The commercial contribution of clinical studies for pharmaceutical drugs

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ABSTRACT

Pharmaceutical drugs are rigorously evaluated through clinical studies. The commercial consequences of such clinical studies, both to the promotion for and sales of drugs, are largely under-researched. The present study answers the following research questions: 1) How does the evolution of clinical study outcomes affect product sales? 2) How does the evolution of clinical study outcomes affect a firm's promotion expenditures to physicians and consumers? 3) Is the assessment of the responsiveness of sales to promotion expenditures biased when the analyst omits the role of clinical studies? We summarize a comprehensive body of clinical studies in three metrics: valence, dispersion, and volume. We extend the literature with the following findings. A higher valence and volume of clinical studies (i.e., more positive and larger number of studies) increase sales. A higher valence of clinical studies increases spending on both direct-to-consumer advertising and direct-to-physician promotion. A higher dispersion among clinical studies decreases spending on direct-to-consumer advertising. A higher volume of clinical studies has no effect on direct-to-physician promotion, but decreases direct-to-consumer advertising. Furthermore, the results show that omitting these metrics from a market response model leads to an overestimation of the responsiveness of sales to promotion expenditures.

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1. Introduction

Pharmaceutical firms or independent researchers conduct clinical studies to test and compare the efficacy of drugs with therapeutic alternatives or placebos. They use standardized protocols under controlled conditions to generate scientifically valid results. Firms, researchers, or journal publishers, among others, often translate clinical studies published in scientific journals in press releases that are picked up by mass media (Polidoro & Theeke, 2012). Thereby the outcome of clinical studies may affect sales of and promotion for the respective drug. The most common promotion efforts in the pharmaceutical industry are direct-to-physician promotion (DTP), such as detailing and journal advertising, and direct-to-consumer advertising (DTCA) (Stremersch, 2008; Stremersch & Van Dyck, 2009).

Consider, for example, the publication of three clinical studies on Lipitor in the last quarter of 2002 (Athyros et al., 2002; Colivicchi et al., 2002; Olsson et al., 2002). All three clinical studies reported a lower drug efficacy of Lipitor than earlier studies over three different patient populations. In that quarter, the sales of Lipitor grew only 2%, compared to a median

growth of 3.5% of prior periods. Pfizer also substantially decreased its promotion efforts towards both physicians and consumers to its lowest level in four years. To uncover what relationships of such type exist in a large sample, we address the following questions:

- How does the evolution of clinical study outcomes affect the sales of a drug?
- How does the evolution of clinical study outcomes affect a firm's promotion expenditures to physicians and consumers for that drug?
- Is an assessment of the responsiveness of sales to promotion expenditures biased when the analyst omits the role of clinical studies?

We collected a comprehensive body of clinical studies on statins, published both prior to and after approval. The sample also includes published meta-analyses of clinical trials. Inspired by the marketing literature on user and expert reviews, we characterize the evolution of clinical studies using three time-varying metrics: valence, dispersion, and volume (Basuroy, Chatterjee, & Ravid, 2003; Chevalier & Mayzlin, 2006; Chintagunta, Gopinath, & Venkataraman, 2010; Godes & Mayzlin, 2004; Liu, 2006; Onishi & Manchanda, 2012; Sun, 2012). We define valence of clinical studies as the average efficacy of a drug to achieve a pre-determined outcome across a sample of studies. For example, we measure the valence of clinical studies of a statin at a certain point in time as the average reduction in low-density lipoprotein (LDL) cholesterol reported across all clinical studies available at that time. Dispersion of clinical studies at a certain point in time is the variance in this efficacy reported across all clinical studies available at that time. Volume of clinical

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studies at a certain point in time is the total number of clinical studies that report a drug's efficacy up to that point in time.

The application of these three concepts to clinical reviews (i.e., clinical studies are "reviews" of a treatment by trained scientists) is new and we show below that this new conceptualization leads to relevant insights. Currently, the predominant approach in pharmaceutical research to account for conflicting evidence from multiple studies is to meta-analyze such studies (Whitehead, 2002), which include summarizing the body of clinical studies on a drug by valence, and to a certain extent, dispersion. Prior studies have also examined the number of studies (i.e., volume of studies) (Adams & Griliches, 1996).[3] However, none studies the joint evolution of valence, dispersion, and volume of clinical studies and their effects on promotion expenditures and sales.

In this paper, we develop hypotheses on the effects of valence, dispersion, and volume on direct-to-consumer advertising, direct-to-physician promotion, and sales. We model the dynamic impact of these variables on one another through a random coefficients vector error correction model that controls for the heterogeneity across drugs and the endogeneity of promotion expenditures. Depending on the outcomes of unit root tests, we use the long-term or cumulative effects to test our hypotheses.

We extend the sparse literature in this domain in several ways. First, we use a richer conceptualization of clinical studies, i.e., the exact outcome measure of each clinical study. While Azoulay (2002) and Chintagunta, Jiang, and Jin (2009) code studies as negative, neutral or positive, we operationalize valence as a continuous measure. Also, we add dispersion and volume, thereby offering a more complete conceptualization. Second, Azoulay (2002) studies H_2-antagonists from 1977 to 1993. This means his sample predates DTCA, while ours does not, as it runs from the category's inception in 1982 till 2007. Therefore, Azoulay (2002) studies only detailing and journal advertising, not DTCA. Since 1997, DTCA has become an important component of pharmaceutical firms' promotion strategy, especially in the statin category. The contrast between firms responding through detailing to physicians or advertising to consumers is conceptually interesting. Third, Azoulay (2002) estimates a static demand model with homogeneous effects across brands. We develop a dynamic model, which is, as also conceded by Azoulay (2002), a more appropriate modeling framework, and we allow for heterogeneous effects across brands. Fourth, we assess whether the omission of clinical study outcomes in sales response models biases the promotion estimates, which has not been done before.

We derive the following new findings that extend the literature cited above. A higher valence of clinical studies increases direct-to-consumer advertising, direct-to-physician promotion, and sales. A higher dispersion of clinical studies decreases spending on direct-to-consumer advertising, but does not affect direct-to-physician promotion or sales. A higher volume of clinical studies has no effect on direct-to-physician promotion, but decreases direct-to-consumer advertising. A higher volume of clinical studies also increases sales. Taken together, these results suggest that while firms rush to inform physicians and consumers of improved clinical evidence, they reduce advertising to consumers when the results disconfirm prior findings (higher dispersion) or when many studies are released (higher volume). Furthermore, we find that omitting clinical study outcomes from a market response model leads to an overestimation of the responsiveness of sales to promotion expenditures.

These results hold several relevant insights for managers and researchers. First, our method is able to quantify the commercial value of clinical studies. We show how the total effect of a clinical study on sales is composed of the direct effect on sales, ceteris paribus, and an indirect effect on decisions on promotion expenditures, which subsequently may affect sales as well. Second, our results provide insights

into pharmaceutical firms' reaction to clinical study outcomes. Firms can use this information to anticipate competitors' actions. Third, for analysts measuring the impact of pharmaceutical promotion on sales, we show that one needs to account for clinical studies in the econometric model.

2. Theory

This section provides the theoretical background on clinical studies and pharmaceutical firms' promotion to patients and physicians. We then develop hypotheses on how clinical studies may affect both firms' promotion expenditures and drug sales.

2.1. Background: clinical studies and drug promotion to patients and physicians

Trained scientists conduct clinical studies through systematic observation, measurement of, and experimentation with a drug using the scientific method. They adhere to strict protocols of regulators and institutes. Scientists from drug manufacturers, their competitors, or independent research institutes (e.g., universities) may conduct clinical studies. We use clinical studies to refer only to testing on humans.

One typically discerns clinical studies across four phases. Phase 1 testing is typically conducted on healthy volunteers to monitor safety and side effects. Phase 2 and Phase 3 testing is typically conducted on patients suffering from the disease that the drug targets. After approval and launch, Phase 4 clinical studies test the drug on even larger numbers of patients or on specialized groups of patients.

Independent clinical studies are more common post-launch than pre-launch. When a drug manufacturer sponsors researchers, the latter are required to reveal this sponsorship. Regulatory bodies or scientific journals publish guidelines for the reporting of clinical studies, such as on drug safety, side effects, and efficacy.

The sponsorship of clinical studies (see for more details DeAngelis & Fontanarosa, 2008), their diversity in design, and patient population may drive dispersion in study outcomes. Sponsorship bias – manufacturers often report a higher efficacy of their drug than competitors or independent researchers – may have multiple causes. First, selection bias may exist in project selection (e.g., by choosing a weaker competitor or a more favorable testing condition) (Doucet & Sismondo, 2008). Manufacturers may also stop a clinical study before completion if the initial results are unfavorable (Lexchin, Bero, Djulbegovic, & Clark, 2003). Both strategies may inflate the valence of the body of clinical studies. Another important goal of manufacturer-sponsored studies is to establish a consistent profile of the drug across studies (Sismondo, 2009). Independent researchers or competitors may have an incentive to balance positive claims by testing the drug in less favorable conditions, affecting valence, dispersion, and volume.

