimate of Accumulated Effect (Column C * Column D)	Elasticity {(*dy*/*dx*) * (*mean* x)/ (*mean* y)}
Anti-depressants	Child_pcpdx_pct	-.025 (.013)	279	-7.0%	-.043
	Child_ssri_pct	-.084 (.0010)	279	-23%	-.094
	Child_pcpAD_pct	-.020 (.0054)	279	-5.6%	-.066
	Adult_pcpAD_pct	-.023 (<.0001)	279	-6.4%	-.028
Asthma/ allergy	Montelukast fills pmm	-47[a] (.041)	24	-1,128	-.047
Smoking Cessation	Varenicline fills pmm	-8.4[a] (.0021)	29	-240	-.33
Diabetes	Rosiglitazone fills pmm	-26[b] (<.0001)	58	-1,508	-.25

INCC= News that increases concern about the FDA warning
Models *n*A = Statistical models 1A…7A
[a] converted to pmm from the original per 1,000
[b] converted to per month from the original per day

Table 15 is finally a useful exhibit to note that the regression modeling conducted for this research assumed a linear additive relationship between the *cumulative* number of items and the response of the dependent variable rather than assuming any "diminishing returns" or "news fatigue". For all but the antidepressant warnings which had well below one INCC news item per month, this "non-diminishing news impact" assumption seems reasonable because news coverage was relatively low throughout. Additionally, the fact that short term (5 month accumulating) versus long term (accumulating across as many as 50 months) typically yielded less significant effects might be viewed as suggesting that a non-diminishing accumulating signal

was not an unreasonable assumption. Still, it would be interesting in future work to explore the use of non-linear functional forms and/or alternative assumptions about decay rates for news effects over time.

INCC versus NEUTRC

Despite the fact that most of the news coverage observed in this research was not rated as increasing concern (INCC), the remaining neutral coverage (NEUTRC) about each type of medication did not offset the negative outcome impact apparent from the INCC signal, with the exception of the varenicline warning. This result is contrary to the a priori hypothesis that NEUTRC coverage would matter. More specifically, it was anticipated that NEUTRC news, defined by the absence of any cause for concern about the warning, would likely enhance consumer comfort with the drug as a legitimate and trusted remedy. The absence of significant NEUTRC effects may result from one or both of the following explanations. First, perhaps the public attends and reacts more strongly to dramatic or controversial media messages compared to more ordinary statements or stories about prescription drug use. Second, perhaps some of the NEUTRC coverage was neutral regarding the FDA warning, but still raised concern about the pharmaceutical use for other reasons (e.g., other side-effects, cost, or absence of efficacy). Future work is required to discern which explanation of uni-directional media news coverage is empirically supported, but based on the current findings it appears that the NEUTRC results are enigmatic.

One notable example of a another study that found that media coverage influenced consumer attitudes in one direction, but not in the hypothesized counter-direction, was that pertaining to smoking cessation news impacts on teenager attitudes towards smoking (Clegg Smith et al., 2008). Articles reviewed in this study were rated as “positive” when they encouraged smoking

cessation by emphasizing the related health benefits or the success of legislation and legal cases aimed at reducing tobacco use, or as "negative" when articles emphasized equivocal health findings or political and legal failures to curb tobacco use. Consistent with their hypotheses, these researchers found that "positive" cessation coverage correlated significantly with teens' increased sentiments in favor of non-smoking, but counter to their hypotheses, the "negative" coverage did not yield the opposite effect. This observation that news media messaging acts in one direction, but not the counter-direction, is consistent with the effects observed in this research regarding FDA drug warnings, and may relate to the fact that is it easier for news coverage to promulgate skepticism rather than acceptance of health-related behavior.

Weighted predictor variables (based on detailed article coding)

Beyond the general effects of news coverage regarding each warning, content analysis was used to code and explore the effects of details about each news item (e.g., front page placement, quality). Weighting the INCC variables by various coding details offered some, albeit limited, support for the a priori hypothesis that such details would intensify any observed significant effects between news coverage and each outcome. Table 16 offers a simple diagram that summarizes where each of the seven coding details yielded stronger INCC effects than those observed based with unweighted news item counts. That table shows that most of the "checked" cells (✔) pertained to the antidepressant warning and to front page (i.e., front page, lead, or cover story), broadcast (i.e., TV or radio), and quality ratings (i.e., a score from 0-5 based on the completeness and accuracy of the article (described in the Methods section)). Each of these significant and apparently intensifying effects is considered further below.

The front page and broadcast effects both support the simple idea that more visible news coverage has greater impact than less visible news. Though this intensified effect may appear

obvious, it has not been reported by other important studies of health care, even as they have reported the frequency of front page coverage as a descriptive variable (Barry & Busch, 2010; Barry et al., 2011; Karlsson, 2011; Shih et al., 2008). The absence of front page effects for all but the antidepressant warnings may be related to the fact that very little front page coverage was evident for those other warnings. For instance, there was only one front page article pertaining to the montelukast warning, so testing front page effects was not statistically feasible.

The article quality rating was a predictor related to two of four antidepressant outcomes and the diabetes warning outcome. This findings suggests that more complete reporting intensifies the response to warnings that are either relatively dramatic in nature (i.e., children and suicide), or supported by a substantial evidence base (Nissen & Wolski, 2007; Starner et al., 2008). Given, however, that the antidepressant quality result is limited to only 2 of 4 outcomes studied, this result is inconclusive, perhaps leaving only the montelukast result as the singular instance studied where the quality of the reporting was a truly significant predictor of medication use over time. Additionally, it should be noted that, overall, the quality of the articles reviewed was generally quite low, averaging above one quality unit per month (out of five possible, per item; see Methods) only for the antidepressant (mean= 6.1, Table 3) and rosiglitazone (mean= 1.9, Table 12) warnings, thereby demonstrating that media coverage about the four warnings studied generally offered readers far from complete descriptions of the “who”, “what”, strength of evidence, costs versus benefits, and alternatives pertaining to the pharmaceutical use under scrutiny. Other work assessing the quality of drug news coverage has previously found that such coverage is typically quite limited regarding the completeness of its content (Yong, Bigman, Flynn, Mittermaier, & Long, 2009).

