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IMPACT OF FDA DRUG RISK COMMUNICATIONS ON HEALTH CARE UTILIZATION AND HEALTH BEHAVIORS: A SYSTEMATIC REVIEW

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Abstract

Objective—To review literature on the impact of FDA drug risk communications on medication utilization, health care services use, and health outcomes.

Data Sources—The authors searched MEDLINE and the Web of Science for manuscripts published between January 1990 and November 2010 that included terms related to drug utilization, the FDA, and advisories or warnings. We manually searched bibliographies and works citing selected articles and consulted with experts to guide study selection.

Study Selection—Studies were included if they involved an empirical analysis evaluating the impact of an FDA risk communication.

Data Extraction—We extracted the drug(s) analyzed, relevant FDA communication(s), data source, analytical method, and main outcome(s) assessed.

Results—Of the 1432 records screened, 49 studies were included. These studies covered sixteen medicines or therapeutic classes; one-third examined communications regarding antidepressants. Most used medical or pharmacy claims and few rigorously examined patient-provider communication, decision-making or risk perceptions. Advisories recommending increased clinical or laboratory monitoring generally led to decreased drug use, but only transient and modestly increased monitoring. Communications targeting specific subpopulations often spilled over to other groups. Repeated or sequential advisories tended to have larger but delayed effects and decreased incident more than prevalent use. Drug-specific warnings were associated with particularly large decreases in utilization, though the magnitude of substitution within therapeutic classes varied across clinical contexts.

Conclusions—While some FDA drug risk communications had immediate, strong impacts, many had either delayed or no impact on health care utilization or health behaviors. These data demonstrate the complexity of using risk communication to improve the quality and safety of

prescription drug use, and suggest the importance of continued assessments of the effect of future advisories and label changes. Identifying factors that are associated with rapid and sustained responses to risk communications will be important for informing future risk communication efforts.

INTRODUCTION

The Food and Drug Administration (FDA) is responsible for protecting the public by ensuring the safety of prescription drugs. However, new safety information often emerges after drug approval, requiring the FDA to systematically evaluate and respond to new evidence about drug safety as it accumulates. This authority increased with the passage of the 2007 FDA Amendments Act (FDAAA) (1).

After identifying a new safety concern, the FDA must decide how to effectively communicate this risk information to the general public and providers (2). These communications range from minor revisions to the drug's label to major safety advisories. Historically the FDA has communicated such risks through a combination of methods, including "Public Health Advisories" and "Safety Alerts" directed to the general public (referred to as "advisories" throughout), or "Dear Healthcare Provider" letters directed to prescribers. Additionally, the FDA may modify the drug label by including a "Black Box warning" when risks are particularly severe (3). During the past two decades the Agency has used these methods to communicate hundreds of drug risks discovered after market approval (4).

Risk communication is a complex science (5–8) and understanding the intended and unintended outcomes from prior FDA advisories and label warnings may help to guide future risk communication. We sought to summarize the current literature regarding the impact of FDA risk communications on utilization of drugs, use of other health care services, and health outcomes.

METHODS

Data Sources and Searches

We searched MEDLINE (via PubMed) and Web of Science (Thomson Reuters) for relevant studies published between January 1, 1990 and November 10, 2010. A series of MeSH headings were specified to identify terms related to each concept: (1) drug utilization, (2) the FDA, and (3) advisories or warnings (Appendix). Each search string was executed in PubMed and the three completed searches were combined after excluding duplicated records. A similar search was executed in the Web of Science and results from both searches were combined.

Study selection

Our systematic search identified 1,432 non-duplicated articles for review (Figure 1). We included manuscripts that analyzed empirical data on the impact of FDA risk communications on healthcare utilization or health behaviors. We defined risk communication as activities used to inform the public or healthcare providers of a medical product's risk. We excluded letters to editors, commentaries, news articles, and studies of populations or advisories issued by regulatory authorities outside of the United States. We also excluded articles evaluating the impact of risk management plans, market withdrawal, studies of non-drug medical products or devices, and those whose primary focus was not an assessment of an Agency communication.

Using these criteria, one investigator (AH) and a research assistant (MY) independently evaluated articles retrieved through the search strategy, reference lists of selected articles, and articles citing included studies. There was 98% agreement between the reviewers regarding article selection ($\kappa=.73$, 95% confidence intervals .63–.83). A second author (GCA) evaluated the 26 articles where disagreement was present; 20 were excluded. Forty-nine studies were selected for inclusion.

Data Extraction and Synthesis

Our primary goal was to synthesize information about the effect of FDA advisories across the studies identified. To do so, we categorized studies into one of four non-mutually exclusive groups based on whether the study examined Agency recommendations regarding: (1) avoiding co-prescribing due to drug-drug interactions; (2) avoidance of use among a subpopulation; or (3) general caution regarding a product. We reasoned that this categorization might provide a useful taxonomy for considering the intended and potential unintended consequences of FDA communications (Figure 2). Given the distinct nature of studies based on surveys or qualitative methods, we examined these investigations separately.