Firms may respond to clinical study outcomes through direct-to-consumer advertising or direct-to-physician promotion, the two most important types of marketing spending among branded pharmaceutical firms. Direct-to-consumer advertising may increase drug awareness, simplify complex information on the drug to facilitate comprehension, encourage patients to discuss new treatment options with their physicians, or increase compliance as a result of better education and involvement. While direct-to-consumer advertising positively influences stock returns (Osinga, Leeflang, Srinivasan, & Wieringa, 2011), most research finds direct-to-consumer advertising to have only a weak effect on category sales (Iizuka, 2004). Research on brand sales concludes that direct-to-consumer advertising may moderately increase physician visits (Liu & Gupta, 2011), while it has an even more limited effect on brand choice, if it has any effect at all (Iizuka & Jin, 2007; Stremersch, Landsman, & Venkataraman, 2013).

Direct-to-physician promotion typically has a positive impact on prescriptions (Manchanda & Honka, 2005), though some studies have reported these effects to be modest (Mizik & Jacobson, 2004).

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[3] While this measure is sometimes weighted by citations, we choose not to do that as citations are noisy measures of knowledge flows (Roach & Cohen, 2013). Instead we measure the volume by only selecting clinical studies from the top quartile of journals.

Venkataraman and Stremersch (2007) show that brand sales may respond very differently to detailing expenditures, according to the effectiveness and side effect profile of the drug. Prior research suggests that physicians may be cautious about the information given by sales representatives (Cooper, Schriger, Wallace, Mikulich, & Wilkes, 2003; Ziegler, Lew, & Singer, 1995). Manchanda and Honka (2005) suggest that physicians have negative to neutral attitudes toward sales representatives. Many physicians are risk averse (Camacho, Donkers, & Stremersch, 2011) and may show persistence in drug preferences, which could act as a barrier to the adoption of new drugs or to switching between drugs, even if the drug is heavily promoted to physicians.

2.2. Hypotheses

Fig. 1 graphically presents our conceptual framework and guides the hypotheses and model development on the effects of valence, dispersion, and volume of clinical studies on promotion expenditures and sales. According to this framework, the total effect of clinical studies on sales is composed of the direct effect on sales and an indirect effect through decisions on promotion expenditures, which subsequently may affect sales as well. We now propose our hypotheses on these effects.

2.2.1. Impact of valence of clinical studies on promotion expenditures and sales

Higher valence (i.e., more positive clinical study results) may support the firm's beliefs about the true efficacy of the drug and validate past promotion expenditures. A higher valence of clinical studies may increase managerial confidence in the drug, which in turn, increases the extent to which managers can justify future promotion spending (Mantrala, 2002). The firm may increase its promotion expenditures to both patients and physicians to communicate higher valence (Ippolito & Mathios, 1990).

Note that one may argue that an increase in valence could also lead to a decrease in promotion expenditures since the firm might not need to "advertise" the product and instead might choose to let the positive news spread by word-of-mouth. We believe this choice to be uncommon among pharmaceutical firms for two reasons. First, not all physicians actively follow the scientific literature and surveys show that most physicians tend to scan important findings infrequently (Burke, DeVito, Schneider, Julien, & Judelson, 2004). Second, the duration of patent protection for prescription drugs is limited, within which branded firms must maximize their earnings from the drug. Hence, firms have a strong incentive to aggressively market their product before patent expiry and to push news on higher valence to the market quickly instead of patiently waiting for the information to reach the market.

Thus, we posit:

H1. Valence of the body of clinical studies affects both a) direct-to-consumer advertising and b) direct-to-physician promotion, positively.

A higher valence of clinical studies for a drug may indicate its higher quality to both patients and physicians. Product quality is positively related to sales (Tellis & Johnson, 2007). Thus, positive clinical studies may increase sales. Indeed, the few studies relating information from clinical studies to sales, find that positive studies increase drug sales (Azoulay, 2002; Ching & Ishihara, 2010; Chintagunta et al., 2009; Cockburn & Anis, 2001).

Hence, we propose:

H2. Valence of the body of clinical studies affects sales positively.

2.2.2. Impact of dispersion of clinical studies on promotion expenditures and sales

An increase in dispersion across clinical studies may increase the perceived uncertainty about a drug. The firm may try to reduce that uncertainty by directing higher marketing spending towards physicians, who may find it easier to understand the cause of higher dispersion than patients (Ching & Ishihara, 2010; France & Bone, 2009). The firm may decrease promotions to consumers, because all three typical forms of direct advertising towards consumers – disease awareness advertising, product claim advertising, and reminder advertising – have low educational potential and mainly focus on an emotional appeal towards patients (Frosch, Krueger, Hornik, Cronholm, & Barg, 2007; Wolfe, 2002). Hence, these forms of advertising have limited scope for educating consumers about probable causes for variation of drug efficacy across settings (Hollon, 2005).

$H_4(-)$

$H_2(+)$

$H_{1b}(+)$ $H_{1a}(+)$

$H_{3a}(-)$

$H_{3b}(+)$

$H_{5a}(+)$

$H_{5b}(+)$

$H_6(+)$
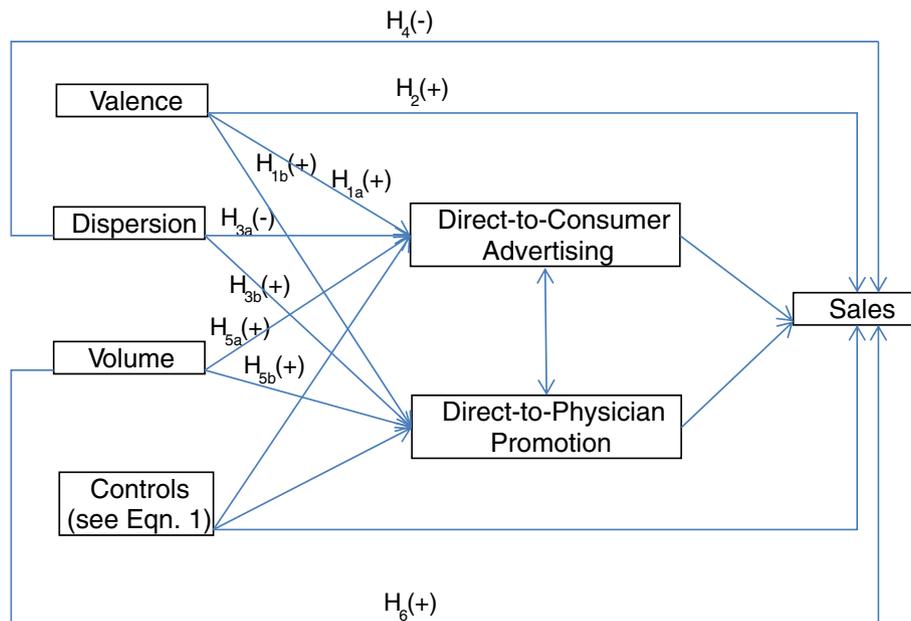
H_{1a}, H_{1b}, H_2, H_{3a}, H_6 supported; H_{5a} is significant but negative.

Fig. 1. Conceptual framework.

Hence, we propose the following:

H3. Dispersion of the body of clinical studies affects a) direct-to-consumer advertising negatively and b) direct-to-physician promotion positively.

As an increase in dispersion across clinical studies may increase the perceived uncertainty about the drug, it may subsequently reduce sales. Patients may refrain from using the drug if they learn – from searching the Internet, mass media reports or word-of-mouth – that the efficacy of the drug is mixed across study populations. Physicians may abstain from prescribing the drug if they learn – from competing sales reps, competitive journal advertisements, reading scholarly journals or word-of-mouth – that different clinical studies of a drug contradict each other. These effects may be pronounced in the context of prescription drugs, because the product itself often increases risk-averse behavior (Camacho et al., 2011; Crawford & Shum, 2005; Eeckhoudt, 1985).

Hence, we propose:

H4. Dispersion of the body of clinical studies affects sales negatively.

2.2.3. Impact of volume of clinical studies on promotion expenditures and sales

Pharmaceutical firms have economic incentives to conduct more studies on drugs with a higher clinical potential. An increasing number of studies may support pharmaceutical managers' confidence on the market potential of the drug (Mantrala, 2002). Such increased confidence may translate into higher promotion expenditures, as confident managers may overestimate the return on their investments (Malmendier & Tate, 2005). A higher volume of clinical studies may also indicate a higher commitment of the manufacturer to the drug, which may likely also extend to increased promotion expenditures.

