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EFFECT OF DIRECT-TO-CONSUMER ADVERTISING (DTCA) ON STATIN USE IN THE UNITED STATES

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Abstract

Importance—The value of direct-to-consumer advertising (DTCA) of prescription drugs is widely debated, as is the effect of DTCA on prescription sales and health care utilization.

Objective—We examined the association between DTCA intensity for statin medications and prescription sales and cholesterol-related health care utilization.

Design, setting and participants—We conducted an ecological study for 75 designated market areas (DMAs) from 2005 to 2009 in the United States using linked data regarding televised DTCA volume; non-DTCA marketing and promotion; retail, mail order and long-term care prescription drug sales; prescription drug and ambulatory care health care utilization; and contextual factors such as health care density and socioeconomic status. Main outcomes and measures were volume of sales; number of dispensed prescriptions; and high cholesterol-related outpatient visits. Analyses were conducted in 2016.

Results—The intensity of rosuvastatin and atorvastatin ad exposures per household varied substantially across DMAs. After adjustment for socioeconomic, demographic and clinical characteristics, each 100-unit increase in advertisement viewership was associated with a 2.22% (95% confidence interval [CI] 0.30 to 4.19%) increase in statin sales. Similar patterns were observed between DTCA and statin dispensing among the commercially insured. DTCA was

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associated with increases in high cholesterol-related outpatient visits among adults 18–45 years of age (3.15% increase in visits per 100-unit increase in viewership, 95% CI: 0.98 to 5.37%) but not among those 46–65 years of age (0.51%, 95% CI: –1.49 to 2.55%).

Conclusion—DTCA for statins is associated with increases in statin utilization and hyperlipidemia-related outpatient visits, especially for young adults.

INTRODUCTION

The United States is one of only two countries in the world that allows for direct-to-consumer advertising (DTCA) of prescription drugs.^{1,2} While such advertising is highly concentrated and accounts for a relatively small proportion of all marketing and promotion,² it remains common and controversial and has both supporters and detractors. Proponents argue that such advertising provides valuable information to patients and improves patient-provider communication which, in turn, may result in improved adherence and health outcomes.^{3,4} Opponents argue DTCA misinforms patients, promotes drugs with unknown safety profiles and encourages over-utilization of prescription drugs and health care services.⁴

Several studies have examined the effect of DTCA on outcomes including diagnostic frequency, ambulatory office visits and prescription drug utilization.^{5–8} Some of these have focused specifically on statins. For example, an analysis of the Simmons National Consumer Surveys administered between 2001 and 2007 found that exposure to statin ads increased the odds of both being diagnosed with high cholesterol and using statins by 16% to 20%; the impact of the DTCA was most pronounced among individuals at low risk for future cardiac events.⁵ Similarly, a second study that analyzed visits to 2768 physician offices in the US found that the effect of DTCA for statins on the likelihood of identifying new patients with high cholesterol varied substantially across patient sub-groups.⁹ Reviews summarizing this evidence suggest that the effect of DTCA on physician prescribing behavior is ambiguous or even debatable, with no evidence of improvements in quality of care.^{10,11}

Despite the insights provided by studies examining the effects of DTCA, many of these investigations have used national DTCA expenditures to define advertising exposure. Such estimates are imprecise measures of exposure both because they are geographically aggregated and also because expenditures may not accurately reflect the actual exposure of individuals to such messaging.^{6,7,10} In addition, many prior studies have been unable to account for physician-targeted promotion, yet the use of samples and office-based detailing is common and may be heavily correlated with consumer-targeted promotion.^{5,7,11} Finally, contextual factors such as health care density and socioeconomic status may also be influential in driving the outcomes of interest, yet studies of the effects of DTCA have not consistently accounted for these factors.^{5–7,10} In order to address these limitations, we examined the association between statin advertising and both non-drug and prescription drug health care utilization for each of the top 75 designated market areas (DMAs) in the United States. We hypothesized that DTCA would be associated with an increase in statin use, albeit with smaller effects than that observed for symptomatic conditions such as asthma.¹² Assuming that DTCA would generate patient interest in getting their cholesterol tested, we

also hypothesized that the effect of statin DTCA on hyperlipidemia-related visits would be greater for younger individuals who may be more likely to have undiagnosed high cholesterol.