In addition to extracting details of the primary outcomes studied, we also identified the drug(s) analyzed, type(s) of FDA communication assessed, data source, analytic method, and any secondary outcomes assessed. We categorized outcomes into one of six groups: (1) utilization or dispensing of the targeted drug or therapeutic class, (2) use of substitutes for the targeted drug or drug class, (3) spillover effects, such as a communication targeting children impacting adults, (4) diagnoses and non-prescription utilization, (5) health behaviors and health outcomes (e.g., glycemic control), and (6) patient or physician knowledge, attitudes or beliefs regarding risk communication messages (9).

RESULTS

Drugs or therapeutic areas, data sources, and statistical methods

Tables 1 and 2 characterize the 16 drugs or classes examined and provide an example of the types of FDA communications studied.

The studies utilized a variety of data sources including: medical or pharmacy claims, surveys, medical records, prescribing audits, focus groups, and vital statistics (Table 3). Sample size and composition varied widely; from a focus group of 35 health professionals (10) to a retrospective analysis of nearly 800,000 privately insured patients' health claims (11). Statistical methods also varied widely and many studies used multiple methods. Twelve studies (24%) employed time series analyses, 17 (35%) used other types of regression, 11 (22%) used descriptive statistics alone, and 9 (18%) used other means of analysis such as Pearson's chi-square test. The most common outcomes assessed were use of the targeted drug or drug class (40 studies), changes in diagnosis and non-prescription utilization (18 studies), and changes in substitute use (18 studies) (Table 4).

Recommendation for increased laboratory or clinical monitoring

Assessments of the impact of FDA recommendations on laboratory or clinical monitoring included studies of glucose testing for patients taking atypical antipsychotics (12,13), liver enzyme monitoring for patients taking troglitazone (14,15) or pemoline (16), and increased follow-up visits for patients taking antidepressants (17–19). Of studies that assessed laboratory monitoring, there was no evidence of a large or sustained impact of the FDA recommendations. For example, rates of glucose testing among patients taking antipsychotics were unchanged following the FDA's recommendation to monitor patients

for hyperlipidemia and diabetes (12,13). Rates of liver enzyme monitoring following a black-box warning for troglitazone were low prior the first FDA advisory, increased modestly over subsequent advisories, and waned over time (14,15), ultimately contributing to market withdrawal. Recommendations to increase clinical monitoring also appeared to have little impact on clinical practice (17–19).

Recommendations against co-prescribing due to drug-drug interactions

Studies of co-prescribing focused on drug-drug interactions related to three therapies: cisapride, terfenadine, and tramadol. Most studies suggested that although clinical practice is slow to respond to such warnings, often taking months to years, inappropriate co-prescribing decreases over time. For example, several studies suggested the largest declines in cisapride co-prescribing occurred following the FDA's third such warning (20–23), although not all studies indicated such a change (24). Declines in terfenadine co-prescribing also occurred although the largest effects were not observed until 18 months or more following the initial warnings (25–27). Only one study concluded there was an increase in terfenadine co-prescribing between 1991 and 1992, although the authors examined absolute rather than relative co-prescribing events (28). Finally, a study of tramadol found a non-significant change in co-prescribing following an FDA warning, although the observed trend suggested that co-prescribing decreased (29).

Recommendations against use in patient subpopulation

Several studies examined communications cautioning use of a medicine or therapeutic class among a patient subpopulation, including over-the-counter [OTC] cough medicines and promethazine among children under 2 years of age, antidepressants among children and adolescents, angiotensin-converting enzyme [ACE] inhibitors among pregnant women, telithromycin among patients with myasthenia gravis, and antipsychotics among the elderly with dementia or those with or high risk of diabetes or metabolic syndrome.

Most, but not all (30, 31), investigations focused on changes in utilization among the subpopulation as well as spillover effects whereby non-targeted populations may have been impacted. For example, between January 2006 and February 2007 the FDA issued a series of communications contraindicating telithromycin use in patients with myasthenia gravis, and removing indications for bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis. Claims for telithromycin from a large commercial insurer dropped by 80% between January 2006 and February 2007, while the proportion of all telithromycin prescribed for revoked indications was similar before and after the label change (32). A nationally representative physician audit identified substantial decreases in atypical antipsychotic use among elderly with dementia following an April 2005 black box warning that were accompanied by more modest decreases in use among those without dementia and for FDA-approved indications (33). ACE inhibitor exposure among pregnant women in Medicaid from 1986–2003 appeared to increase four-fold, with no decrease following the FDA's warning (31).