There was no evidence to support that the volume of reporting observed (i.e., total word length) or the emotional content (i.e., valence) of the news items studied demonstrated any discernible effect on the outcome beyond the item counts alone (Table 16). This suggests that headline tallies per se (i.e., INCC item counts), rather than article word counts or emotional content, are enough to motivate change in patients and physicians. The absence of a valence effect is supported by Iyengar and colleagues who, in their seminal work, also observed that emotional content (i.e., the vividness or inclusion of personal vignettes) did not significantly influence the attitudes of news consumers (Iyengar & Kinder, 2010). It contradicts, however, the notion that narratives are an influential component of news coverage leading to behavioral change (Maier, Rothmund, Retzbach, Otto, & Besley, 2014).

Finally, the results in Table 16 show that mentioning the FDA by name intensified the INCC effect substantially only for the rosiglitazone warning, and mentioning the FDA's warning action only intensified the effect for one of the four antidepressant outcomes. These generally null findings regarding FDA mention thus indicate that citing the agency's involvement or authority in a news report does not seem to motivate news recipients towards a heightened behavioral response. The absence of these FDA effects is surprising given the agency's dominant and long-established role as a regulator of pharmaceuticals (Carpenter, 2010). As such, it could be that the FDA's trust-worthiness as a source for post-marketing safety information was not viewed as particularly high in the years surrounding the warnings studied (2003-2009).

Table 16. Schematic Overview of News Item Details that Enhanced the Observed INCC to Outcome Effect

Warning	Outcome	Front page	Quality	Length	FDA mention	Valence	Warning mention	Broadcast
Anti-depress-ants	*Child_pcpdx_pct*	✔	✔	ø	ø	ø	ø	✔
	Child_ssri_pct	✔	✔	ø	ø	ø	✔	✔
	Child_pcpAD_pct	✔	ø	ø	ø	ø	ø	✔

	Adult_pcpAD_pct	✔	ø	ø	ø	ø	ø	ø
Asthma	*Montelukast Rx Count*	ø	ø	ø	✔	ø	ø	ø
Smoking	*Varenicline Rx Count*	ø	ø	ø	ø	ø	ø	ø
Diabetes	*Rosiglitazone Rx Count*	ø	✔	ø	ø	ø	ø	ø

INCC= increased concern about the warning
✔= revealed a stronger effect than the general INCC count
Ø= did not reveal a stronger effect than the general INCC count

Spillover effects?

When news coverage does influence consumer behavior, the influence may "spillover" to persons or scenarios not targeted by the warning. In this study, the news effects observed in child and adolescent antidepressant use seem to have spilled-over to adult consumers of antidepressants. This result confirms prior research which revealed that both child and adult antidepressant use declined markedly in conjunction with the FDA warning (Libby et al., 2007; Valuck et al., 2007). The contribution of the present study is the demonstration that INCC news coverage, rather than the warning alone, may have been the mediator of a large portion of this response.

Form of the Regression

The regression models used for this research adjusted for autocorrelations pertinent to time-series analysis in two ways, via an autoregressive error term and via a lagged dependent variable (DV). These two approaches are widely used in time-series analysis, and the lagged DV often dominates the *R-square* calculation because it not only captures components of the serial autocorrelation, it further represents "habit persistence" (Achen, November 2, 2001; Kennedy, 2008). In terms of the outcomes measured in this study, habit persistent or status quo prescribing and consumer prescription drug use is related to clinician/patient comfort with (including the true effectiveness of) specific medications. The lagged DV versus AR1 results presented in this

research were typically consistent in magnitude and significance for the main variable of interest, INCC news media coverage, thereby supporting the validity of the general statistical findings or at least the robustness of these different time-series specifications. The single exception to this general observation occurred for the child_ssri_pct analysis where the lagged DV coefficient was so strong (β=.98, p<.0001) that it greatly diminished the INCC coefficient in magnitude and significance, but even for that result the INCC coefficient was negative and not far from the 0.1 threshold *p-value* (see Table 5a).

Three noteworthy points are relevant to the time-trend adjustments. First, seasonal adjustments for the asthma/allergy and smoking cessation drugs both empirically demonstrated anticipated seasonal trends reported in the literature. That is, asthma/allergies drug use increased in spring and fall, and smoking cessation drug use declined in summer. These findings confirm the form of the regressions for the time-variant dimension of seasonality in a way that comports with what is known about asthma triggers and smoking behavior (Chandra & Chaloupka, 2003; Gardarsdottir et al., 2010), thereby suggesting that at least this component of the time-trend appears appropriate. Second, each set of multiple regressions tested the hypothesis that the INCC news effect might be far more short-lived than 49 to 50 months of each study period. Somewhat arbitrarily, a five month sum was used to test this news signal 'half-life' concern. The five month models (Models 1B to 7B) generally found similar results to cumulative news signal models, though the short-duration sum suggested a superior fit for the child_pcpAD_pct and varenicline models, thereby suggesting that these outcomes may be more susceptible to proximal rather than long-accumulating media signal. For the varenicline result, the short-duration impact may be tied to the fact that the warning concern overall was relatively low (compared to the

potential benefits of the medicine), and that the black box warning was nearly reversed by the FDA some years after it was issued (Yeh et al., 2016).