Hence, we propose:

H5. Volume of the body of clinical studies affects both a) direct-to-consumer advertising and b) direct-to-physician promotion, positively.

A higher volume of clinical studies may increase awareness and knowledge about the drug among patients and physicians. For instance, if a drug is covered in many clinical studies, a patient who seeks information online is more likely to find relevant information about it. Additionally, if a drug is covered by many studies and is frequently mentioned in scientific literature, it may also have a higher salience and trigger more word-of-mouth among physicians. Salience and word-of-mouth are important drivers of physician prescription behavior (Camacho et al., 2011; Venkataraman & Stremersch, 2007). In general, because clinical studies often lead to news mentions, both patients and physicians may be more frequently exposed to such mentions the more studies appear (Polidoro & Theeke, 2012).

Hence, we propose:

H6. Volume of the body of clinical studies affects sales positively.

3. Data

This section presents the research context, describes the data collection procedure, and provides descriptive statistics.

3.1. Research context: the statin market

Statins represent the largest therapeutic category in the U.S. in terms of dollar sales, during a large part of our observation window (Donohue, Cevasco, & Rosenthal, 2007). Statins (HMG-CoA reductase inhibitors; ATC: C10AA) influence the rate-limiting enzyme in cholesterol synthesis and lower excessive cholesterol buildup, particularly low-density lipoprotein (LDL) cholesterol. Cholesterol can cause the buildup of plaque on the inside walls of arteries. Plaque in a blood vessel to the heart may cause a

heart attack. Plaque in a blood vessel to the brain may cause a stroke. If blood supply to the arms or legs is reduced, a patient may suffer from difficulty in walking and eventually incur gangrene or tissue death.

We collected clinical studies of the seven main drugs in this category (approval dates, brand names, and firms in parentheses): lovastatin (1987, Mevacor by Merck & Co.), pravastatin (1991, Pravachol by Bristol-Myers Squibb), simvastatin (1991, Zocor by Merck & Co.), fluvastatin (1993, Lescol by Novartis), atorvastatin (1996, Lipitor by Pfizer), cerivastatin (1997, Baycol by Bayer; cerivastatin was withdrawn from the market in 2003), and rosuvastatin (2003, Crestor by AstraZeneca).[4] We excluded pitavastatin because it was not approved in the U.S. at the time this study was conducted.

3.2. Data collection

We consulted electronic bibliographic databases, including Medline, EMBASE, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CCTR), the Database of Abstracts of Reviews of Effects (DARE), the Science Citation Index, the NHS Economic Evaluation Database (NHS EED), and the Health Technology Assessment Database (NHS HTA). We decided to limit the search to the top quartile of journals (62 journals in total) in the following fields: cardiac and cardiovascular systems, critical care medicine, internal medicine, and peripheral vascular disease. The resulting clinical studies cover the period from the category's inception in 1982 until 2007. Approximately 26% of all studies were conducted before the approval of the drug by the FDA. The data collection took almost two years due to the intricate process of the data collection and the complex nature of the content in the clinical studies.

We gathered the LDL reduction of statins, in percentage terms, as primary measure of their efficacy, across all these studies. Statins may also increase high-density lipoprotein (HDL) cholesterol and decrease excessive triglyceride levels. However, to primarily achieve an HDL increase or triglyceride decrease, physicians often use other classes of drugs, such as Omega-3 fatty acids or niacin for HDL and fibrates or niacin for triglycerides, possibly in combination with a statin (for LDL reduction). In our dataset, 97% of clinical studies report the efficacy regarding LDL reduction, whereas only 78% and 73% of all studies report the efficacy regarding HDL and triglycerides, respectively. We acknowledge recent studies (e.g., Liao & Laufs, 2005) that demonstrate the so-called pleiotropic effects of statins beyond LDL reduction (e.g., anti-inflammatory properties).

We excluded two types of clinical studies: (1) Studies that do not provide the efficacy of the drug versus a placebo, because we use this placebo comparison as a base level to measure efficacy (without such a base level, we cannot compare valence or dispersion across clinical studies); and (2) studies of multi-interventional therapies (e.g., statins and fibrates) wherein the independent effect of the statin could not be separated from the combined effect. Using these rules, we extracted 171 studies with 470 unique drug–dosage combinations. This extraction was performed before any model estimation.

We trained two research assistants to extract data from the clinical studies and fill out a standardized form. We checked for consensus by having the research assistants code a random sample of clinical studies independently. The research assistants also coded whether the drug's manufacturer sponsored the study. We measured valence of clinical studies as the average efficacy of a drug to achieve a pre-determined outcome across a sample of studies. We measured dispersion of clinical studies at a certain point in time as the variance in this efficacy reported across all clinical studies available at that time. We measured volume of clinical studies at a certain point in time as the total number of clinical studies that report a drug's efficacy up to that point in time.

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[4] Our study does not include red yeast rice. It contains naturally occurring lovastatin as an active ingredient. Precise data are unavailable because it is sold both as a drug and as a dietary supplement in our observation window.

To relate clinical studies on statins to direct-to-physician promotion and sales, we obtained quarterly U.S. data on direct-to-physician promotion and sales between 1997 and 2007 for each of the seven drugs, from IMS Health in the Netherlands. Sales are measured in kilograms per active ingredient of the branded drug (i.e., it does not include the generics if these are available) at the wholesale level (which is a close approximation of the prescriptions written during the quarter, because the retail channel for pharmaceuticals keeps limited stock). Direct-to-physician promotion is the sum of detailing and advertising expenditures in medical journals targeting physicians. We obtained quarterly data on direct-to-consumer advertising expenditures for every drug in the sample over the same time period from KantarMedia.

3.3. Descriptive statistics

We now present descriptive statistics for both the study design and the outcome of the 470 clinical studies across all drugs in our sample from 1982 to 2007. There is substantial variation in the dosages tested in clinical studies across drugs with an average dosage of 32.1 mg (with cerivastatin excluded as cerivastatin has a different mechanism of action). We find that studies in this category typically last between 6 months and a year with an average duration of 34 weeks. Interestingly, the share of studies sponsored by the manufacturer varies quite substantially across drugs. Pfizer funded 65% of all studies of Lipitor (atorvastatin), while Bayer only funded 27% of all studies of Baycol (cerivastatin). Overall in our sample, we find that manufacturers sponsored 55% of all studies. On average, the valence of studies was highest for rosuvastatin and lowest for fluvastatin with an average valence of 36%. The dispersion among studies was largest for atorvastatin and smallest for fluvastatin with an average dispersion of 10.4%. The largest number of studies appeared on atorvastatin and rosuvastatin, while fewest appeared on cerivastatin with an average volume of 67 studies per drug. Table 1 provides the sales and promotion expenditures for all drugs between 1997 and 2007. Note that direct-to-physician promotion expenditures are smaller than direct-to-consumer advertising expenditures for four out of the seven drugs.

Fig. 2 plots descriptives of the clinical studies for the top-selling three drugs in our sample. Fig. 2A shows the evolution of valence over time. We find that valence is neither monotonically increasing nor decreasing. Fig. 2B plots dispersion over time. The plot shows that dispersion is mostly monotonically decreasing over time except for simvastatin. Fig. 2C shows volume of clinical studies over time. Fig. 2C shows particularly rapid increases in the number of clinical studies of atorvastatin (Lipitor), while the growth in clinical studies is slower for simvastatin (Zocor) and pravastatin (Pravachol).
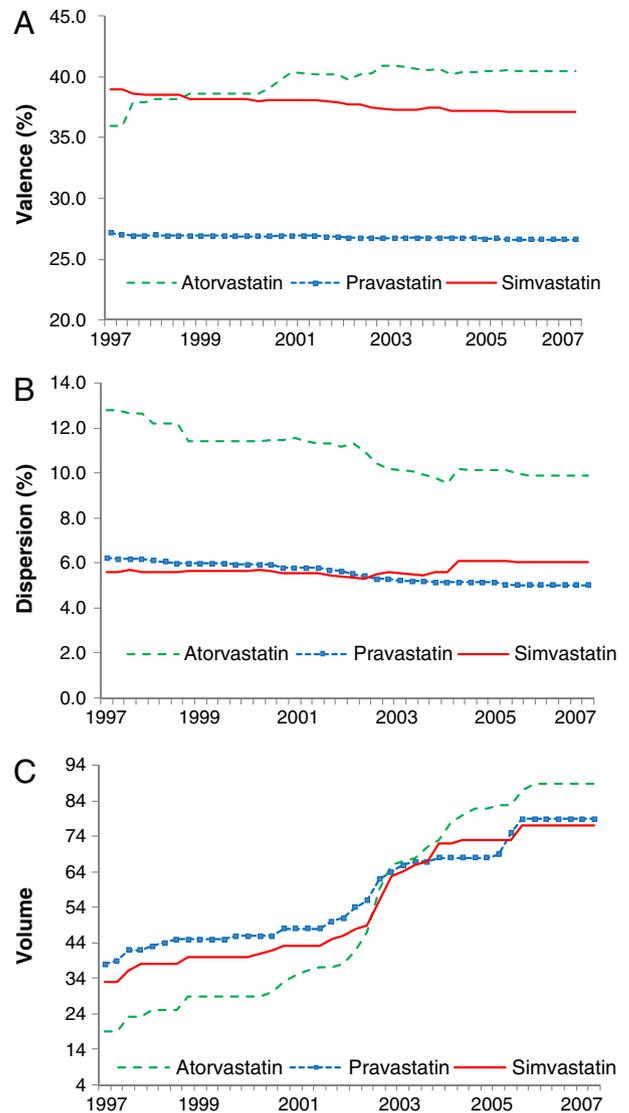

Fig. 2. A: Valence of clinical studies for top-selling drugs over time. B: Dispersion of clinical studies for top-selling drugs over time. C: Volume of Clinical Studies for Top-Selling Drugs over Time.