Most studies of FDA communications targeting a subpopulation have focused on a series of FDA communications about antidepressant use among children and adolescents that were issued between June 2003 and October 2004. Most evidence suggests there were substantial decreases in prescribing among children (11,18,34–39) with more modest decreases among adults (34,36). The antidepressant advisories also had a variety of other effects, such as shifts in the market share accounted for by paroxetine, fluoxetine and escitalopram(40), a shift away from diagnoses from primary care physicians (11,34,41), and a lack of non-antidepressant drug substitution (11,34,38,41,42). There is mixed evidence as to whether there were changes in psychotherapy utilization rates among children (11,18,41,43). Little is

known regarding the health outcomes associated with these advisories, although the single study examining the relationship between antidepressant warnings and suicides among youth in the U.S. and the Netherlands found that suicide rates increased following declines in prescribing (44).

Serious Adverse Event Warnings Recommending Cautious Use of Product

A final series of communications have related a general safety concern regarding a drug or therapeutic class without emphasis regarding specific monitoring schedules, co-medication use, or avoidance in select subpopulations. Investigations have examined settings including topical calcineurin inhibitors, depo-provera, droperidol, long-acting beta-agonists (LABAs) and glitazones. The response to these communications has varied considerably. A study of droperidol saw a significant decrease of use following the December 2001 black box warning, accompanied by an even greater increase in use of ondansetron, a known substitute (45). Studies examining the use of LABAs among patients with asthma suggested infrequent controller use (e.g., inhaled corticosteroids) among individuals prior to their receiving a LABA, and neither investigation suggested large changes in rates of controller use following the FDA warnings (46,47). By contrast, studies of rosiglitazone and pioglitazone following a May 2007 (rosiglitazone) and August 2007 (classwide) advisory identified significant decreases in rosiglitazone use (48–51) with stable pioglitazone prescribing (48) and significant increases in use of other anti-diabetes drugs (51).

Parental and provider attitudes and beliefs regarding communications

Of the 49 studies included in the systematic review, 8 studies used surveys and 1 used focus groups in order to examine parental or provider attitudes, beliefs, or experiences regarding FDA communications about a drug or therapeutic class. These analyses suggested high levels of provider awareness regarding general communications or labeling changes (10,52,53), though lower levels of awareness of specific recommended monitoring schedules in the case of antidepressants (10,52). Provider agreement with the content of the communication was high in the case of OTC cough and cold treatments among young children (54) and much lower in the case of LABAs (53), droperidol (55,56), and recommendations for monitoring patients taking antiepileptic drugs (19). In the only study examining parental attitudes and beliefs, the majority of respondents, though aware of the 2008 advisory regarding OTC cough and cold treatments, did not believe the products were potentially dangerous (54).

Study quality

Many of the nine survey-based or qualitative studies examining providers' and patients' knowledge, attitudes, and beliefs were of small or selected populations (e.g., convenience samples), and few provided adequate information to assess efforts to minimize the effects of non-response and socially-desirable response bias (57,58). The majority of studies in this review consisted of empirical analyses of patients' health care utilization, and most used either descriptive analysis or regression discontinuity approaches. Of studies employing regression models, several included methods to account for the outcome frequency (e.g., binomial or poisson models), to examine and correct for first-order and higher levels of correlation (e.g., seasonality) within the data, and to account for the potential of a lag between an FDA communication and its impact. Despite this, none of the quasi-experimental studies analyzed used a difference-in-difference approach with a control group, often difficult to identify in these types of studies, to account for secular trends. Similarly, few studies statistically adjusted for influential scientific reports, media coverage, litigation, or industry promotion, although several acknowledged their potential influence on the outcomes of interest. Finally, most studies looked at aggregate patterns of prescribing rather

than patient-level changes in utilization, including changes in treatments among disease-specific cohorts.

DISCUSSION

Regulatory advisories are a common method of disseminating emerging safety risks from prescription drugs, and the role of the FDA in communicating will grow with the Sentinel Initiative and other regulatory efforts to improve safe prescription use (59,60). Most studies we examined were empiric analyses of drug and non-drug utilization; many fewer examined patient-provider communication and decision-making or risk perception. Since the communications had highly variable effects, the small number of contexts investigated relative to the number of settings where advisories have been issued is noteworthy.