METHODS

Data

We combined five different sources of information that extended from January 2005 through December 2009 for the top 75 designated market areas in the United States. These five data sets provided information regarding: (1) televised DTCA volume for statins (Nielsen television ratings), (2) non-DTCA marketing and promotion (IMS Health Integrated Promotion Services), (3) retail, mail order and long-term care prescription drug sales (IMS Health Xponent), (4) prescription drug and ambulatory care health care utilization (Truven MarketScan Commercial Claims and Encounters data), and (5) contextual factors such as health care density and socioeconomic status (Area Resource File).

We derived monthly statin DTCA data, our primary independent variable, at the DMA-level from Nielsen. For information gathered at county level, such as contextual factors from Area Health Resource File (AHRA), we used a county-to-DMA crosswalk, which links a county to a DMA, to convert all county-level explanatory and outcome data to the DMA-level.

We used IMS Health Integrated Promotion Services (IPS) to derive data on physician detailing activities to control for national levels of physician-targeted promotion for the statins of interest. We did this by adjusting for the estimated expenditures on free samples distributed through providers, targeted advertising to health care professionals and direct promotional contact with providers such as discussions during office visits.²

We used the Health Resources and Services Administration's Area Health Resource File (AHRF) to control for relevant demographic and socioeconomic characteristics that affect the demand for healthcare in each DMA. The AHRF is supplied by the U.S. Health Resources and Services Administration, Bureau of Health Professions.¹³ The AHRF provides annual data at the county-level, using information gathered from various organizations such as the American Medical association, the Bureau of the Census and the American Hospital Association; it has been widely used in various research.^{14–16} Characteristics of interest included median age, median income, hyperlipidemia prevalence, smoking prevalence, physician density, total population and the number of insured individuals.

We obtained data on statin sales from IMS Health's Xponent, which captures prescriptions from all payers, including private insurance, Medicare, Medicaid and self-pay. Using a national random sample of 57,000 retail, 327 non-governmental mail service pharmacy outlets and approximately 3,000 long-term care pharmacies, these data provide estimates of new, refill and mail-order prescription drug sale activity within a geographic region. Sales activity is measured in doses which in this study represents the number of statin tablets dispensed. Each record includes the state and county name, the product name, the estimated

number of total and new prescription doses dispensed, and the month and year of the transactions.

We used Marketscan Commercial Claims and Encounters data from Truven Health Analytics to examine the effect of DTCA on the number of statin prescriptions dispensed to and high cholesterol-related outpatient visits made by the commercially insured. Marketscan covers over twenty million individuals annually and provides de-identified, individual-level healthcare utilization data including demographic characteristics, information on medical and pharmacy services provided, cost of the claim and the insurance plan paying for the service. We identified relevant prescription claims using National Drug Codes (NDC), and high cholesterol-related outpatient visits using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (ICD-9-CM:272.0 – 272.4). We linked healthcare utilization data from Marketscan to advertising intensity information provided by Nielsen at the DMA level.

Analysis

All analyses were conducted in 2016. We first identified the target drugs for our evaluation. There were six cholesterol medications with any amount of DTCA during our study period (Crestor™, Lipitor™, Caudet™, Pravachol™, Zetia™, Zocor™). Of these six products, only rosuvastatin (Crestor™) and atorvastatin (Lipitor™) were consistently advertised and available from 2005 to 2010; therefore, we limited our analyses to these two products.

Advertisers quantify DTCA intensity in gross ratings points (GRPs) which is a sum of percentages. Each percentage reflects the proportion of the target audience reached multiplied by the frequency of advertisement exposure. Therefore, an ad that airs four times reaching 50% of its target audience each time it aired receives 200 GRPs (4 X 50%). We calculated GRPs for the statins of interest (rosuvastatin, atorvastatin, or both) within each DMA and scaled the GRPs by 100.

We used IMS Health Xponent, all-payer sales data to identify all records with rosuvastatin and atorvastatin and to summarize the number of new and total doses by DMA, product and the month and year of dispensing. In addition to examining sales volume based on doses dispensed, we also calculated a dispensing rate by dividing the number of doses by the number of insured individuals in each DMA; we derived this latter value from the ARF.