Main regression models for all four warnings included a warning time-interruption term (0 before, and 1 after), and inclusion of this term did not diminish the INCC effects observed, even as INCC coverage was certainly correlated to the warning (presumably because news activity follows FDA deliberations and more formal and definitive pronouncements). This suggests that the accumulating INCC news variable is a better predictor of pharmaceutical use outcomes than the point in time that the FDA officially promulgates a major warning. Having noted that, these observations do not mean that the warning per se was not important, but instead that its impact seemed to be more significantly captured and disseminated by news coverage. Moreover it must be noted that though the regressions relied on a binary term to characterize the warning using a simple "before-after" framework, review of the FDA *Medwatch* website reveals that each of the warnings actually were one of a more complex collection of multiple events which occurred over many months- including escalation/evolution of the FDA's opinion regarding each warning, external advisory committee deliberations/opinions, scientific journal reports, media coverage, and Congressional hearings. Though news signals often covers these events and may be a key source of such information for most persons, it remains possible that some of the signal received by doctors and consumers bypasses the news media altogether (see figure 1). One way to consider this would be to better identify sets of otherwise similar warnings where one was heavily covered by the news media, and the other was not. In a way that was accomplished here as the antidepressant and rosiglitazone warnings received relatively high media coverage (see figure 9) compared to the other two warnings studied. The problem is that these four warnings had many distinctions from one another besides the presence or absence of news coverage so

equivalent comparisons are not possible, other than to comment cautiously that all four warnings, irregardless of the amount of news coverage, appear to show at least subtle INCC news coverage effects.

The only other sensitivity analysis not yet discussed was that second order error terms were tested for each regression and were generally not significant. This result is taken to mean that more than a 1 month lagged of the error term is not significantly correlated to the DV. Yet not tested in this work were higher order lags for the independent variables because just the first lag was use as a predictor. Since, however, an accumulation of signal of at least 5 months composed the predictor, such additional lags are not likely to contribute much additional explanatory power to the model. For instantaneous event analysis, i.e., no assumed accumulation of news signal from one month to the next, such higher order independent variable lags may later prove to be useful in lieu of, or in conjunction with, the accumulation models described here.

Limitations

Non-news Sources of Health Information

As is the case with most scientific studies that rely on observational data, a key limitation to this work is the fact that "correlation is not causation." More specifically, in this case, it is plausible that the INCC observed news effects were merely correlated to declines in pharmaceutical use or diagnosis trends because other (i.e., non-traditional news) communication sources drove the behavioral change observed. Figure 1, a schematic for this work, proffers a simple listing of factors that may influence the prescription fill process. Notable forces depicted in that figure, but not included in the regressions presented, are communications from the FDA (typically via pharmaceutical firms) directly to physicians (Drake, 2008; Weatherby, Nordstrom,

Fife, & Walker, 2002), direct communications from pharmaceutical purveyors to patients (so-called “direct to consumer” advertising) (Kravitz & Bell, 2013; Kravitz et al., 2003; Kravitz et al., 2005; N. Ostrove, 2001), and non-professional news sources such as blogs (Talbot & Bergman, February 13, 2007; Wartella et al., 2016) and entertainment programming (e.g., The Daily Show, cinema) (Hoffner & Cohen, 2015).

As one example of correspondence directed to physicians, two waves of “Dear Doctor” letters were initiated by the FDA in 1995 and 1998 to caution prescribers about the use of the heartburn medication cisapride in conjunction with other medications. Such simultaneous use increased one’s risk for serious cardiac arrhythmias. The 1995 communications had no appreciable impact on reducing the risky prescription drug use, but the 1998 communications did reduce such prescribing by 66%, based on multiple regression analyses, after adjusting for significant age and secular time-trend effects. The authors noted that these letters directed to doctor were likely to have altered prescribing habits in the manner intended by the FDA, but only after the second mailing, which coincided with substantial media publicity. As was the case with the novel research presented in this dissertation, the research on cisapride could not disentangle the multiple streams of FDA warming dissemination.

Direct to consumer advertising signal was not quantified for this dissertation research, so it remains an untested component of the forces that certainly influenced consumer and doctor medication decisions. That signal could have been substantial. In 2001, an FDA official testified before the U.S. Congress that the agency tendered 32,000 promotional items (to potential patients and doctors, including video) from the pharmaceutical industry in that year alone (N. Ostrove, 2001). The FDA requires industry to submit such items for FDA review, though the timing and form of that review was not made clear in the Congressional testimony cited.

To consider the potential impact of non-traditional news sources on health care related behaviors, one need only look at the tremendous change the internet and smart phones have brought to the way information is generated and disseminated. Since the mid-2000s, traditional journalism, especially newspapers, has been challenged by fundamental alterations in its revenue, production, and dissemination streams; and these challenges have largely been precipitated by two now ubiquitous technological innovations- the world wide web and the smart phone (Talbot & Bergman, February 13, 2007). In recent comments to an academic audience, the current FDA Commissioner actually held aloft his smart phone and said: "Thanks to *this*, we can reach (just) about everyone."[18] A recent national survey study reported that 84% of U.S. teenagers said they obtain health information from online sources, far more than those stating TV news (9%) or newspapers (3%) as a source (Wartella et al., 2016). The researchers, however, did further note that only 25% of teenagers obtained "a lot" of health information from the internet, whereas 55% reported obtaining "a lot" form their parents. Accordingly, the internet's influence on health behaviors is certainly prominent, but at least for the moment, in concert with other sources which presumably include traditional news reporting.

Still, the FDA has taken direct interest in internet-based social media channels for their safety communications, with much of that interest focused on food-borne illness as well prescription drug use. Analysis presented by the FDA to their Risk Communication Advisory Committee in 2011 indicated social media tracking was then somewhat new for the agency (N. M. Ostrove, May 5, 2011). That analysis further suggested that social media "buzz" surrounding FDA notifications were often (>50% of time) "article/info sharing" communiqués, and presumably

[18] Fireside Chat with Robert Califf, MD Food and Drug Administration Commissioner , Friday, October 28, 2016 1-2 PM, Chevy Chase Bank Auditorium, The Johns Hopkins Hospital, sponsored by The Johns Hopkins Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health

some of those articles were from sources like the *New York Times* or *Washington Post*- common sources of news items analyzed for this thesis work. Other FDA analysis has indicated that social media use is expanding and leads to complex dissemination networks which typically peak and recede within days of an official announcement. Although such signal is dominated by blogs and "micro media" it also includes at least some traditional news references (Busse, May 5, 2011).