Table 1
Descriptive statistics on average quarterly sales and promotion expenditures.

Drug	Sales (kg)	DTP ('000 $)	DTCA ('000 $)
Atorvastatin	8284.1	12,422.2	21,371.3
	(3266.3)	(4506.9)	(15,459.8)
Cerivastatin	3.4	2022.4	2.3
	(6.5)	(2844.8)	(8.7)
Fluvastatin	1763.6	3117.8	53.0
	(457.6)	(1929.6)	(141.6)
Lovastatin	1674.6	995.3	.0
	(1272.3)	(1660.5)	(0.0)
Pravastatin	2950.2	4683.9	6112.5
	(511.7)	(2567.6)	(7954.4)
Rosuvastatin	375.8	7434.7	14,227.3
	(510.0)	(9046.7)	(24,573.2)
Simvastatin	5510.4	8265.8	13,970.1
	(2425.2)	(4708.2)	(11,451.5)

Note: Standard deviations in parentheses.
Note: These descriptives are based on data on branded drugs from the third quarter of 1997 until the fourth quarter of 2007.

4. Model

Our goal is to uncover the impact of clinical studies on sales and promotion expenditures. Ideally, our model is able to do the following:

- Estimate the dynamic effects of clinical studies on direct-to-consumer advertising (DTCA), direct-to-physician promotion (DTP), and sales. For example, a negative clinical study may hurt the brand's sales for more than one period.
- Control for possible endogeneity of DTCA and DTP. Not properly accounting for potential endogeneity may bias the estimation of the impact of clinical studies.
- Allow for heterogeneity across brands, as ignoring heterogeneity across cross-sectional units may bias the parameters (Pesaran & Smith, 1995).
- Control for external shocks to the market such as a new product introduction or other events that may influence the dependent variables or confound clinical studies.
- Ensure parsimony.

To satisfy these requirements, we select a random coefficients vector error correction model (VECM) with explanatory variables (Dekimpe &

Hanssens, 1999). This model jointly estimates a system of endogenous variables – DTCA, DTP, and sales – as a function of lagged endogenous variables, summary metrics of clinical studies, and control variables. The model accounts for endogeneity and allows for a dynamic impact of the endogenous and exogenous variables.

There are various approaches to allow for heterogeneity across brands, from including brand-specific fixed effects to estimating separate regressions for each brand. In our application, we have only a limited number of cross-sectional units and time periods. Horváth and Wieringa (2008) have tested various approaches to control for heterogeneity across cross-sectional units and found that the random coefficients approach is a robust and parsimonious way to account for different forms of heterogeneity. We select this approach, which computes a variance-weighted estimate of the brand-specific parameters and the average parameters across brands. The approach is especially useful for brands with a limited number of observations. We further ensure parsimony by using a variable selection mechanism that is discussed in more detail in the estimation section. We also estimated a fixed effects model and found it to fit the data worse than the random coefficients model.

Before specifying our model, we need to perform panel unit root and cointegration tests to avoid misspecification, which may arise if one or more of the endogenous variables is evolving (see Breitung and Pesaran (2008) for a comprehensive discussion on the various available tests).

4.1. Testing for panel unit roots and cointegration

We perform a panel unit root test outlined in Im, Pesaran, and Shin (2003) to test for the presence of unit roots in the endogenous variables. We test the null hypothesis that all brands contain a unit root. This test relies on brand-specific augmented Dickey–Fuller test statistics and averages these test statistics across brands to test for the joint presence of a unit root across brands. This test allows us to correct for unbalanced panels, as our dataset contains one drug (cerivastatin) that was withdrawn from the market and one drug (rosuvastatin) that was introduced during our sample period (Breitung & Pesaran, 2008).

To perform the unit root test, we need to decide which deterministic variables, a constant and/or linear trend, to include in the test. As the test statistic for the panel unit root test is dependent on the deterministic components included in the test, we need to include similar deterministic components for each individual series. Following the procedure outlined in Dolado, Jenkinson, and Sosvilla-Rivero (1990) and in Enders (2010), we start by including a constant and linear trend for each individual series and assess the significance of the trend term. If the trend term is insignificant for the majority of the series, we test for unit roots by only including the constant, and repeat the process. For each individual series, we separately select the optimal lag length for the unit root test to eliminate possible serial correlation using the Schwarz information criterion.

In addition, we test for the presence of structural breaks, because not properly accounting for structural breaks typically biases the unit root test towards finding a unit root. We include step dummies that take the value one during and after the period of the possible structural break. We consider three moments at which a structural break may occur: when cerivastatin was withdrawn (3rd quarter of 2001), when rosuvastatin was introduced (3rd quarter of 2003), and when simvastatin and pravastatin lost their patent protection (2nd quarter of 2006).

If more than one endogenous variable contains a unit root, we test for cointegration between the evolving variables. In line with the panel unit root test of Im et al. (2003), we use the panel cointegration test of Larsson, Lyhagen, and Löthgren (2001). This test computes the cointegration rank trace test statistic based on Johansen's (1988) cointegration test for each cross-sectional unit and combines those into one test statistic. This test allows for multiple cointegration relationships among the integrated variables. We include step dummies, deterministic terms, structural breaks, and optimal lag lengths using the procedure explained for the unit root test above.

4.2. Model specification

We specify a random coefficients vector error correction model of order P, VECM(P). The most general form, allowing for unit roots and cointegration, for brand j at time t is as follows:

$$
\begin{bmatrix} d\log\left(DTCA_{jt}\right) \\ d\log\left(DTP_{jt}\right) \\ d\log\left(Sales_{jt}\right) \end{bmatrix} = \begin{bmatrix} \mu_{j,DTCA} \\ \mu_{j,DTP} \\ \mu_{j,Sales} \end{bmatrix} + \begin{bmatrix} \alpha_{j,DTCA} & 0 & 0 \\ 0 & \alpha_{j,DTP} & 0 \\ 0 & 0 & \alpha_{j,Sales} \end{bmatrix} \begin{bmatrix} e_{j,t-1,DTCA} \\ e_{j,t-1,DTP} \\ e_{j,t-1,Sales} \end{bmatrix}
$$

$$
+ \sum_{p=1}^{P} \begin{bmatrix} \beta_{j11}^{p} & \beta_{j12}^{p} & \beta_{j13}^{p} \\ \beta_{j21}^{p} & \beta_{j22}^{p} & \beta_{j23}^{p} \\ \beta_{j31}^{p} & \beta_{j32}^{p} & \beta_{j33}^{p} \end{bmatrix} \begin{bmatrix} d\log\left(DTCA_{j,t-p}\right) \\ d\log\left(DTP_{j,t-p}\right) \\ d\log\left(Sales_{j,t-p}\right) \end{bmatrix}
$$

$$
+ \begin{bmatrix} \gamma_{j11} & \gamma_{j12} & \gamma_{j13} \\ \gamma_{j21} & \gamma_{j22} & \gamma_{j23} \\ \gamma_{j31} & \gamma_{j32} & \gamma_{j33} \end{bmatrix} \begin{bmatrix} d\log\left(Valence_{jt}\right) \\ d\log\left(Dispersion_{jt}\right) \\ d\log\left(Volume_{jt}\right) \end{bmatrix}
$$

$$
+ \begin{bmatrix} \phi_{j11} & \cdots & \phi_{j18} \\ \phi_{j21} & \cdots & \phi_{j28} \\ \phi_{j31} & \cdots & \phi_{j38} \end{bmatrix} \begin{bmatrix} d\log\left(TimeSinceLaunch_{jt}\right) \\ d\log\left(Time_{jt}\right) \\ WithdrawalCeriva_{jt} \\ IntroRosuva_{jt} \\ PatentExpiry_{jt} \\ d\log\left(CompDTCA_{j,t-1}\right) \\ d\log\left(CompDTP_{j,t-1}\right) \\ d\log\left(CompSales_{j,t-1}\right) \end{bmatrix} + \begin{bmatrix} \eta_{jt,DTCA} \\ \eta_{jt,DTP} \\ \eta_{jt,Sales} \end{bmatrix}.
$$