The communications examined differed in several ways, such as whether they focused on a single drug, targeted a specific subpopulation, or addressed an idiosyncratic risk. Although the nature of the studies precludes quantitative comparisons, several suggestive conclusions can be drawn. First, advisories recommending greater monitoring do not appear to have led to large and sustained changes. For example, increases in laboratory monitoring for troglitazone, pemoline or antipsychotics and clinical monitoring for antidepressants were generally incomplete and/or temporary and often led to decreases in medication use. Second, in settings where incident and prevalent use was examined, such as in the case of cisapride, terfenadine, and antidepressants, warning information appears to have been adopted more quickly for new rather than continuing medication users. Despite this, it is not clear from these reports whether continuing users or their providers were well informed regarding the specific risks addressed. Third, principles of risk communication suggest that warnings will be most effective in cases where they are specific, where acceptable alternatives are available and where the messaging is reinforced over time (5). The case of cisapride provides one example, where the first and less specific messaging did not lead to large changes in co-prescribing with contraindicated therapies, compared with subsequent more specific communications (21,22). Interestingly, the magnitude of substitution within a class where an advisory was issued for a single agent varied across settings, from little evidence of substitution of pioglitazone for rosiglitazone, to modest increases in clarithromycin for telithromycin, to larger increases in antidepressants other than paroxetine, albeit with additional advisories regarding other specific anti-depressants. Finally, based on the selected primary data collected from surveys and focus groups, most physicians appeared aware of general safety concerns, though many provider respondents disagreed with advisory content. The single study examining parental attitudes and beliefs suggest they had limited understanding or awareness of the OTC cough medicine communication.

As with other public policies, FDA communications have the potential for unintended consequences. Antipsychotic and antidepressant advisories were associated with decreased use in non-targeted populations, and there is evidence of increases in suicides among children following the antidepressant advisories (44). Decreases in telithromycin use also appeared to occur non-selectively; the advisory did not appear to affect the proportion of all uses that were for off-label indications (32). These studies are not the first to suggest the potential for unintended consequences from regulatory warnings regarding prescription drugs (61,62), and their potential demonstrates the challenge that policy-makers face to design risk messages that are maximally effective, specific, and that don't become risks themselves.

Our study has a number of limitations. First, the number of different therapeutic areas, communications, outcomes, and study designs used precluded anything more than a qualitative analysis of findings from the studies that we gathered (63). The heterogeneity of

studies does not permit for an “average effect” of FDA communications to be estimated, nor an estimate of the relative potency or impact of one form of communication compared with another. Second, regulatory advisories exist within a sea of information that may influence health care utilization and behaviors (64,65), and thus the complexity of the phenomenon studied, and multitude of potential influences that may shape behavior, also limit conclusions drawn from this type of review. Third, our study was limited to the peer-reviewed literature regarding FDA drug risk communications. Finally, although the behavioral responses that most studies examined are relevant to stakeholders, they provide incomplete information on the efficacy of a communication; the absence of a strong response may indicate a previously informed population, or a population where the new information was insufficient to prompt different decision-making, whereas the presence of a strong response may indicate over compensation on the part of patients and providers (8).

Our review also raises several questions. None of the studies examined included rigorous assessment of how the effect of advisories may vary across groups of physicians, practices, or other communities. Given the complex determinants of health care utilization and health behavior, there is likely substantial variation in responsiveness to FDA communications among different subsets of providers and patients (66). In addition, although one-fifth of the studies examined were based on surveys or qualitative investigations, little is known regarding how these risk communications affected patients’ communication with health care providers or their risk perceptions. Also, few studies(43) examined medication switching among individual patients. Thus, although some studies provide insights regarding how a regulatory communication may lead to changes in market share within a therapeutic class, almost none provide a window for understanding how individual patients’ pharmacotherapies change as a result of an advisory or label warning. Finally, few studies examined health outcomes associated with medication changes that may have ensued following an FDA communication. Since the goals of risk communication are to minimize potential harms, understanding the impact of an FDA communication’s intended (and unintended) consequences on patient health outcomes should be a priority.

CONCLUSIONS

The FDA’s primary mission is to protect the public health (67), yet there are numerous challenges in designing and disseminating risk information, including a finite and ever evolving evidence base as well as social, psychological, and cognitive dimensions of risk perception and communication (5–8). The Sentinel Initiative, as well as the FDA’s greater authority to enforce post-approval Risk Evaluation and Mitigation Strategies, will increase the volume of safety information that must be conveyed to providers and the general public (68). This review indicates the varied and unpredictable impact that such outreach can have, and suggests the importance of continuing to characterize the effect of advisories and warnings on a variety of behaviors to enhance the science of risk communication regarding prescription drugs.

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FIGURE 1.
STUDY SELECTION FOR SYSTEMATIC REVIEW.

FIGURE 2.
CONCEPTUAL APPROACH TO SYSTEMATIC REVIEW OF THE EFFECT OF FDA COMMUNICATIONS.

TABLE 1
CHARACTERISTICS OF STUDIES EXAMINING FDA COMMUNICATIONS (N=49 STUDIES).