Popular culture references to health information, including pharmaceutical use, may also influence public perception and behavior regarding health care. An example of this type of influence is drawn from a recent survey among viewers of the popular television crime drama, "Monk." The program's protagonist is a police detective whose obsessive compulsive disorder (OCD) facilitates his superb attention to detail. A survey of "Monk" viewers reported that the television program reduced their negative stereotypes about persons with OCD and the treatments available to them (Hoffner & Cohen, 2015). The research presented in this thesis was not sensitive to fictional mass media content, unless it was described in a news article about such programming.

Some insight into non-traditional news dissemination of FDA warnings can be found in considering what types of scientific news receives coverage. Ideally, news coverage of FDA warnings is tied to the public interest and journalism's responsibility to convey information that is timely and useful. Certainly, by FDA prompting via press releases, warnings are often covered by the lay press (Kesselheim et al., 2015; Yong et al., 2009). It is also the case that pharmaceutical developments, like other scientific news (Anderson et al., 2012; Nisbet & Huge, 2006; Shih et al., 2008), may be covered because of dramatic events outside the sphere of the FDA which capture the attention of journalists and the public separate or in parallel with the FDA signal. This research does not differentiate between FDA to doctor and consumer signaling

and other events which may influence news signal and consumer outcomes. Accordingly, to the extent these other precipitators are influential, the news effects observed here may be over-stated (i.e., too high because of "positive omitted variable bias").

Personal Characteristics That Influence News Consumption and Behavioral Change

Another limitation of this work is that it did little to discern who received the media message and who, in particular, responded to it. A recent psychology-based review about how individuals seek and respond to reporting on scientific issues including health care concluded that a person's world view and general cognitive abilities influence both their attention and response to news signal. The researchers claim that these differential attention and response patterns explain why, for example, 67% of Republicans but only 20% of Democrats believe that news coverage of global warming is generally hyperbolic.

The research described in this dissertation sometimes focused on specific sub-populations, including incident cases of adults and children examined separately for the antidepressant warning, and Medicaid populations (i.e., low income) for the smoking cessation and asthma drug warning, but it did not explore whether these sub-populations specifically yielded different consumption of news (i.e., different exposure "doses") that led to different responses. The work presented here was based on the assumption that limited media effects would be discernible in the aggregated populations studied, even as certain sub-components of those populations likely consume and respond to news more than others (Wartella et al., 2016). As such, the effects observed may suffer from negative omitted variable bias (on the observed INCC effects) because it is likely, especially for obscure news, that many persons never receive the news media signal directly or otherwise. Indeed, two recent scientific studies regarding the antidepressant and

diabetes warnings studied in this thesis suggest that responses to a warning are influenced by disease severity and race. More specifically, one study found that children with mild forms of depression were more responsive to the SSRI warning than those with major depression- a result that suggests the warning appropriately attenuated suspect (i.e., likely non-indicated) use (Valluri et al., 2010). A second study found that blacks discontinued use of rosiglitazone more rapidly than whites when the warning for this medication was issued- the explanation offered for this behavior was that blacks were more distrustful of medical interventions at the outset (Qato, Trivedi, Mor, & Dore, 2016). Accordingly, it is plausible that the effects observed in this work would be clarified (and for some populations intensified) if race, disease severity, and other individual-level attributes were included in the statistical modeling.

Related to individual effects, it should be noted that all the analyses presented in this thesis relied on claims data, and thus it relied on payer records of filled prescriptions to define the dependent variable pertaining to use of the drug under study. Accordingly, the work did not capture potentially important factors that cloud the interpretation of results. For example, actual use of the drug may not occur with a filled prescription by the consumer (or only partial use may occur). Additionally, if a prescription is issued, but not filled, consumer use behavior will diverge from provider prescribing behavior (even though consumer use behavior is accurately reflected in filled prescriptions. The former phenomenon might be studied via a careful review of dose and re-fill records, as well as direct consumer surveys; and the latter by comparing electronic health records (kept by the clinician) to administrative records (kept by payers).

Deconstructing the Quality Measure

The “quality” measure for this research was based on content analyses that reduced five somewhat complex components (“who”, “what”, “evidence”, “costs-benefits”, “alternatives”)

into a single score ranging from 0 to 5, low to high quality, respectively. Generally, this score was low (<2 total quality units per month) and non-predictive of the outcomes studied. The fact that such details did not generally intensify consumer response is counter-hypothetical to the research expectations put forth, though an alternative explanation is possible. Perhaps more informative articles (i.e., higher quality articles) about the warnings conveyed greater uncertainty or confusion than less informative ones, thereby inhibiting consumer disruptions or rejection of a therapy in the face of its potential benefits. Whatever the case, the mostly non-significant results obtained suggest that deconstruction of quality rating may help discern more precise effects of article quality on consumer response outcomes. For example, comprehensive descriptions of alternative (i.e., substitutes) alone may promote reductions in use of the therapy subject to a warning. As another example, it is plausible that the presence of a cost-benefit description is not sufficient to predict the direction of a consumer response. Instead, a cost-benefit argument made in each news item must be rated as tilting in favor or against the warning, and then the effect of such article content, specifically, should be considered. As this thesis research currently stands, these types of coding constructs may have been too conflated and thus too non-specific to yield significant findings in the directions hypothesized.

Policy Implications

The results of this investigation suggest that lagged (i.e., prior), accumulating, news media coverage may have had a significant effect on consumer response to FDA warnings regarding the post-market status of prescription medications across four distinct therapeutic classes. What remains unclear is 1) how these apparent news effects compare to other communication vectors used by the FDA and other entities influencing prescription drug use behavior, and 2) how news coverage itself may be influenced by prior precipitating events. The latter point reminds us that

news coverage is not a random occurrence and that understanding the role of news coverage in affecting consumer or provider behavior often requires inquiry into the context and events that precipitate such coverage.