$$(1)$$

We collect all brand-specific parameters per brand in a common vector, $\pi_j = [\mu_{j,DTCA}, ..., \mu_{j,Sales}, \alpha_{j,DTCA}, ..., \alpha_{j,Sales}, \beta_{j11}, ..., \beta_{j33}, \gamma_{j11}, ..., \gamma_{j33}, \phi_{j11}, ..., \phi_{j38}]'$ of dimension 48×1 (the total number of brand-specific parameters for P equal to one). π_j is normally distributed across brands, $\pi_j \sim N(\overline{\pi}, \Sigma_\pi I)$, with $\overline{\pi}$ a 48×1 vector and $\Sigma_\pi I$ a 48×48 diagonal covariance matrix. The disturbance terms follow a multivariate normal distribution, $[\eta_{jt,DTCA}, \eta_{jt,DTP}, \eta_{jt,Sales}]' \sim MVN(0, \Sigma)$, within a brand and are independent across brands. $dlog$ indicates that we take first differences from the log-transformed variable. Log-transformed variables reduce the impact of outliers and allow us to interpret the parameters for the clinical studies as immediate elasticities. Table 2 summarizes the variables in the model.

When we find no unit root for one or more endogenous variables, the model is estimated for those variables in logs instead of first differences of the logs. In cases where evidence for cointegration is found, e represents the error correction term. If no evidence of cointegration is found, e drops out of the model. e_{t-1} is the lagged residual from the long-term equilibrium relationship between the endogenous variables. This lagged residual is obtained from regressing each cointegrated variable on the other cointegrated variables and possibly an intercept and deterministic trend terms (Dekimpe & Hanssens, 1999). α constitutes the speed of adjustment to the long-term equilibrium for each of the three endogenous variables, and β represents the autoregressive parameters up until order P.

The μ-vector includes the constants for DTCA, DTP, and sales. The γ-parameters capture the immediate elasticity of valence, dispersion, and volume on promotions and sales. We use the long-term or cumulative elasticities of these variables to test our hypotheses, which we compute using impulse response functions as discussed below.

We also control for four important factors that may affect promotion expenditures and sales. First, we include the time that a drug has been on the market to control for lifecycle effects and a time trend starting at the beginning of our data period. Second, we control for key events that may have an impact on promotion expenditures and sales — the withdrawal of cerivastatin, the introduction of rosuvastatin, and the patent expiry of pravastatin and simvastatin. These dummies are equal to one in and after the quarter in which the event happened, as

Table 2
Variables in Eq. (1).

Variable	Description
$DTCA_{jt}$	DTCA (in $ 000s) for drug j at time t
DTP_{jt}	DTP (in $ 000s) for drug j at time t
$Sales_{jt}$	Sales (in kg) for drug j at time t
$Valence_{jt}$	Average efficacy of drug j across all clinical studies available at time t
$Dispersion_{jt}$	Standard deviation in efficacy of drug j across all clinical studies available at time t
$Volume_{jt}$	Number of clinical studies on drug j available at time t
$TimeSinceLaunch_{jt}$	Number of quarters since the launch of drug j to the market at time t
$Time_{jt}$	A linear trend term (value equal to 1 in period 1 and so on)
$Withdrawal\_Ceriva_{jt}$	A dummy (=1 in and after the period in which cerivastatin is withdrawn from the market, 0 otherwise)
$IntroRosuva_{jt}$	A dummy (=1 in and after the period in which rosuvastatin is introduced to the market, 0 otherwise)
$PatentExpiry_{jt}$	A dummy (=1 for drugs at and after their patent expiration, 0 otherwise)
$CompDTCA_{j,t-1}$	Lagged sum of DTCA (in $ 000s) in quarter $t-1$ across all drug j's competitors
$CompDTP_{j,t-1}$	Lagged sum of DTP (in $ 000s) in quarter $t-1$ across all drug j's competitors
$CompSales_{j,t-1}$	Lagged sum of sales (in kg) in quarter $t-1$ across all drug j's competitors

we observe a substantial immediate impact of these events. We combine the dummies for the patent expiry of pravastatin (Pravachol) and simvastatin (Zocor), as their patents expired in the same quarter. Third, we include lagged competitive promotion expenditures and lagged competitive sales. Fourth, we capture the order of entry effect (Fischer & Albers, 2010) implicitly by the brand-specific parameters. We do not control for price, as prices show little variation across quarters in this category, and the price sensitivity of prescription decisions is low (Iizuka, 2012).

4.3. Estimation

We address two issues related to estimation — a computational issue and overparameterization. A computational problem can arise among the independent variables at the brand level, when we use standard estimation to invert the matrix of the explanatory variables, $(X'X)^{-1}$. The reason is that for two brands we only have a limited number of observations — cerivastatin and rosuvastatin. Note that in a random coefficients model, the brand-specific parameters are partly informed by the brand-specific data and partly by the parameters for the other brands. We prevent the inversion of an ill-conditioned matrix by using Bayesian estimation. This allows us to use a random walk Metropolis–Hastings step in our estimation algorithm (instead of a Gibbs step, which requires inversion) to evaluate the brand-specific parameters. We select diffuse priors for all parameters following the Hierarchical Linear Model function in Rossi (2012).

Overparameterization issues can arise as we incorporate heterogeneity into the model, which almost doubles the number of parameters compared with a homogenous model. We use the consistent Akaike information criterion (CAIC), which slightly favors parsimony compared with the AIC. We use backward elimination to select the best model. We start with the full model in Eq. (1). Then we estimate the model and test for the elimination of each variable (except for the constant and the summary metrics for clinical studies to be able to test our hypotheses) across all brand simultaneously and eliminate the variable that improves the CAIC most by being eliminated. We repeat this process until the CAIC does not improve anymore by the elimination of an additional variable. We apply the backward elimination separately for each dependent variable; hence, the explanatory variables in the final model may differ across the dependent variables but are similar across brands. Below, we show that our main results are robust to the variable selection method (backward elimination versus forward selection).

4.4. Impulse response functions

We follow the terminology used in Dekimpe and Hanssens (2004) to summarize the dynamic effects of clinical studies, DTP, and DTCA. We refer to the same-period effect of a temporary shock as the *immediate effect*. If the dependent variables are stationary, the initial shock dies out over time, and we refer to the total effect of a shock over time as the *cumulative effect*. When the dependent variables are evolving, the effect of an initial shock stabilizes at a non-zero level, representing the *long-term effect*.

The immediate effects of the endogenous variables are modeled through the covariance matrix Σ. Hence, we calculate generalized impulse response functions (GIRF) to compute the dynamic effects of marketing on sales. The GIRF measures the time profile of a shock to one dependent variable on future values of the other dependent variables at any given point in time (Pesaran & Shin, 1998). This approach is invariant to the ordering of the variables in the model. We use the procedure outlined in Wieringa and Horváth (2005) to obtain proper cumulative and long-term elasticities (by computing level-impulse response functions first). All the results of our impulse response functions are based on a temporary shock of one percent in the variable of interest.

We also calculate impulse response functions to obtain the dynamic effects of valence, dispersion, and volume of clinical studies. Their immediate elasticities can directly be obtained from the estimates for γ in Eq. (1), but this is not the case for the multi-period elasticities. Depending on the unit root tests, we use the cumulative or long-term effects of valence, dispersion, and volume to test our hypotheses.

5. Results

We first discuss the model specification tests. Then we present the model results and hypothesis tests. We end this section with an assessment of the robustness of our results.

5.1. Model specification tests

We tested for unit roots in DTCA, DTP, and sales. We use the critical value for an exact sample test, i.e., the ratio between the number of cross-sectional units and the number of time periods (Im et al., 2003). For DTCA, we included only a constant in the individual unit root equations. For DTP and sales, we included a constant and a linear trend as deterministic terms, as the trend term was significant in the majority of series. The lag length of the test ranged from one to six across brands. Based on the Im et al. (2003) test, we reject the null hypothesis of a unit root for DTCA ($p = .0001$). We cannot reject the null hypothesis of a unit root for DTP ($p = .27$) and sales ($p = .95$). These results are robust to the inclusion of various possible structural breaks.