	N (%) [*]
Drug or therapeutic class	
Antidepressants	15 (31)
Glitazones	6 (13)
Hepatotoxicity (2 studies)	
Cardiovascular risks (4 studies)	
Cisapride	4 (8)
Long Acting β_2 Agonists	3 (6)
Droperidol	3 (6)
Antipsychotics	3 (6)
Mortality risks (1 study)	
Metabolic risks (2 studies)	
Terfenadine	4 (8)
Multiple classes (e.g., antipsychotics and antidepressants)	2 (4)
Over-the-counter cough medicines	1 (2)
Depo provera	1 (2)
Promethazine	1 (2)
Telithromycin	1 (2)
Angiotensin-converting enzyme [ACE] inhibitors	1 (2)
Topical calcineurin inhibitors	1 (2)
Tramadol	1 (2)
Antiepileptics	1 (2)
Pemoline	1 (2)
Data source	
Health plan claims	24 (49)
Pharmacy claims	12 (24)
Physician or parent surveys	8 (16)
Health records	5 (10)
Ambulatory prescribing audits	3 (6)
Poison center records	1 (2)
Focus groups	1 (2)
Vital statistics	1 (2)
Analytic Approach	
Segmented time series regression	12 (24)
Other types of regression (e.g., Poisson)	17 (35)
Descriptive statistics	11 (22)
Other methods(e.g., Fischer's test)	9 (18)
Communications	
Black box warning	25 (51)

	N (%) [*]
Public health advisory or safety alert	23 (47)
Dear Healthcare Provider letter	14 (29)

* Column totals may exceed 49 as some studies examined multiple drugs or classes, used more than one data source, or assessed the impact of multiple communications

TABLE 2

EXAMPLE OF SAFETY CONCERN AND FDA COMMUNICATION EXAMINED.*

Class or agent	Date and communication type	Communication
Anti-depressants	Oct-04 Black Box warning	Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior.
Glitazones (Hepatotoxicity)	Oct-97 Dear Healthcare Provider letter	Rare cases of severe idiosyncratic hepatocellular injury have been reported during marketed use. It is recommended that serum transaminase levels be checked within the first one to two months and then every three months during the first year of troglitazone therapy, and periodically thereafter.
Glitazones (Cardiovascular risks)	Aug-07 Public health advisory	Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients.
Long-acting beta-agonists	Nov-05 Public health advisory	Long-acting beta 2-adrenergic agonists have been associated with an increased risk of severe asthma exacerbations and asthma-related death.
Droperidol	Dec-01 Black box warning	Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving Inapsine (Droperidol) at doses at or below recommended doses.
Atypical antipsychotics (Metabolic risks)	Aug-04 Dear Healthcare Provider letter	Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment.
Atypical antipsychotics (Mortality)	Apr-05 Public health advisory	Treatment of behavioral disorders in elderly patients with dementia with atypical (second generation) antipsychotic medications associated with increased mortality compared to the placebo-treated patients.
Over-the-counter cough medicines	Jan-08 Public health advisory	These drugs should not be used to treat infants and children under 2 years of age because serious and potentially life-threatening side effects can occur.
Depo-provera	Nov-04 Black box warning	Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible.
Promethazine	Nov-04 Black box warning	This drug should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression.
Telithromycin	Feb-07 Black box warning	Ketek is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek.
ACE inhibitors	Mar-92 Black box warning	When used during the second and third trimesters of pregnancy, ACE inhibitors can cause injury and even death to the developing fetus.
Calcineurin inhibitors	Jan-06 Black box warning	Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.
Antiepileptics	Jan-08 Public health advisory	There is an increased risk of suicidal thoughts and behaviors (suicidality) in patients who take drugs called antiepileptics to treat epilepsy, bipolar disorder, migraine headaches, and other conditions.

* Effect of multiple communications investigated in many reports, communication provided to illustrate a general safety concern with drug or class; content of communications for cisapride (Feb-95 Dear Healthcare Provider letter), terfenadine (Jul-92 Black box warning), and tramadol (Mar-96 Dear Healthcare Provider letter) not available; telithromycin advisory also associated with rescinded indications for bacterial exacerbations of chronic bronchitis and bacterial sinusitis; ACE=Angiotensin-converting enzyme

TABLE 3

ANALYSIS OF IMPACT OF FDA REGULATORY COMMUNICATIONS.