Still, this work suggests that "press releases" and other efforts to disseminate technical health announcements via the news media are important communication lines for the agency. It also suggests that absent considerable controversy (as was the case for the antidepressant and diabetes drug warnings), traditional and professional press coverage surrounding a post-marketing concern may be quite sparse (Figure 9).

Finally, the quality ratings observed with this research suggests that when coverage occurs, it is typically incomplete in reporting basic information about the warning. This means that the FDA should monitor news coverage for issues of on-going interest, and consider responding to that coverage to re-shape or intensify the signal that reaches the public. More importantly, one needs to attend to the possibility that coverage may provoke inappropriate responses among consumer and/or prescribers.

John Kingdon's seminal work on federal policy-making included a specific, albeit short, section on the news media's role (Kingdon, 2003). Based on his scholarly experience and the interviews he conducted regarding the genesis of federal transportation and health care legislation, Professor Kingdon acknowledged that the news media had an agenda setting role, but he also noted that its influence was limited and that news coverage often came late in the policy process, or 'after the fact'. The scientific community seems to have a similar mixed and often negative feelings about the contribution and quality of mainstream news media as a source of health news (Cassels et al., 2003; Coleman, Hartley, & Kannemer, 2006; Comis, 2015; Klotz &

Ceccoli, 2005; Nelkin, 1996; Schwitzer, 2003, 2004). This dissertation research has attempted to quantify the extent to which mainstream news coverage is relevant to the dissemination of federal messaging about technical and circumscribed health issues. With a relatively simple framework presented here, it does seem that news coverage matters, or at least that it appears to impart significant impacts regarding outcomes related to FDA warnings.

Future Directions

The work presented in this thesis could be logically extended in at least four ways. First, future work could include some variables that quantifies other factors influencing the broad prescribing endeavor, such as repeated/evolving FDA responses to scientific journal publications, or the volume and frequency of FDA "Dear Doctor" letters regarding a drug concern; and then test whether these additional variables 1) enhance (or detract from) the effects between news coverage and consumer response or 2) have important indirect effects on consumer response by influencing subsequent news coverage. Second, the use of individual level data or data that further stratifies the populations into those heterogeneous in their exposure and response to news coverage could further support or refute the hypothesis that news coverage is "causal" regarding consumer behavior, rather than merely correlative. Third, future work should expand the outcomes studied to those that address some of the more nuanced suggestions of FDA post-marketing warnings, such as increased clinical monitoring or decreased concomitant prescribing, rather than the more marginal and severe response of complete drug discontinuation (Morrato et al., 2008; Morrato et al., 2009; Morrato, Nicol et al., 2010; Weatherby et al., 2002). And finally, the addition of more warnings to the mix of those studied is necessary to consider case-by-case idiosyncrasies of each, as well as to generalize effects across the thousands of pharmaceuticals the FDA must regulate. It is plausible with such work that patterns will emerge which characterize more specifically "when" and "how much" news media matters for such warning dissemination.

Appendix

Code book for rating news content

1. **SSRIs (e.g., Prozac)** (for depression, anxiety, obsessions)- warning: suicidal ideation

1a. ***General narrative about drug and warning***

When: October 27, 2003

Who: Children and adolescents (0-18 years of age) taking SSRIs (selective serotonin reuptake inhibitors) and paroxetine (Brand: Paxil) especially, and those taking such drugs for the first time. Other SSRIS are sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox).

What: Suicidal ideation, that is, feelings or consideration of suicide rather than actions exclusively. Stated another way, this warning is inclusive of the ideation, not just of an actual attempt to do self harm or takes one's life.

Evidence: FDA data review, adverse event reports.

Cost Benefit: Depression itself can lead to suicide, and separate from that depression is debilitating including symptoms such as extreme fatigue, anxiety, sadness, negativity which are all themselves quite impairing impacting on one's productivity (school performance) and social life (making and keeping friends). SSRIs have side-effects outside of suicidality, they also cost money, and they may impact negativity on the development of the child and adolescent brain (though such effects are presently unknown).

Alternatives: Talk therapies, psychotherapies; placebo and non-treatment; Prozac is the only drug approved by the FDA for use in children and adolescents; better patient monitoring. Tricyclic antidepressants (e.g., Anafranil, Lomont, Pamelor) (older drug compared to SSRIs) can sometimes be effective, though they are infrequently used because their side-effects profile is generally worse than SSRI. Atypical antipsychotics are also sometimes use, but again the side-effects are a concern, especially weight gain.

1b. ***Notations regarding article selection***

Articles are consider to be appropriate for review if they appear in well-known, English lay publications such as the *New York Times*, and even some foreign sources like *The Economist* of the London Times. Excluded are trade publications such as Psychiatric Times, and Practitioner, as well as congressional testimony, and market disclosure conference calls. TV and radio shows targeting general news audiences are included such as National Public Radio, CNN news, and CBS radio.

Selected content is only to be reviewed if it addresses medical treatment for depression (or other related illness (anxiety, and even things like menopause or neuropathic pain) that includes medications. Accordingly, a story is not to be retained if it only says something like, "He became depressed because his career was not progressing well," and then offered nothing indicating any medical (i.e., pharmacologic or other interventions like talk therapy, and even something like ECT in rare cases) treatment to address that depression.

Calendar/announcement entries for depression classes (i.e., depression/anxiety coping or educational classes or groups) in newspapers are not to be included.

Truncated telecasts or radio broadcasts are only retained if they appear to reflect the full report regarding depression treatment.

If the drug is used to treat other indications (such as bipolar, anxiety, menopause symptoms like hot flashes, or nerve pain), then include.

1c. ***Key field coding details (follow spreadsheet)***

Who: If the article emphasizes children and adolescents taking SSRI (selective serotonin reuptake inhibitors, a.k.a., second generation antidepressants), and those taking the drug for the first time, then **code as 1.0** If only some of those details are expressed then **code as 0.5**. If none are expressed then **code as 0.0**. SSRI drugs include the following: Prozac (fluoxetine) and Paxil, but there are others. One should note here that adults were not originally the subject of the warning, youths were- so the warning should indicate that in some way. If all users or adults only are the target of the discourse in the article without mention of the child warning, then the rating should tend downwards.

