Published in final edited form as:

Gastroenterology. 2009 August ; 137(2): 518–524.e2. doi:10.1053/j.gastro.2009.05.005.

Direct to consumer and physician promotion of tegaserod correlated with physician visits, diagnoses, and prescriptions

Spencer D. Dorn, MD, MPH¹, Joel F. Farley, PhD², Richard A. Hansen, PhD², Nilay D. Shah, PhD^{3,4}, and Robert S. Sandler, MD, MPH¹

¹Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine

²Division of Pharmaceutical Outcomes and Policy, University of North Carolina Eshelman School of Pharmacy

³ Knowledge and Encounter Research Unit, Mayo Clinic, Rochester, MN

⁴ Division of Health Care Policy and Research, Mayo Clinic, Rochester, MN

Abstract

Background & Aims—Direct to consumer advertisement (DTCA) and physician promotion of drugs can influence patient and physician behaviors. We sought to determine the relationship between promotion of tegaserod and the number of office visits for abdominal pain, constipation, and bloating; diagnoses of irritable bowel syndrome (IBS); and tegaserod prescriptions.

Methods—We used an Integrated Promotional Services database to estimate tegaserod DTCA and promotion expenditures, The National Ambulatory/Hospital Medical Care Surveys (1997–2005) to estimate the number of ambulatory care visits for abdominal pain, constipation, and bloating and diagnoses of IBS, and IMS Health's National Prescription Audit Plus to estimate the number of prescriptions. We constructed segmented and multivariate regression models to analyze the data.

Results—In the 3 months immediately following the start of tegaserod DTCA, there was a significant increase in physician visits (by 1 million; 95% CI 0.5–1.6 million) and IBS diagnoses (by 397,025; 95% CI 3,909–790,141). Subsequently, the trend of visits and IBS diagnoses reduced. In multivariate analyses that examined the overall relationship of promotion with visits, diagnoses, and prescriptions, only the relationship between physician promotion and tegaserod prescribing was significant; every \$1 million spent on physician promotion resulted in an additional 4,108 prescriptions (95% CI: 2,526–5,691).

Conclusions—The initial DTCA of tegaserod was associated with a significant, immediate increase in physician visits and IBS diagnoses. This trend reversed and in multivariate models, neither DTCA nor physician promotion correlated with visits or diagnoses. Physician promotion (though not DTCA) correlated with tegaserod prescription volume.

Correspondence: Spencer D. Dorn, MD, MPH, Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, CB 7080, Chapel Hill, NC, 27599-7080, E-mail: sdorn@med.unc.edu.

Financial disclosures/Conflicts of interest: Dr. Farley has received consulting fees and research support from Pfizer and Takeda Pharmaceuticals. Dr. Hansen has received consulting fees and research support from GlaxoSmithKline and Takeda Pharmaceuticals. These consulting fees and/or research support are unrelated to the content of this paper.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Background

Throughout much of the world pharmaceutical companies heavily promote prescription drugs to health care providers.¹ In both the United States and New Zealand such drugs are also directly promoted to consumers.² In fact, direct to consumer (DTC) advertisement is the most rapidly growing component of drug promotion in the U.S.:³⁻⁵ from 1997 through 2006, DTC advertisement increased from \$1.1 billion⁵ to over \$4.8 billion.⁶

DTC advertisements typically use emotional appeals to urge consumers to consider medical causes for their symptoms.^{7, 8} Consequently, consumers gain confidence that makes them more likely to visit and discuss their health concerns with their physicians.⁷⁻¹⁰ This may lead to new diagnoses and new prescriptions,^{11, 12} especially for those patients who also request the advertised drug.^{13, 14} For instance, it has been estimated that each dollar spent on DTC advertisement yields \$4.20 in additional pharmaceutical sales in that class.¹⁵