ARTICLE	COMMUNICATION*	OUTCOMES	DATA SOURCE	ANALYSIS
Antidepressants and risks of suicidality				
Bhatia 2008	Black box warning: Oct-04	Antidepressant use, psychotherapy visits, referrals to specialists, outpatient follow-up	Mailed survey of 1,521 prescribing clinicians in Nebraska (57% response rate)	Descriptive statistics
Busch 2010	Black box warning: Oct-04; Public health advisories: Jun-03, Oct-03, Mar-04, Sept-04	Antidepressant use (overall), paroxetine use, fluoxetine use, changes in monitoring for patients using antidepressants	MarketScan health plan claims	Logistic regression
Forrester 2007	Black box warning: Oct-04; Public health advisories Jan-02, Jun-03, Mar-04, Dec-05	Reports of paroxetine and other SSRI ingestions	Texas Poison Center Network	Descriptive statistics
Gibbons 2007	Black box warning: Oct-04 Public health advisory: Oct-03	Antidepressant use, suicide rates	IMS Health (US) and PHARMO (Netherlands) prescription claims, CDC WISQARS Injury Mortality Report and WONDER Compressed Mortality database (US), Central Bureau of Statistics (Netherlands)	Poisson regression
Hassanin 2010	Black box warning: Oct-04	Antidepressant use among patients with depression or anxiety	Health plan claims from a Hawaiian Insurer	Logistic Regression
Kurian 2007	Black box warning: Oct-04	Antidepressant use among new/prevalent users, fluoxetine use among new/prevalent users, psychotropic substitute use	Tennessee Medicaid claims	Time series regression, adjusted for seasonality
Libby 2007	Public health advisory: Oct-03	New depression diagnoses, antidepressant use, provider type, psychotherapy use, psychotropic substitute use	PharMetrics health plan claims	Linear regression, time series regression, adjusted for seasonality
Libby 2009	Public health advisory: Oct-03	New and recurrent depression diagnoses, antidepressant use, provider type, psychotherapy use, psychotropic substitute use	PharMetrics health plan claims	Linear regression, time series regression, adjusted for seasonality
Morrato 2008	Public health advisory: Oct-03	Outpatient follow-up, acute- and continuation-phase treatment availability, adherence to monitoring recommendations	PharMetrics health plan claims	Time series regression, adjusted for seasonality
Nemeroff 2007	Public health advisory: Oct-03, Mar-04	Antidepressant prescribing volume, provider type treating depression in children, antidepressant class prescribed	Verispan pharmacy claims, Verispan Physician Drug and Diagnosis Audit	Joinpoint regression of smoothed data to adjust for seasonality
Olsson 2008	Black box warning: Oct-04 Public health advisory: Jun-03	Antidepressant use (overall) among new and prevalent users, paroxetine use, provider type prescribing antidepressants	Medco pharmacy claims, American Medical Association Master File	Generalized estimating equations (GENMOD, GEE), z-statistics

ARTICLE	COMMUNICATION*	OUTCOMES	DATA SOURCE	ANALYSIS
Richardson 2007	Black box warning: Oct-04	Physician-perceived barriers to treating children with depression, strategies to assure follow-up, changes in depression treatment	Provider focus groups - 39 pediatric practices contacted, 9 participated; groups consisted of 32 pediatricians and 3 nurse practitioners	Qualitative data analysis
Singh 2009	Black box warning: Oct-04	Refusal of antidepressants by parent or guardian	Chart review at one university affiliated outpatient mental health clinic	Fisher's exact test
Valluri 2010	Public health advisory: Mar-04	Antidepressant use and psychotherapy use among newly diagnosed patients (stratified by diagnosis)	I3 INNOVUS health plan claims	Generalized estimating equations (GEE)
Valuck 2007	Public health advisory: Oct-03	New and recurrent diagnoses, antidepressant use, timing of initial prescription, provider type, psychotherapy use, psychotropic substitute use	PharMetrics health plan claims	Linear regression, time series regression, adjusted for seasonality
Glitazones and risks of hepatotoxicity (troglitazone)				
Cluxton 2004	Dear Healthcare Provider letters: Oct-97, Dec-97, Jul-98, Jun-99	Baseline and follow-up liver enzyme monitoring in patients taking troglitazone	Ohio Medicaid fee-for-service claims	Logistic regression, Life tables, Cox proportional hazard models
Graham 2001	Dear Healthcare Provider letters: Oct-97, Dec-97, Jul-98, Jun-99	Baseline and follow-up liver enzyme monitoring in patients taking troglitazone	UnitedHealth health plan claims	Chi-square analysis
Glitazones and risk of cardiovascular disease (rosiglitazone and pioglitazone)				
Cohen 2010	Black Box warning: Aug-07; Public health advisories: May-07, Aug-07, Nov-07	Changes in rosiglitazone, pioglitazone, and all glitazone use	Audit of office-based prescribing - IMS Health National Disease and Therapeutic Index	Time series regressions
Orrico 2010	Public health advisory: May-07	Rosiglitazone use, glycemic control	Medical chart review of 552 patients	Descriptive statistics
Starnes 2008	Black Box warning: Aug-07; Public health advisories: May-07, Aug-07, Nov-07	Glitazone use among all subjects and subjects stratified by cardiovascular risk	Blue Cross/Blue Shield pharmacy claims	Chi-square analysis
Stewart 2009	Public health advisory: May-07	Use of rosiglitazone and other antidiabetic therapies	TRI-CARE pharmacy claims	Time series regressions
Cisapride and risk of cardiac arrhythmias				
Guo 2003	Dear Healthcare Provider letters: Feb-95, Oct-95, Jun-98	Coprescribing contraindicated drugs with cisapride	Protocare sciences claims	Time series regressions
Smalley 2000	Dear Healthcare Provider letter: Jun-98	Changes in contraindicated cisapride use	Pharmacoepidemiology research databases from 3 managed care organizations and a state Medicaid program	Descriptive statistics
Weatherby 2001	Dear Healthcare Provider letters: Oct-95, Jun-98	Coprescribing contraindicated drugs with cisapride	New England commercially insured database	Time series regressions
Weatherby 2002	Dear Healthcare Provider letters: Oct-95, Jun-98, Jun-99	Coprescribing contraindicated drugs with cisapride	New England commercially insured database	Logistic regression