What: If suicidal ideation is noted and explained/characterized as "feelings" or "thoughts" of suicide rather than actions toward taking one's life, and if actual suicide behavior is noted as very rare, then **code as 1.0**; if suicide (i.e., the act of taking one's own life, or of making such an attempt) is directly suggested as the main side-effect and/or if it is suggested to be a common side-effect, then **code as 0.0**. Intermediate characterization is to be **coded as 0.5**. If homicidal, or strange (i.e., psychotic) behaviors are suggested as the only side-effects, then code as 0.0.

Evidence: Mention of randomized control trials and the FDA study, then **code as 1.0** especially if actual magnitudes are given (i.e., the number of youths who felt suicidal

among all youths tested), rather than adjusted-odds, then tend towards an increased rating. In the absence of randomized control trial or of the FDA study mention, **tend towards coding as 0.0**. If there is only a vague mention of such scientific studies with only mention of anecdotes of children reacting negatively to the medication then **code as 0.0.** If vague mention of scientific studies, with differentiating between randomized and other studies, then **code as 0.5. If multiple scientific studies are mentioned without mention of randomized control studies then a coding of 0.5 is acceptable.**

Cost-benefit: If the benefits and well-established safety of SSRI antidepressants, and risks of untreated depression are not noted then **code as 0.0**; if they are clearly stated then **code as 1.0**. For intermediate mention of these cost-benefit issues, **code as 0.5**.

Alternatives: If psychotherapy (i.e., talk therapy) is mentioned then **code as 1.0**. If the only "other therapies" mentioned are other drugs (for example, SSNRIs) are mentioned without mention of psychotherapy then **code as 0.5**. If no alternatives to SSRIs are mentioned then **code as 0.0**. If other therapies such as meditation, ECT, rest/time, placebo, are noted as potential treatments for depression then tend towards increasing the score (from 0 to 0.5 or from 0.5 to 1.0).

2. **Rosiglitazone (Brand: Avandia)** (for diabetes)- warning: cardiovascular issues

2a. ***General narrative about drug and warning***

When: May 21, 2007

Who: All persons using Avandia to control their Type 2 (acquired) diabetes, but particular risk for those taking nitrates and insulin as well. Those with a history of heart failure and myocardial infarction (heart attack) at heightened risk as well.

What: Ischemia (inadequate blood supply to an organ, especially the heart, i.e., a heart attack). Congestive heart failure (the heart is unable to maintain adequate circulation) can result.

Increased risk odds ratio of 1.43 (43% increased risk), with no increased risk of death.

Evidence: 2004 American Diabetes Association (ADA). Two meta-analyses from May 2007- one high profile study a review of 42 published reports (Nissen and Wolski), the other being a review of manufacturers data. In July an FDA oversight committee met to review the evidence and supported the warning, but noted that the benefit-to-cost ratio of use of the drug still was favorable. On August 14, 2007 a new warning was released which referred to the Nissen and Wolski study, but noted it was short duration (6 months) and other longer duration (42 months) had not replicated the findings.

Cost-Benefit: Diabetes uncontrolled carries many risks including loss of limbs and vision (because of nerve failure), cardiovascular (heart attack and stroke), and kidney disease (leading to the need for dialysis and transplant).

Alternatives: Diet and exercise. Smoking cessation reduces overall risk of complications. Rosiglitazone is second-line therapy for diabetes, AFTER other drugs or remedies such as diet and exercise change have been tried. Should note that pioglitazone (Brand: ACTOS, same class as Avandia) is an alternative and sitigliptin (Januvia, alternative class) as well are substitutes in the second line (e.g., metformin).

2b. ***Notations regarding article selection***

Articles are consider to be appropriate for review if they appear in well-known, English lay publications such as the *New York Times*, and even some foreign sources like *The Economist* of the London Times. Excluded are trade publications such as *Community Pharmacy*, *Practitioner*, *Nursing Times*, *Australian Doctor*, GP magazine, as well as congressional testimony, and market disclosure conference calls. TV and radio shows targeting general news audiences are included such as National Public Radio, CNN news, and CBS radio.

Selected content is only to be reviewed if it addresses medical treatment for diabetes that includes some mention of medications. Accordingly, a story is not to be retained if it only says something like, "She developed diabetes after years of working in a fast food restaurant …," or "diabetes and smoking increase one's risk for premature death…", and then offered nothing indicating any medical or other specific treatments (e.g., exercise and diet) to address that illness.

Calendar/announcement entries for diabetes management classes in newspapers not included.

Truncated telecasts or radio broadcasts are only retained if they appear to reflect the full report regarding diabetes treatment.

2c. ***Key field coding details (follow spreadsheet)***

Who: a. Persons using Avandia (Rosiglitazone) to control their type 2 (acquired) diabetes. b. Those taking nitrates and insulin particularly at risk. c. Persons with history of heart disease are also at increased risk. If just one of the 3 points below is made, **score**

as 0.5, if the 2 or 3 of these points are made **score as 1.0**. Alternatively, if none of these points are made **score as 0.0**.

What: a. Coronary heart failure, b. Heart attack (ischemia), c. 30-40 percent increase in that heart attack risk, d. Drug-drug interaction a problem with nitrates and insulin. If all four of these points are made then tend towards a **score of 1.0**. If none are made then **score as 0.0**. Intermediate reference to these points should place the **score at 0.5**.

Evidence: a. The 42 study meta-analysis (Nissen and Wolski). A meta-analysis is a scientific combining of information from different studies. b. confirmation by industry; c. FDA advisory committee review and agreement, and d. short-term studies, mostly. If 3-4 of these points are made, then **code as 1.0**; if just 2 of 4 are made then **code as 0.5**; if none are made then **code as 0.0**. Tend to increase score if American Diabetes Association (ADA) consensus statement is noted (from 2004).