As we find unit roots for DTP and sales, we use the panel cointegration test of Larsson et al. (2001). We include a constant and a linear trend as deterministic terms for each brand in the test, as the linear trend is significant for five out of seven brands. The optimal lag length varies from one to three across brands. We use the critical values reported in Breitung (2005) and find no significant cointegration between sales and DTP ($p = .02$). Adding step dummies for possible structural breaks also does not provide evidence of cointegration. As we find

unit roots, but no cointegration, for sales and DTP, we specify the model in first differences of the log-transformed variables. The model for DTCA is in logs. Finally, we select a lag length of one for the autoregressive parameters using the CAIC. The results are based on 30,000 draws from the MCMC sampler and we discard the first 15,000 draws for burn-in. The optimal model, after applying backward elimination, is shown in Table 3. Note that the empty cells indicate that the variable is excluded in the backward elimination procedure and the main results below are largely similar when we use forward selection as the variable selection mechanism.

The results are based on 230 observations per dependent variable. Note that the adjusted R^2 for DTP (.29) and sales (.52) is lower than for DTCA (.96), because the former dependent variables contain a unit root and the respective equations are estimated in first differences.

5.2. Hypothesis testing

We can interpret the parameters for valence, dispersion, and volume in Table 3 as the average immediate elasticity across brands. However, to test our hypotheses, we compute impulse response functions for valence, dispersion, and volume to obtain the cumulative and long-term effects. The results are shown in Fig. 3. As we find no unit root for DTCA, the effect one-time shock to valence, dispersion, and volume of clinical studies on DTCA dies out over time. Hence, to test our hypotheses on DTCA we use the cumulative effects of valence, dispersion, and volume of clinical studies. DTP and sales contain a unit root and the effect of a one-time shock to valence, dispersion, and volume of clinical studies on DTP and sales stabilizes at a non-zero level. Hence, we use the level at which this shock stabilizes (the long-term effect) to test the hypotheses on DTP and sales. Below we report cumulative and long-term effects based on Fig. 3 with the 95% highest posterior density interval in parentheses.

The results confirm H_{1a}, that valence is positively related to DTCA spending. The cumulative elasticity is .30 [.05, .58]. The results also confirm H_{1b}, that valence is positively related to DTP expenditures. The long-term elasticity is .04 [.01, .08]. The long-term elasticity of valence on sales is .07 [.05, .10], confirming H_2.

The results confirm H_{3a}, that dispersion is negatively related to DTCA spending. The cumulative elasticity is −.45 [−.77, −.11]. The results do not confirm H_{3b}, which hypothesized that dispersion would be positively related to DTP spending. We find that the long-term elasticity is

insignificant .03 [−.04, .10]. Possibly, firms reduce their DTP expenditures in response to negative studies to the same extent as they increase their DTP expenditures in response to positive studies, rather than responding to mere dispersion as such. Therefore, the effects may cancel out. Contrary to H_4, we find that dispersion is not significantly related to sales; the long-term elasticity is −.02 [−.06, .03]. We speculate that dispersion may come from the testing of the drug under various conditions among different patient populations. This may, on the one hand, lead to more uncertainty, but it may also lead to market expansion opportunities (e.g., more positive study results in a specific population as compared to the general population). In our sample, these effects may cancel out.

Our results do not confirm H_{5a}. Instead, we find a negative effect of the volume of the clinical studies on DTCA expenditures, with a cumulative elasticity of −.79 [−1.09, −.46]. Very likely, if new studies are frequently released, the public attention around these releases and the awareness it creates substitutes DTCA to some extent. The long-term elasticity of volume on DTP is insignificant (.02 [−.01, .08]), contrary to H_{5b}. Two opposing forces may explain the impact of volume on DTP, similar to the reasoning we offered above. Firms may only increase their DTP expenditures if study results are positive and effectively decrease it if study results are negative (we provide some supporting evidence of this in alternative model 1 below). Confirming H_6, we find that the volume of clinical studies has a positive effect on sales (.05 [.02, .08]).

5.3. Other results

Based on the results in Table 3, we use GIRFs to compute elasticities for DTCA and DTP on sales over time, averaged across the seven drugs in the category. Fig. 4 displays these GIRFs and their 95% confidence intervals and shows that the marketing effects rapidly decay over time. The immediate elasticity of a temporary one percent increase in DTCA on kilogram sales is small and only marginally significant at .02 (95% highest posterior density interval [.00, .03]). The long term elasticity of DTCA on sales is very small and insignificant, 006 [−.024, .033], which is consistent with Sismeiro, Mizik, and Bucklin (2012) and Stremersch et al. (2013). The effect of DTP is larger than the effect of DTCA. A temporary one percent increase in DTP leads to an immediate effect on sales of .04 [.03, .04] percent. The long-term elasticity of DTP on sales is small and insignificant, .002 [−.007, .011].

These findings are in line with the existing literature. First, prior literature has also found the impact of DTP to be larger than the impact of DTCA (Kremer, Bijmolt, Leeflang, & Wieringa, 2008). Second, the effect of DTCA and DTP is quite modest which is also in line with prior literature (Mizik & Jacobson, 2004; Osinga et al., 2011; Sismeiro et al., 2012; Venkataraman & Stremersch, 2007). However, we must be cautious with the interpretation of these effects. The contemporaneous effect of promotion may suffer from aggregation bias, as our data are only observed at the quarterly level (Tellis & Franses, 2006). Moreover, we can only reliably report average elasticities across brands, although we know from prior research that promotion responsiveness greatly varies across brands (Venkataraman & Stremersch, 2007). For instance, prior research has argued that pharmaceutical promotion elasticities for new brands are higher than those for mature brands (Kremer et al., 2008; Stremersch & Lemmens, 2009).

We find the effect of competitive DTP expenditures on DTP and sales to be insignificant, though the effect differs substantially across brands. We also find that the patent expiry of simvastatin and pravastatin led to a significant decrease in promotion expenditures and sales for these two drugs. The withdrawal of cerivastatin decreased DTCA across other drugs, although this effect was not significant.

### 5.4. Impact of omission of clinical studies on the responsiveness to promotion expenditures

We investigate whether the responsiveness of sales to promotion expenditures is biased when information on clinical studies is omitted from

Table 3
Parameter estimates for Eq. (1).

Mean parameters[a]	Main Model: Eq. (1)		
	DTCA	DTP	Sales
Constant	.00	−.05	.00
DTCA(t−1)	**.35**		−.02
DTP(t−1)		−.20	.04
Sales(t−1)	.08	−.05	**.28**
Valence	.07	**.08**	**.12**
Dispersion	**−.15**	.06	−.06
Volume	**−.15**	.07	**.09**
CompDTP(t−1)		.05	.03
Patent expiry simva/prava	**−.28**	**−.39**	**−.45**
Withdrawal cerivastatin	−.40		
Covariance matrix			
DTCA	**.36**	.01	.01
DTP	.01	**.38**	**.01**
Sales	.01	**.01**	**.02**
Summary statistics			
Adjusted R^2	.96	.29	.52
CAIC	−209.21	−166.39	−907.11
N	230	230	230

Note: The 95% highest posterior density interval of the values in bold does not contain zero.
 [a] The empty cells indicate that the variable is excluded in the backward elimination procedure.
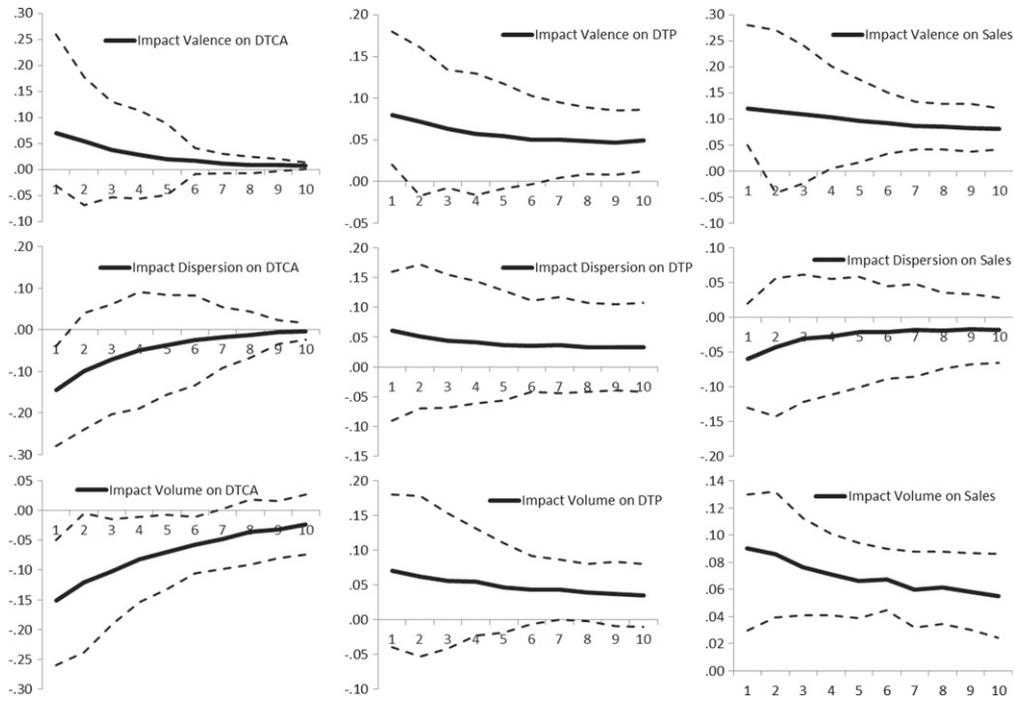
Note: The 95% confidence interval is indicated by the dotted lines.