After DTCA and dispensing rates were constructed, we first visually inspected the data. Next, we used descriptive statistics to examine trends in statin DTCA and dispensing across DMAs and time. From May to June 2008, dispensing of rosuvastatin and atorvastatin in six of the 75 DMAs increased between four to ten-fold. Thus, we conservatively excluded these six DMAs from further analyses (Appendix Figure S1 & S2). The 69 DMAs we examined accounted for 72.6% of the 306.8 million total population of the U.S. in 2009; the size of the DMAs ranged from 1.02 million to 21.02 million individuals in 2009. We defined our outcomes of interest as: (1) pharmacy sales of rosuvastatin and atorvastatin as determined using IMS Health Xponent, (2) the dispensing rate of rosuvastatin and atorvastatin to the commercially insured, and (3) the number of high cholesterol-related outpatient visits made by the commercially insured as assessed using Marketscan. We applied negative binomial

regression models to examine the relationship between DTCA and our outcomes of interest. We ran both time-only and fully-adjusted models that accounted for the correlation across monthly observations from the same DMAs using generalized estimating equations (GEE). The full model adjusted for median age, median income in thousands, prevalence of high cholesterol, prevalence of smoking, physician density per 1000 people in the population, promotional expenditures on free samples (low, medium and high) and the number of insured individuals (in millions). For the outcome of pharmacy sales using IMS Health Xponent, we included the log of the number of population in a DMA, derived from the AHRF, as an offset variable; for the outcomes of dispensing rates and outpatient visits using Marketscan, we included the log of the number of commercially insured individuals in a DMA, derived from the Marketscan files, as an offset variable. In secondary analysis, we quantified the cross-advertising elasticity of demand, namely the effect of DTCA for rosuvastatin on rate of atorvastatin dispensing and vice versa.

Subgroup and Sensitivity Analysis

We performed several subgroup and sensitivity analyses to assess the robustness of our conclusions. First, we assessed where the effect of DTCA for statins on high cholesterol-related outpatient visits varied between genders and across age groups. Second, we determined the impact of excluding the 6 DMAs that showed significant increases in statin dispensing on our conclusions by recalculating each model using all 75 DMAs in the dataset. Finally, we evaluated the impact of assuming one- and two-month lags between advertising exposure and each outcome of interest.

RESULTS

Trends in direct-to-consumer advertising and statin dispensing

The magnitude of advertising for both rosuvastatin and atorvastatin varied across DMAs and over time (Figure 1). Despite these differences in magnitude, when either drug was advertised, advertisements aired across all 75 DMAs. The average rate of total doses dispensed per 100 insured individuals for these two statin medications across DMAs slightly decreased from 125 in January 2005 to 85 in December 2009 (Appendix Figure S2).

Association between DTCA and statin sales

Table 1 summarizes the association between DTCA and statin sales. Each 100-unit increase in viewership was associated with a 6.71% (95% confidence interval [CI] 3.82 to 9.67%) increase in the number of rosuvastatin and atorvastatin doses dispensed. After controlling for potential confounders, the magnitude of increase reduced to 2.22% (CI 0.30 to 4.19%) but remained statistically significant. Similar patterns were observed when examining rosuvastatin and atorvastatin separately (rosuvastatin 5.18%, CI 2.35 to 8.09%; atorvastatin 4.21%, CI 0.67 to 7.87%), as well as when stratifying by new versus refilled prescriptions. Using the information in Table 1, assuming the mean value of every control variable at month 30 across 69 DMAs, we estimate that an increase in GRP (scaled by 100) from 8 to 9 would lead to an increase of 58,516 in the number of total statin prescriptions, 20,690 in the number of new statin prescriptions, and 38,162 in the number of refill statin prescriptions.

Association between DTCA, statin dispensing and outpatient encounters

Table 2 presents the association between DTCA and the dispensing of statins to the commercially insured. After controlling for other covariates, each 100-unit increase in DTCA was associated with a 2.73% (CI 0.77 to 4.73%) increase in dispensed rosuvastatin and atorvastatin. Drug-specific advertising had marginally higher effects. For example, the number of rosuvastatin doses dispensed increased by 5.17% (CI 1.52 to 8.97%) per 100-unit increase in rosuvastatin-specific ad viewership; similar effects were observed with atorvastatin (5.03%, CI 1.32 to 8.88%). Among the commercially insured, the effect of DTCA for rosuvastatin and atorvastatin was greater on refill than new prescriptions (4.25%, CI 1.14 to 7.44% vs. 2.28%, CI 0.04 to 4.58%). We did not observe evidence of statistically significant cross-advertising elasticity of demand.