Cost-benefit: If it is noted that the FDA advisory committee determined the benefit-cost risk profile (i.e., trade-offs) favorable for continued use, and if they list some of the many serious complications of diabetes (heart/circulatory problems, kidney problems, lost vision, loss of limbs), then **score as 1.0**. If they don't refer to both of these points, but to just one, then **score as 0.5**. If they refer to neither then **score as 0.0**.

Alternatives: Should note Rosiglitazone as second line therapy for diabetes, AFTER other drugs or remedies such as diet and exercise change have been tried, if they do not note this then **score as <1.0**. Should note that pioglitazone (same class) is an alternative and sitigliptin (new class) as well are substitutes in the second line (after metformin a first line therapy). If these above two point are noted only then **score as 0.5**. If good diet

and exercise are added to the description then **score as 1.0**. If none of these points are made then **score as 0.0**.

3. **Varenicline (Chantix)** (for smoking cessation)- warning: irritability, suicidal ideation

3a. ***General narrative about drug and warning***

When: July 1, 2009

Who: Anyone taking these drugs for smoking cessation, especially those initiating (i.e., those beginning the drug for the first time or for a new episode of care); and including those without a history of neuropsychiatric disease. Symptoms can persist after cessation of Chantix.

What: Serious neuropsychiatric concerns including: changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts. Previous warnings from 2008 cautioned about vivid dreams and dangers of operating heavy equipment while on Chantix.

Evidence: Adverse event reports made to and tracked by the FDA. Nicotine withdrawal (absent use of Chantix) increases neuropsychiatric effects noted above.

Cost Benefit: Smoking shortens life as a result of increased cardiovascular, lung, and other disease. Smoking further has same effects on persons near the smoker (i.e., second-hand smoke effects are similar). Medication is new and costly. FDA advisory committee determined benefits of drug to be strong relative to costs (risks) of use.

Alternatives: Nicotine patches, psychotherapy, buproprion (Zyban, also subject to warning), nicotine gum. The rater can assume that these alternatives do not carry the

same neuropsychiatric risks as Chantix, but that should not alter one's rating of their mention as alternatives, though it might shift the cost-benefit presentation if it is well articulated that all treatments have side-effects which are as serious as the one ascribed to Chantix.

3b. ***Notations regarding article selection***

Articles are consider to be appropriate for review if they appear in well-known, English lay publications such as the *New York Times*, and even some foreign sources like *The Economist* of the *London Times*. Excluded are trade publications such as *Community Pharmacy*, and *Practitioner*, as well as congressional testimony, and market disclosure conference calls. TV and radio shows targeting general news audiences are included such as National Public Radio, CNN news, and CBS radio.

Selected content is only to be reviewed if it addresses medical treatment for diabetes that includes some mention of medications. Accordingly, a story is not to be retained if it only says something like, "smoking was common on Hollywood sets of the 1950s, but essentially non-existent now," and then offered nothing indicating any medical or other specific treatments that led to the reductions in smoking. Moreover, many articles selected via word searches use "smoking" or "smoke" as an adjective or noun which has nothing to do with tobacco use, such as "smoking gun", or "smoke from a large forest fire," are to be ignored if they are absent other direct references to tobacco use and treatment.

Calendar/announcement entries for smoking cessation classes in newspapers are not to be included.

Truncated telecasts or radio broadcasts are only retained if they appear to reflect the full report regarding smoking treatment.

If the drug is used to treat other indications (such as alcohol or other drug addiction), then include.

3c. ***Key field coding details (follow spreadsheet)***

Who: If any smokers using drug is mentioned, including those with or without psychiatric history, and especially those initiating are mentioned then **score as 1.0**, else **score as 0.5** if any users are noted, or **0.0** if none of these points are made. If they also note that stopping the drug does not necessarily lead to stoppage of symptoms, then tend to increase the score (from 0.0 to 0.5; or from 0.5-1.0).

What: If nearly all of these potential symptoms are noted (changes in behavior, hostility, agitation, depressed mood, suicidal thoughts) then **score ≥0.5**. If the article further notes that previous warnings (from 2008) indicated vivid dreams and dangers operating heavy machinery, then **score as a 1.0.** Alternatively, **score as 1.0** if they note most of the symptoms and they further note these same constellation of symptoms can be the result of tobacco withdrawal. Score as 0.0 if none of these items are mentioned.

Evidence: If they note that concern is based on Adverse Event Reporting System (AERS) maintained and monitored by the FDA, and if they describe clinical studies and mention randomized control trials, then **score as 1.0**. If they report absolute magnitudes, i.e., 200 people in 100,000 users, then tend towards a higher score, than if they give relative risks or percent increases in risks. In the absence of quantitative data the highest rating is likely to be 0.5, but only if they note studies by the FDA or other scientists. For

example, if that a randomized control trial indicated strong evidence that …. or that adverse event reports from FDA suggest… then it can be scored as 0.5. If they language is very strong regarding randomized files showing large and definitive effects in one direction or another then even absent an effect size it may be rated as 1.0 assuming they also described how an RCT is a standard trial type.

Cost-benefit: Here, to score 1.0, they must describe several of the many adverse effects of smoking: lung and other cancers and lung disease, heart disease including high blood pressure. A **score of 1.0** would further be obtained if they compare the risks of smoking to those of using Chantix (i.e., very high versus very low, respectively). If only moderate levels of such description exists, then **score as 0.5**, otherwise if no such description exists then **score as 0.0**.

Alternatives: If most or all of the following alternatives to Chantix use are noted then **score as 1.0:** nicotine replacement gum, patches, e-cigs since 2004 (though this latter item has not been tested scientifically), lozenges and liquids also less commonly available, and psychotherapy (talk therapy, hypnosis). If few of these are mentioned then **score as 0.5**. If no alternatives for smoking cessation are mentioned then **score as 0.0**. If "cold turkey" is mentioned, i.e., quitting without any medical support, tend to score the rating slightly higher than otherwise (i.e., if you are scoring as 0.0, then consider scorings as 0.5 if there is other reason to do so).