ARTICLE	COMMUNICATION*	OUTCOMES	DATA SOURCE	ANALYSIS
Long Acting β_2 Agonists and risk of asthma exacerbations and death				
Friedman 2009	Black Box warning: Mar-06; Public health advisories: Nov-05	Use of fluticasone propionate/salmeterol	United States commercially insured database	Descriptive statistics
Karpel 2009	Black Box warning: Nov-05	Awareness/attitudes toward warning, reported changes in practice	Internet survey of 11,147 physicians (9.9% response rate)	Chi-square tests, fisher exact test
Stockl 2008	Black Box warning: Aug-03; Public health advisory: Nov-04	Use of long acting beta agonists	Pharmacy and medical claims from five states	t-tests, chi-square tests
Droperidol and prolongation of the QT interval, torsade de pointes, and sudden death				
Habib 2007	Black Box warning: Dec-01	Use of droperidol and other postoperative antiemetics	Internet survey of 1,179 physicians (25% response rate)	Logistic regression
Richards 2003	Black Box warning: Dec-01	Use of droperidol by emergency room physicians	Internet survey of 2,000 physicians (25% response rate)	Wilcoxon test
Wax 2006	Black Box warning: Dec-01	Use of droperidol and other postoperative antiemetics	Electronic health records	Logistic regression
Antipsychotics and risk of mortality				
Dorsey 2010	Public health advisory: Apr-05	Use of atypical drugs among all subjects and elderly with dementia	Audit of office-based prescribing - IMS Health National Disease and Therapeutic Index	Time series regressions
Antipsychotics and metabolic risks				
Morrato 2010a	Label change: Dec-03; Dear Healthcare Provider letter: Aug-04	Glucose and lipid testing amongst children and adults using atypical antipsychotics	Medicaid data from three states	Time series regressions
Morrato 2010b	Label change: Dec-03; Dear Healthcare Provider letter: Aug-04	Glucose and lipid testing amongst children using atypical antipsychotics	Medicaid data from three states	Logistic regression
Terfenadine and risk of cardiac arrhythmias				
Burkhardt 1997	FDA Committee Meeting: June 1990; Dear Healthcare Provider letter: Aug-90; Dear Healthcare Provider: Jul-92;	Concurrent use of terfenadine and a contraindicated drug	Pharmacy claims	Logistic regression
Carlson 1996	Black Box warning: Jul-92; Dear Healthcare Provider letter: Aug-90	Concurrent use of terfenadine and a contraindicated drug	Large Midwestern management firm of several health maintenance organizations (HMOs)	Descriptive statistics
Thompson 1996	Black Box warning: Jul-92; Dear Healthcare Provider letter: Aug-90	Concurrent use of terfenadine and a contraindicated drug	Pharmacy claims	t-tests
Zelnich 1994	Dear Healthcare Provider letter: Aug-90; Public Health Advisory: Sep-92; Dear Healthcare Provider letter: Oct-92	Concurrent use of terfenadine and a contraindicated drug	Oregon Medicaid program	Descriptive statistics
Analysis of advisories for more than one therapeutic class				