On unadjusted analysis, DTCA for rosuvastatin and atorvastatin was associated with a 5.03% (CI 2.15 to 7.99%) increase in the number of high cholesterol-related outpatient visits per 100-unit increase in ad viewership (Table 3). However, after adjusting for potential confounders, this association was no longer statistically significant (1.44%, CI: -0.38 to 3.29%).

Subgroup and Sensitivity Analyses

The effect of DTCA for rosuvastatin and atorvastatin on the number of high cholesterol-related outpatient visits varied by patient age but not sex. For each 100-unit increase in DTCA, there was a 1.34% (CI -0.61% to 3.35%) increase in high cholesterol-related outpatient visits among females compared to 1.57% (CI -0.19% to 3.35%) in males. For adult patients under 45 years, DTCA was associated with a 3% to 5% increase in high cholesterol-related outpatient visits per 100-unit increase in ad viewership whereas there was no statistically significant impact on patients between the ages of 45 and 64 (Table 3). Inclusion of the 6 DMAs where there were unusually large increases in statin dispensing after May 2008 did not significantly alter the study's conclusions (Table S1), nor did allowing for a one- and two- month lag between advertising viewership and outcome ascertainment (Tables S2 and S3).

DISCUSSION

We linked multiple sources of information to conduct an ecological study examining the association between DTCA for statins and the volume of statin sales, the rate of statin dispensing to the commercially insured and the number of high cholesterol-related outpatient visits made by the commercially insured. We focused on rosuvastatin and atorvastatin, given that these were consistently advertised across the 75 top DMAs over the 5-year window. DTCA for these products was associated with significant increases in the sales and dispensing, as well as increases in high cholesterol-related outpatient visits, particularly among adults aged between 18 and 44.

Our findings add to the growing literature on the effects of DTCA for cholesterol-lowering drugs.^{5,6,9,17-19} Consistent with previous studies, we found an increase in the demand for advertised statins following DTCA.^{5,9} However, in contrast to previous work, we examined

ad exposure and statin sales at the DMA level thus exploiting variation in advertising across the DMAs examined. In addition, we used a more granular measure of DTCA intensity than most prior studies have employed, thus reflecting the magnitude of an ad's reach to a target audience. Finally, we adjusted for expenditures on free samples distributed through physician offices.^{20,21}

Interestingly, we found a greater effect of DTCA on young than middle-aged adults. Previous work suggests that the effect of DTCA on physician visits may be related to the background service utilization rate within the population. For example, a nationwide study of physician practices found a significant increase in diagnoses of high cholesterol cases after DTCA exposure among patients of lower socioeconomic status in routine cholesterol screening is less prevalent.⁹ Similarly, the observed effect of DTCA on high cholesterol-related outpatient visits among younger patients in this study may be explained by the relatively lower background rate of cholesterol screening and statin use for primary prevention in this population. We also identified a considerably stronger association between DTCA and rates of refills compared with that for new prescriptions among the commercially insured, which suggests that DTCA may improve adherence among the insured who have already been diagnosed and treated for high cholesterol.

Several strategies have been proposed to balance the apparent benefits and harms of DTCA. Some have called for a ban of DTCA citing the likelihood for misinformation and the potential contribution that such marketing may make in driving increased drugs spending.^{22,23} Others have suggested restrictions on the timing and content of pharmaceutical advertising so as to prevent this type of advertising until sufficient evidence regarding the utility of new products has been amassed.²⁴ These types of proposals would require legislative changes through the U.S. Congress. The 'Responsibility in Drug Advertising Act', which was introduced to Congress in February 2016, aims to accomplish the latter by placing a 3-year moratorium on advertising for products approved under the new drug application (505(b)) pathway.²⁵ The bill also gives the FDA the leeway to permit earlier advertising if deemed in the public's interest. In an effort at self-regulation, the Pharmaceutical Research and Manufacturers of America published industry guidelines in 2008 that recommended the submission of ads to the FDA prior to dissemination and the inclusion of non-pharmaceutical treatment alternatives in the ad where appropriate.²⁶ The feasibility of these approaches and their impact on the public's health remain to be seen.