4. **<u>Leukotriene inhibitors</u> Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR)** (for asthma) warning: neuropsychiatric issues

4a. ***General narrative about drug and warning***

<u>When</u>: June 2009

<u>Who</u>: Children or adults (i.e., anyone) taking these drugs for asthma or rhinitis (stuffy, runny nose)

<u>What</u>: Precaution update, concerns about various neuropsychiatric symptoms such as agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior (including suicide), and tremor.

<u>Evidence</u>: well below 1% risk according to clinical trials data. The problem apparently was discovered by reviewing adverse event report data maintained by the FDA.

<u>Cost Benefit</u>: Asthma crises (severe difficulty breathing) are debilitating, even life threatening. Their occurrence is highly disruptive to daily functioning, and typically can result in an emergency room visit, or a hospitalization.

<u>Alternatives</u>: other containment medications exist, strategies to minimize in-home pathogens (dust, insect and other vermin, pet hair), avoiding exposure to high humidity, mold. Generally, this is about "containment medications", but if "rescue" medication are mentioned then tend towards higher scores if other factors suggest such increase in score is warranted.

4b. ***Notations regarding article selection***

Articles are consider to be appropriate for review if they appear in well-known, English lay publications such as the *New York Times*, and even some foreign sources like *The Economist* of the *London Times*. Excluded are trade publications such as *Community Pharmacy*, and *Practitioner*, as well as congressional testimony, and market disclosure conference calls. TV and radio shows targeting general news audiences are included such as National Public Radio, CNN news, and CBS radio.

Selected content is only to be reviewed if it addresses medical treatment for asthma or rhinitis that includes some mention of medications. Accordingly, a story is not to be retained if it only says something like, "in addition to be slightly overweight, he was also asthmatic, so he couldn't run very fast…" , and then offered nothing indicating any medical or other specific treatments to address illness (e.g., avoidance of allergens).

Calendar entries for asthma management classes in newspapers are not to be included.

Truncated telecasts or radio broadcasts are only retained if they appear to reflect the full report regarding asthma treatment.

4c. ***Key field coding details (follow spreadsheet)***

Who: Children or adults taking Singulair (Montelukast) or other leukotriene inhibitors: Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR) for asthma (mainly), and sometimes for simple rhinitis (runny nose). If all of these points are made, then tend towards **score of 1.0**. If only asthma is noted, or only Singulair is cited as target of warning then **score as 0.5**. If no such details are given then **score as 0.0**.

What: If they note it as a precaution update for various symptoms including: agitation, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior, and tremor, and they include most of these points **score as a 1.0**. If they include less than half of these points then **score as a 0.5**. If they do not mention these concerns then **score as 0.0**. If depression is included along with at least 3 others, then tend towards a higher rating.

Evidence: If they note the risk is way below 1% of users according to clinical trials from industry, and if they further note the concern is tied largely to review of an FDA request to industry collected adverse event data, then **score as a 1.0**. If they do not state all of these details, but some, then **score as 0.5**. If they fail to mention any of this evidence, then score as 0.0. If they give specific absolute numbers, i.e., there were X total bad reactions out of Y total users, then score higher than if they give percent increase in risk (i.e., if they only give a number without a denominator).

Cost-benefit: Absent clear description of benefits of leukotriene inhibitors over risks of asthma **score as 0.5** if they talk at all about negative impacts of asthma, and importance of controlling it. If no mention of cost-benefit (i.e., tradeoffs of medication use versus asthma risk), then **score as 0.0**. If the cost-benefit discourse is very detailed, then **score as 1.0**.

Alternatives: If they mention or describe that there are many alternative long-term control medications (inhaled corticosteroids, Cromolyn, Omalizumab, inhaled long-acting $beta_2$-agonists, theophylline) for asthma including rescue medications, and if they mention in-home abatement work (cleaning) like HEPA filters, as well as avoidance of allergens and other was to mitigate asthma exacerbation then **score as 1.0**. If they only

mention one of these points then **score as 0.5**. Otherwise**, score as 0.0**. Generally, this is about "containment medications", but if "rescue" medication are mentioned then tend towards higher scores if other factors suggest such increase in score is warranted.

General information/notation that pertains to all 4 warnings

If the number in the random look-up sheet does not match any number or item in the actual document with the articles, note it as "not used-not in series". If the Time Magazine article cannot be found then state it as "not used-not found".

For the other news coverage item (column F on rating spreadsheet): a "yes" must correspond to other lay news coverage, not to reporting on a scientific publication.

If article is about developing treatments (i.e., new and yet untested or unapproved technologies) and makes absolutely no mention of *existing* treatments, then do not rate the article, it should be classified simply as "not used-not diabetes tx" or "not used-not depression tx", etc.

Notations that emerged during coding training:

*Mention of an illness as a risk factor for something else is not sufficient to include the article as relevant (rate-able). For example, if it is noted that smoking increases one's risk for another condition and the article only talks about treatments for that other condition and not treatments to cease smoking, then exclude the article from consideration.

**For transcripts of broadcasts, assume that truncations (which would lead to exclusion of the item from rating) only occur at the end of the article (i.e., the beginning of the article can be assumed to be complete).

***In selecting articles about “medical treatments” for the warning in question, note that reference to such treatments can be quite brief. For example, if an article only once refers to the disease in question (e.g., asthma), and only by noting that asthma drugs interact with other drugs, then score the article.

****regarding evidence, if credible experts are cited or quoted, then it is possible to score as 0.5, but not above that unless those experts or the text otherwise explicitly cite data from RTC or other clearly noted scientific study.

*****”Orientation” ratings on spreadsheet are to be explicitly tied to the warning. (Whereas, the anecdotal valence, is not necessarily tied to the warning).

****** If it is not clear if an article is a lead or on front page, then score as “n/a”, which in this case means not available.

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