Fig. 3. Generalized impulse response functions for valence, dispersion, and volume.

the model. Omitted variable bias applies if the omitted variables are (i) a determinant of the dependent variable (i.e., sales) and (ii) correlated with one or more of the independent variables (i.e., DTCA and DTP). Above we show that both conditions are satisfied and hence omitting clinical studies from a sales response model may lead to biased marketing response parameters.

We estimate Eq. (1) without the inclusion of valence, dispersion, and volume of clinical studies. The results of this model show that the immediate elasticity of DTCA on sales is 5% higher and the cumulative elasticity is 40% higher than in the model which includes the clinical study variables. Similarly, the immediate and long-term elasticities of DTP are 2% and 11% higher, respectively.

Omitting clinical studies from the model will lead to an overestimation of the marketing response parameters if the sign of the effect of clinical studies on sales is similar to the sign of the effect of

clinical studies on DTCA (DTP). In our application, we find that in two of the three metrics (valence and dispersion), the effects of clinical studies on sales/DTCA have similar signs indicating an overestimation of the DTCA effectiveness (which is what we indeed find). Similarly for DTP, two of the three metrics (valence and volume) have similar effect signs on sales/DTP and hence we also expect an overestimation here (which is again what we find). For all robustness checks that we ran on our dataset, we consistently find that the effect of promotion is overestimated when clinical studies are not included.

In addition, we tested whether the operationalization of volume as cumulative number of clinical studies (which is monotonically increasing over time) may lead to a variable that is likely confounded with any unobserved trend in this market. We tested for a trend by including a trend term in our original model (Eq. (1)), but it is eliminated during the backward elimination stage suggesting lack of any such trend.
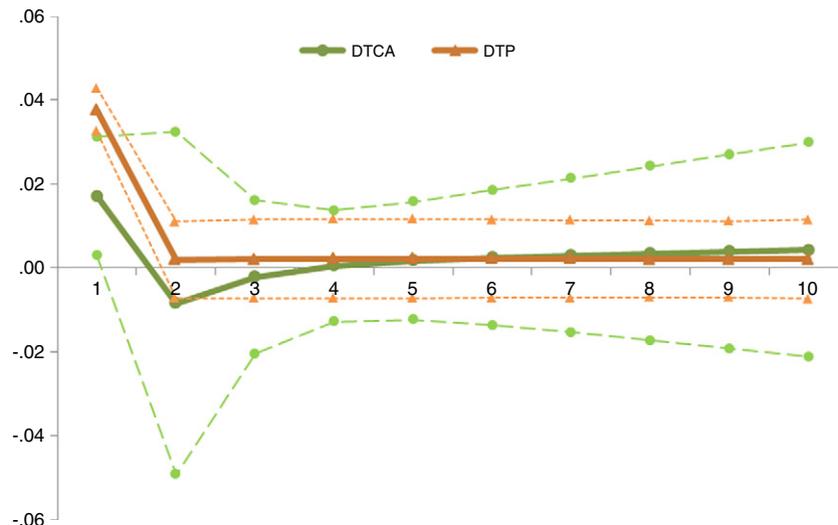

Fig. 4. Generalized impulse response functions for DTCA and DTP.

We re-estimated the model by forcing the trend term in our model and find again that the marketing responsiveness is overestimated when clinical studies are omitted from the model. Hence, the operationalization of volume as cumulative number of clinical studies is unlikely to be confounded with an unobserved market trend.

5.5. Robustness

To explore the results further, we conduct several robustness checks using alternative models. For the alternative models, we focus on the contemporaneous elasticities and do not report the population variance matrix Σ or the outcomes of the impulse response functions due to space constraints.

5.5.1. Alternative model 1: asymmetric effects

We test for asymmetry in the effects of valence and dispersion, i.e., an increase in valence/dispersion may have a different effect than a decrease in valence/dispersion. To test this, we create two different variables. One measure includes only the periods in which the valence or dispersion increased, and the other measure includes only the periods in which the valence or dispersion decreased. We show the results in the left panel of Table 4. The CAIC indicates a worse fit compared to the main model. The autoregressive terms and control variables have similar effects as in the main model. We find limited evidence for asymmetric effects. A decrease in dispersion spurs an immediate increase in DTCA ($-.19$), while an increase in dispersion has no effect. Moreover, increased valence has a positive immediate effect on sales (.16) but a decrease has no effect.

5.5.2. Alternative model 2: sponsorship

To investigate the role of sponsorship of clinical studies, we compute separate measures for valence, dispersion, and volume for studies sponsored by the manufacturer and for studies not sponsored by the

manufacturer. The right panel in Table 4 contains the results. The CAIC indicates that the fit for DTCA and sales is better, while the fit for DTP is worse. The results suggest that non-sponsored studies have a bigger and more significant impact than sponsored studies. Non-sponsored studies probably have higher credibility (Lexchin et al., 2003), which may explain their larger impact.

5.5.3. Alternative model 3: interaction effects

Chintagunta et al. (2010) find some evidence of interaction between volume and valence in the context of user reviews for movies. Sun (2012) finds a significant interaction between valence and dispersion. To test whether the findings on user reviews extend to the context of clinical studies, we tested for interactions between valence, dispersion, and volume. The results are shown in the left panel of Table 5. The results are comparable to those of the main model. The CAIC indicates lower fit compared to the main model. The autoregressive terms and control variables have similar effects as in our main model. Only the interaction between volume and dispersion on sales is significant and equal to $-.11$.

5.5.4. Alternative model 4: endogeneity

We tested whether sales, promotion expenditures, and clinical studies are jointly endogenous. We estimate a model where all these variables are handled endogenously. We found no unit roots for valence, dispersion, or volume, and the results for a VECM with six endogenous variables are shown in the right panel of Table 5. Note that the model structure slightly changes compared to the main model, because the main model only includes contemporaneous variables of the clinical studies. However, any simultaneous equation model with at least one lagged endogenous variable can be rewritten as a VAR model (Zellner & Palm, 1974). Hence, we can obtain similar results on the immediate, cumulative, and long-term effects of clinical studies from both models. In addition, treating the summary metric of clinical studies endogenously allows us to control for the potential serial correlation in these variables. The CAIC indicates lower fit compared to the main model. Based on the GIRFs, the results on the effects of valence, dispersion, and volume on promotions and sales are comparable to our main model, though the confidence intervals are wider. These results suggest that endogeneity of clinical studies is not a concern. This makes intuitive sense because it takes substantial time to plan, design, and perform a clinical study (this last step takes, on average, 34 weeks in our sample). Due to this long delay between the start of the study and publication (there may also be a publication lag), firms or researchers have limited control on the exact timing of the publication (see also Azoulay, 2002).

5.5.5. Alternative model 5: alternative metrics

We tested whether the results of our models hold if valence, dispersion, and volume are computed as a moving average over the last 24, 20, 16 and 12 quarters, respectively. The models with moving averages over more than 16 quarters largely confirm our main results. For moving averages over shorter periods (e.g., 12 quarters), the outcomes are unstable (i.e., the standard errors increase), because few clinical studies appear in smaller time periods for some brands. In addition, we have operationalized our metrics using a decay factor for past clinical studies. We have tested for several decay factors, but setting the decay rate equal to zero fits the data optimally. This is similar to the finding of Azoulay (2002) and shows that science is sticky and cumulative in nature.

6. Discussion

This paper extends the limited prior literature on the topic of commercial contribution of clinical studies in several dimensions: (1) a richer conceptualization of clinical studies along their valence, dispersion, and volume; (2) inclusion of DTCA in the model; and (3) estimation of a dynamic model that allows for heterogeneous effects across brands. These differences lead to the following novel insights.

Table 4
Parameter estimates for alternative models 1 and 2.