Our study had several limitations. First, while we accounted for physician-distributed free drug samples in our analyses, such promotions do not account for the full extent of pharmaceutical promotional activities directed towards prescribers, and physician-directed promotion may have a stronger impact on prescribing than DTCA^{20,21} Therefore, if much more other promotional activities occurred on the same month as higher DTCA, we may over-estimate the impact of DTCA in our study; on the contrary, if much less occurred, we would underestimate the impact of DTCA. Second, we did not examine the effect of DTCA on appropriateness of care, nor adjust for levels of non-broadcast DTCA within the DMAs, such as advertising through magazines or other print materials, since that information was not available to us. Third, we did not adjust for the effect of so called "help-seeking ads" that may have run concurrently with the DTCA that we examined for rosuvastatin and

atorvastatin. Previous studies suggest that help-seeking ads, in which general information on a disease is provided, are more effective at changing patient health behavior than specific product claim ads.²⁷ Fourth, residual confounding is always possible. Fifth, our study was conducted based on data from 2005–2009, and since then there have been continued changes in the pharmaceutical marketplace, including a large growth in specialty products as well as other dynamics forcing changes in how manufacturers promote products. Despite these changes, the fundamental structure of pharmaceutical marketing remains based on physician detailing, free sample use and DTCA. Finally, our study was an ecologic one, and thus subject to the usual constraints of ecological studies with respect to causal inference.

CONCLUSIONS

Nearly twenty years after the loosening of regulations governing direct-to-consumer advertising of prescription drugs, the merits of this type of consumer outreach continue to be debated. Recent focus on the high cost of branded prescription drugs, as well as safety concerns about specific FDA-approved products, have led once again to calls to impose further limits on DTCA²⁵ or to ban it outright.^{23,24} However, it is unclear whether policy-makers and regulators have an appetite for such restrictions, and the recent Supreme Court decision to prevent the FDA from prosecuting a pharmaceutical manufacturer for truthful and non-misleading off-label promotion actually suggest the courts moving in the opposite direction.^{28–30} In the meantime, our study adds to a growing body of evidence about the effects of DTCA on one of the most commonly used class of medicines, demonstrating the association between DTCA and both prescription and non-prescription health care utilization for this widely used class of medicines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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* Values represent advertising intensity for Rosuvastatin (CrestorTM) and Atorvastatin (LipitorTM) within 75 Designated Marketing Areas as described in Methods
Source: NielsenTM Ratings

Figure 1.

Quarterly Statin DTCA for Rosuvastatin (Crestor) and Atorvastatin (Lipitor) across all DMAs, 2005–2010.*

Table 1

Bivariate and Multivariate Association between Direct-to-Consumer Advertising and Statin Sales

	Both Drugs	Rosuvastatin (Crestor)	Atorvastatin (Lipitor)
Total Prescriptions			
Crude ¹	6.71% ** (3.82%, 9.67%)	8.86% ** (4.37%, 13.55%)	10.46% ** (5.64%, 15.50%)
Adjusted ²	2.22% * (0.30%, 4.19%)	5.18% ** (2.35%, 8.09%)	4.21% * (0.67%, 7.87%)
New Prescriptions			
Crude ¹	6.57% ** (3.31%, 9.91%)	10.59% ** (5.87%, 15.52%)	8.97% ** (3.84%, 14.34%)
Adjusted ²	2.46% * (0.07%, 4.91%)	6.69% ** (3.58%, 9.90%)	3.56% (-0.56%, 7.86%)
Refilled Prescriptions			
Crude ¹	6.79% ** (3.96%, 9.69%)	7.96% ** (3.42%, 12.70%)	11.18% ** (6.34%, 16.24%)
Adjusted ²	2.12% * (0.31%, 3.96%)	4.43% ** (1.57%, 7.36%)	4.52% ** (1.11%, 8.05%)

*
p<0.05**
p<0.01

Values represent incidence rate ratio and 95% confidence intervals

¹Predictors include advertising as average views per household and time in months as categorical variable 1–60.²Predictors include ads ratings for any indication per 100 views, months as categorical variable 1–60, three promotional expenditures as free samples categories (low, medium or high), median age, median income in thousand, high cholesterol prevalence, smoking prevalence, physician density in thousand, population insured in million.