ARTICLE	COMMUNICATION*	OUTCOMES	DATA SOURCE	ANALYSIS
Pamer 2010	Public health advisory: Jun-03	Use of antidepressant and antipsychotic therapies	Vector One Total Patient Tracker, IMS Health National Sales Perspective, IMS Health Integrated Promotional Services	Time series regressions
Wilkinson 2004	Dear Healthcare Provider letters: Feb-95, Oct-95, Jun-98, Jun-99, Jan-00 (Cisapride); Public health advisories: Oct-97, Dec-97, Jul-98, Jun-99 (Triglizone)	New and continued cisapride and troglizone use	Idaho Medicaid Claims Data	Descriptive statistics
Over the counter cough medication and life threatening side effects				
Garbutt 2010	Public health advisory: Jan-08	Advisory awareness, beliefs, and self reported practice	U.S. mail survey of 197 pediatricians (53% response rate); survey of 725 parents (77% response rate)	Logistic regression
Depo-Provera and risk of bone mineral density loss				
Paschall 2008	Black Box warning: Nov-04	Obstetrician-Gynecologist use and attitudes regarding of depo-provera	U.S. mail survey of 425 obstetrician-gynecologists (149 returned, 35.1% response rate)	Descriptive statistics Fisher's exact test
Promethazine and risk of respiratory depression				
Kessler 2010	Black Box warning: Nov-04	Promethazine use	Medical chart review of 255 patients	Descriptive statistics; z-tests
Telithromycin and risk of hepatotoxicity and use in patients with myasthenia gravis				
Gleason 2007	Black Box warning: Feb-07	Telithromycin use	Medical and pharmacy claims from commercial insurer	Descriptive statistics
Acc Inhibitors and risk of fetopathy				
Bowen 2008	Black Box warning: Mar-92	Acc inhibitor use during pregnancy	Tennessee Medicaid data	Poisson regression
Topical calcineurin inhibitors and risk of malignancy				
Ceillely 2009	Black Box warning: Feb-05	Percent of patients on calcineurin inhibitors and other therapies	In-person survey of convenience sample of 504 dermatologist conference attendees	Descriptive statistics
Tramadol and abuse, seizures, and anaphylactoid reactions				
Shatin 2004	Dear Healthcare Provider letter: Mar-96	Use of antidepressant with tramadol	United Health Group pharmacy claims	Logistic regression
Antiepileptics and suicidality				
Shneker 2009	Public health advisory: Jan-08	Reactions to the alert, approach to depression and suicide, and anticipated change in practice	Internet survey of 780 members of American Epilepsy Society (22% response rate)	Descriptive statistics
Penoline and hepatotoxicity				
Willy, 2002	Black Box Warning: December 1996	Use of pemoline as second-line therapy and liver enzyme monitoring	United Health Group pharmacy claims	Logistic regression

* Some communications associated with FDA Advisory Meetings and many communications (e.g., Dear Healthcare Provider letters for cisapride) associated with label changes

TABLE 4
OUTCOMES OF STUDIES ANALYZING FDA RISK COMMUNICATIONS (N=49 STUDIES).

	Use of drug or class	Use of substitutes for drug or class	Spillover effects	Diagnosis, testing, and non-drug utilization [†]	Health behavior and outcomes	Knowledge, attitudes, and beliefs
ANTIDEPRESSANTS						
Bhatia 2008 [*]	X			X		X
Busch 2010	X			X		
Forrester 2007	X					
Gibbons 2007	X		X		X	
Hassanin 2010	X					
Kurian 2007	X	X				
Libby 2007	X	X		X		
Libby 2009	X	X	X	X		
Morrato 2008			X	X		
Nemeroff 2007	X	X	X	X		
Olson 2008	X	X	X	X		
Richardson 2007 [*]	X			X		X
Singh 2009	X			X		
Valluri 2010	X			X		
Valuck 2007	X	X		X		
GLITAZONES						
Cluxton 2005				X		
Cohen 2010	X					
Graham 2001				X		
Orrico 2010	X				X	
Starnes 2008	X	X		X		
Stewart 2009	X	X				
CISAPRIDE						
Guo 2003	X					
Smalley 2000	X					

	Use of drug or class	Use of substitutes for drug or class	Spillover effects	Diagnosis, testing, and non-drug utilization [†]	Health behavior and outcomes	Knowledge, attitudes, and beliefs
Weatherby 2001	X					
Weatherby 2002	X					
LONG ACTING BETA-AGONISTS						
Friedman 2009	X	X				
Karpel 2009 *	X	X				X
Stockl 2008	X	X				
DROPERIDOL						
Habib 2007 *	X					X
Richards 2003 *	X	X				X
Wax 2006	X	X				
ANTIPSYCHOTICS						
Morrato 2010a				X		
Morrato 2010b				X		
Dorsey 2010	X	X	X			
TERFENADINE						
Burkhart 1997	X					
Carlson 1996	X					
Thompson 1996	X					
Zelnich 1994	X					
MULTIPLE CLASSES						
Pamer 2010	X	X				
Wilkinson 2004	X					
OVER THE COUNTER COUGH MEDICINES						
Garbutt 2010 *	X					X
DEPO PROVERA						
Paschall 2008 *	X	X		X		
PROMETHAZINE						
Kessler 2004	X					

	Use of drug or class	Use of substitutes for drug or class	Spillover effects	Diagnosis, testing, and non-drug utilization [†]	Health behavior and outcomes	Knowledge, attitudes, and beliefs
TELITHROMYCIN						
Gleason 2007	X	X		X		
ANGIOTENSIN CONVERTING ENZYME INHIBITORS						
Bowen 2008	X					
CALCINEURIN INHIBITORS						
Ceilley 2009 *		X				X
TRAMADOL						
Shatin 2004	X					
ANTEPILEPTICS						
Shneker 2009 *						X
PEMOLINE						
Willy 2002	X			X		

* Survey-based studies that included outcomes based on respondent self-report;

[†] includes studies examining diagnosis rates (e.g., diagnosis of major depression after antidepressant advisory) as well as usage patterns stratified by diagnosis (e.g., rates of gliatrazone use stratified by diagnoses indicating elevated cardiovascular risk)