Mean parameters[a]	Alternative model 1: Asymmetric effects			Alternative model 2: Sponsorship		
	DTCA	DTP	Sales	DTCA	DTP	Sales
Constant	.13	−.05	.00	−.29	−.06	.00
DTCA(t−1)	**.35**		−.02	**.33**		−.02
DTP(t−1)		**−.21**	.05		−.19	.05
Sales(t−1)	.07	−.04	**.28**	.16	−.02	**.31**
Valence						
Dispersion						
Volume[b]	**−.16**	.08	**.09**			
Decreased valence	.14	.13	.07			
Increased valence	.00	.10	**.16**			
Decreased dispersion	**−.19**	−.03	−.01			
Increased dispersion	.00	.11	−.03			
Valence — sponsored				.07	.12	.06
Valence — not sponsored				**.21**	.05	**.16**
Dispersion — sponsored				.01	−.00	.03
Dispersion — not sponsored				.20	**.16**	−.06
Volume — sponsored				−.00	.07	.06
Volume — not sponsored				**−.18**	.00	.07
CompDTP(t−1)		.09	.01		.09	.01
Patent expiry simva/prava	.01	**−.39**	**−.42**	**−.18**	**−.38**	**−.45**
Withdrawal cerivastatin	−.15			−.14		
Summary statistics						
Adjusted R²	.96	.28	.51	.97	.29	.56
CAIC	−181.77	−165.28	−906.47	−229.21	−164.90	−921.91
N	230	230	230	230	230	230

Note: The 95% highest posterior density interval of the values in bold does not contain zero.
[a] The empty cells indicate that the variable is excluded in the backward elimination procedure.
[b] Volume is not asymmetric as volume is monotonically increasing over time.

Table 5
Parameter estimates for alternative models 3 and 4.

Mean parameters[a]	Alternative model 3: Interaction effects			Alternative model 4: Endogeneity					
	DTCA	DTP	Sales	DTCA	DTP	Sales	Valence	Dispersion	Volume
Constant	.05	−.06	.01	.01	−.06	.01	.00	−.03	−.04
DTCA(t−1)	**.34**		−.02	**.31**		−.02	−.02	−.03	−.01
DTP(t−1)		−.23	.05		−.18	.04	.03	.05	.02
Sales(t−1)	.03	−.05	.30	.06	−.14	**.26**	**.14**	.06	**.14**
Valence	.26	**.10**	.10						
Dispersion	**−.17**	.05	−.04						
Volume	**−.33**	.05	.07						
Valence(t−1)				−.03	.02	.06	**.60**	.13	−.03
Dispersion(t−1)				−.12	.00	.00	.13	**.56**	.00
Volume(t−1)				**−.21**	−.01	.02	−.01	−.02	**.76**
Valence * dispersion	.08	.05	−.14						
Valence * volume	.01	.13	.01						
Dispersion * volume	−.04	.05	**−.11**						
CompDTP(t−1)		.05	.03		.13	.08			
Patent expiry simva/prava	−.05	**−.35**	−.45	−.15	**−.36**	−.44			
Withdrawal cerivastatin	**−.04**			−.26					
Summary statistics									
Adjusted R²	.96	.27	.52	.96	.24	.51	.93	.92	.94
CAIC	−203.77	−159.25	−901.57	−190.31	−132.66	−882.76	−561.20	−761.48	−590.46
N	230	230	230	230	230	230	230	230	230

Note: The 95% highest posterior density interval of the values in bold does not contain zero.

[a] The empty cells indicate that the variable is excluded in the backward elimination procedure.

First, our model allows an estimate of the value of a clinical study in terms of its effect on sales. For example, The Lancet published in the first quarter of 2001 a clinical study, sponsored by a subsidiary of Pfizer, which showed higher than average efficacy for atorvastatin, compared to simvastatin and placebo (Smilde et al., 2001). This study increased the valence, dispersion, and volume. We can use our model to assess the impact of this clinical study on sales and apply level-impulse response functions, as our model is estimated in logs (Wieringa & Horváth, 2005). We first calculate sales based on our model estimates, including the publication of the clinical study. Then, we revise the values for valence, dispersion, and volume assuming that the study was not published and use these values to re-calculate the sales. We estimate that the total effect (including both the direct effect on sales and the indirect effects through DTP and DTCA) of the clinical study of Smilde et al. (2001) increased the same-period sales of atorvastatin in the U.S. by $3.91 million. The total impact of the study on sales ten quarters later in the U.S. is $24.18 million. 89% of the total impact is due to the direct effect on sales and the remaining 11% is due to the indirect effects through a change in marketing expenditures.

Across all clinical studies in our sample (manufacturer-sponsored, independent, and competitor-sponsored studies) that were published after the approval of the drug under study, a clinical study increases the sales of a drug in the U.S., on average, by $1.23 million in the same period and by $4.72 million ten quarters later. These calculations are informative for drug manufacturers, because it allows them to calculate the ROI on clinical studies after approval. Also, the method can be adopted to make similar calculations for other categories of drugs.

Second, our study provides various unique insights into pharmaceutical firms' reactions to clinical study outcomes and extends prior literature, notably Azoulay (2002). We show that pharmaceutical firms respond to valence (positively), dispersion (negatively), and volume (negatively) of clinical studies, in their DTCA spending. They respond to valence of studies positively in their DTP spending. In other words, when positive studies appear on a drug, the respective manufacturer can be expected to increase both DTCA and DTP spending. When more conflicting studies appear, ceteris paribus, the manufacturer can be expected to reduce its DTCA spending. These insights into firms' reaction patterns can enable firms to better predict their competitors' spending on DTCA and DTP and, thus, also pre-emptively set DTCA and DTP spending levels for their own brands accordingly.

Third, we show that it is important to account for clinical studies in estimating the effectiveness of pharmaceutical promotions. This is a typical omitted variable bias problem. We find that not including clinical studies in the sales response model leads to an upward bias of the marketing effectiveness estimate. The implication for firms and researchers is to specify a sales response model that includes the outcomes of clinical studies, in addition to the marketing variables. Since collecting all clinical studies for a category can be time-consuming, an alternative econometric solution may be chosen. For example, one might incorporate a time-varying constant in the model (Osinga, Leeflang, & Wieringa, 2010) or include time- and brand-specific fixed effects. The problem of omitting clinical studies from the model is similar to the bias that may arise from not correcting for time-varying intrinsic brand preferences (Sriram, Chintagunta, & Neelamegham, 2006).

Fourth, our findings can potentially be extended to other industries, beyond the pharmaceutical industry. In this paper we provide a relevant and parsimonious way to summarize the body of studies on a product (valence, dispersion, and volume) and study their impact on sales and marketing expenditures. Interestingly, there are several industries in which firm's researchers publish as much or even more actively in scientific journals than is common in the pharmaceutical industry (Godin, 1996). For example, firm's researchers or independent analysts release reports on such diverse products, such as telecommunication infrastructure, insurances, investment products, medical electronics, nanotechnology, semiconductors or chemicals. At the same time, in these industries, technically trained experts also serve as influencers of buyers in their decision-making. It would be valuable to assess the effects of such technical reports on the marketing efforts for and sales of the respective products. A relevant question for such research is whether the effects we documented are contingent upon context.

Our paper has several limitations that offer future research opportunities. First, due to the time-consuming nature of data collection, we have data on only one category. Examining the effect of clinical studies in other categories or over a cross-section of categories may lead to valuable insights. Second, we have quarterly data on direct-to-consumer and direct-to-physician spending from 1997–2007. Despite our efforts to be as comprehensive as possible in data collection, it would be preferable to conduct this study on monthly or weekly data, to prevent aggregation bias, and for the complete life cycle of the category.

Third, we only assess the impact of clinical studies on the U.S. market, while many of these studies will have a global impact. It would be worthwhile for further research to determine the total (global) value of a clinical study. This is especially so because countries have different regulatory environments, which have been documented to have significant effects on drug sales (Stremersch & Lemmens, 2009) and decisions by pharmaceutical firms (Verniers, Stremersch, & Croux, 2011).

Fourth, we have explored various alternatives to incorporate time-varying moderators of clinical studies (i.e., valence, dispersion, and volume) on marketing effectiveness, but failed to identify an approach that worked in our sample. Time-varying moderators imply time-varying marketing effectiveness unlike prior research where the moderators are time invariant (e.g., Nijs, Dekimpe, Steenkamp, & Hanssens, 2001; Pauwels, 2004; Srinivasan, Pauwels, Hanssens, & Dekimpe, 2004). Comparing the marketing effectiveness across brands with high and low valence becomes infeasible in our case, because we only have seven brands. Also, including the interaction terms between valence and DTCA (or DTP) in the sales equation would only capture a contemporaneous interaction, while our results show significant carryover effects. Finally, comparing the promotion effectiveness for periods in which valence is either high or low is challenging in a dynamic model because lagged effects need to be included in the model and valence rarely increases/decreases for multiple consecutive periods. Therefore, we leave the moderating effect of clinical studies for further research.

This study aims to be a stepping-stone for future research in the pharmaceutical and other industries on the commercial impact of scientific and technical studies. This study clearly documents the great value of assessing the sales value of science and its intersection with marketing spending decisions.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijresmar.2013.07.007.

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