Source: IMS Health Xponent 2005–2010

Table 2

Bivariate and Multivariate Association between Direct-to-Consumer Advertising and Statin Prescription Claims among Commercially Insured

	Both Drugs	Rosuvastatin (Crestor)	Atorvastatin (Lipitor)
Total Prescriptions			
Crude ¹	5.24% [*] (2.35%, 8.21%)	6.52% [*] (1.42%, 11.88%)	8.41% ^{**} (3.85%, 13.18%)
Adjusted ²	2.73% [*] (0.77%, 4.73%)	5.17% [*] (1.52%, 8.94%)	5.03% [*] (1.32%, 8.88%)
New Prescriptions			
Crude ¹	5.36% [*] (1.76%, 9.09%)	7.50% [*] (1.80%, 13.51%)	7.92% [*] (2.59%, 13.51%)
Adjusted ²	2.28% [*] (0.04%, 4.58%)	5.38% [*] (1.24%, 9.68%)	3.57% [*] (0.10%, 7.15%)
Refill Prescriptions			
Crude ¹	6.67% ^{**} (3.81%, 9.61%)	6.07% (−0.17%, 12.70%)	11.73% ^{**} (5.46%, 18.36%)
Adjusted ²	4.25% [*] (1.14%, 7.44%)	6.14% [*] (1.57%, 10.90%)	8.03% [*] (2.04%, 14.36%)
Mail Order Prescriptions			
Crude ¹	11.64% ^{**} (7.18%, 16.29%)	13.42% ^{**} (7.20%, 20.01%)	18.89% ^{**} (11.25%, 27.05%)
Adjusted ²	5.48% [*] (1.90%, 9.17%)	7.04% [*] (1.70%, 12.66%)	10.33% ^{**} (4.47%, 16.52%)

*
p<0.05

**
p<0.001

Values represent incidence rate ratio and 95% confidence intervals

¹ Predictors include advertising as average views per household and time in months as categorical variable 1–60,

² Predictors include ads ratings for any indication per 100 views, months as categorical variable 1–60, three promotional expenditures as free samples categories (low, medium or high), median age, median income in thousand, high cholesterol prevalence, smoking prevalence, physician density in thousand

Source: Marketscan® Commercial Claims and Encounter Data 2005–2010

Table 3

Bivariate and Multivariate Association between Direct-to-Consumer Advertising and High Cholesterol-Related Outpatient Visits

	Analysis	
	Crude ¹	Adjusted ²
Same Month	5.03% ** (2.15%, 7.99%)	1.44% (-0.38%, 3.29%)
1 month lag	5.09% ** (2.19%, 8.07%)	1.49% (-0.30%, 3.32%)
2 month lag	4.91% ** (2.13%, 7.76%)	1.56% (-0.12%, 3.27%)
Stratified by Sex		
Males	4.82% ** (2.08%, 7.64%)	1.57% (-0.19%, 3.35%)
Females	5.37% ** (2.31%, 8.52%)	1.34% (-0.61%, 3.32%)
Stratified By Age Group		
0 – 19 years	7.69% ** (3.00%, 12.60%)	4.58% * (0.26%, 9.08%)
20 – 44 years	5.56% ** (2.87%, 8.33%)	3.15% ** (0.98%, 5.37%)
45 – 64 years	3.74% * (0.95%, 6.59%)	0.51% (-1.49%, 2.55%)

*
p<0.05

**
p<0.01

Values represent incidence rate ratio and 95% confidence intervals

¹ Predictors include advertising as average views per household and time is months as categorical variable 1–60,

² Predictors include ads ratings for any Indication per 100 views, months as categorical variable 1–60, three promotional expenditures as free samples categories (low, medium or high), median age, median income in thousand, high cholesterol prevalence, smoking prevalence, physician density in thousand

Source: Marketscan® Commercial Claims and Encounter Data 2005–2010