Most DTCA spending is concentrated on a relatively select group of new drugs designed to treat chronic conditions.⁵ Irritable bowel syndrome (IBS) and chronic constipation are two such chronic conditions that are highly prevalent, with each affecting well over 10% of the US population.¹⁶⁻²⁰ Despite this, only a minority of these individuals seek medical care.¹⁹ Reasons for this low consulting rate likely include a general lack of public awareness, social isolation due to the stigma associated with bowel dysfunction, and an historic absence of effective prescription medications.²¹ However, in July, 2002 tegaserod (**Zelnorm**, Novartis AG, Basel, Switzerland) was approved for the treatment of these conditions. Shortly thereafter, tegaserod was intensely marketed to the public through the “tummies” advertisement campaign which informed individuals -- often provocatively with images of women with phrases such as “I feel better” written across their abdomens -- that their abdominal symptoms might be caused by chronic constipation or IBS and advised them to “ask [their] doctor if Zelnorm is right for [them].²²” In 2004, \$122 million was spent on these highly memorable,²³ award winning²⁴ DTC advertisements, the 5th most among all prescription drugs.²⁵

In addition to potential consumers, tegaserod was also heavily promoted to physicians: in 2005 professional promotion exceeded \$127 million.²⁶ The various forms of physician promotion, which includes in-office “detailing” by pharmaceutical sales representatives,²⁷⁻³⁰ provision of free drug samples,^{31, 32} and advertisements in professional journals,³³ have all been shown to influence prescribing patterns.^{34, 35}

The heavy DTC advertisement and professional promotion of tegaserod continued until March, 2007 when concern over a small, but statistically significant increase in associated cardiovascular events led to a complete suspension of any drug marketing.³⁶ Still, these promotional efforts were likely effective in leading at least some individuals with abdominal symptoms to see their physician and leading some physicians to diagnose a portion of these individuals with IBS and/or to prescribe them tegaserod. Considering the high prevalence of these symptoms, the number of clinic visits, diagnoses, and tegaserod prescriptions may have increased significantly.

Therefore, the aim of this study was to determine the relationship between tegaserod promotion and the number of individuals who sought health care for abdominal symptoms, as well as the diagnoses and treatments that they ultimately received. We hypothesized that the introduction and promotion of tegaserod correlated with an increase in physician office visits for abdominal symptoms (e.g., constipation, abdominal pain, and bloating), diagnoses of IBS, and prescriptions of tegaserod. Additionally, we attempted to parse out the relationships between various promotional strategies and patient and physician behavior as shown in figure 1.

Methods

Data Sources

To estimate expenditures on DTC advertising and professional promotion of tegaserod we used data from IMS Health's Integrated Promotional Services data.²⁶ This database estimates total national expenditures by month and product spent on provider detailing, patient samples, journal advertising, and DTC advertising (including television, radio, newspaper, consumer magazine, and billboard advertisements). Expenditures were adjusted to 2004 dollars using the medical component of the Consumer Price Index (US Department of Labor). The influence of promotion can be thought of as immediate and cumulative, whereby previous promotional advertisements may influence current patient behavior. Therefore, we estimated cumulative monthly spending for DTC advertising and physician detailing by summing current month spending with discounted spending for the previous 6 months. Based on previous studies we used an 11% discount rate for DTCA and 0.3% discount rate for detailing.^{37, 38} These cumulative monthly spending variables were then aggregated by quarter to match the NAMCS and NHAMCS data (see below).

To estimate the number of ambulatory care visits for abdominal pain, constipation, and bloating, as well as diagnoses of IBS in the United States we used administrative data from the 1997-2005 National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) with sampling weights. The NAMCS is an annual sample of outpatient visits to office-based community physicians who are principally engaged in patient care. Visits in this survey are recorded through a multistage clustered probability sample design based on geographic location, provider specialty, and visits within individual physician practices. The NHAMCS is an annual sample of ambulatory care services in hospital emergency and outpatient departments. Because we hypothesized that any effect of tegaserod DTC advertising and physician promotion would be primarily in non-emergent settings, emergency department visits were excluded. Visits in this survey are sampled based on geographic locations, hospitals within these areas, and clinics within the outpatient departments of these hospitals. In sum, when patient weights are used, these NAMCS and NHAMCS data can be extrapolated to the over 1 billion visits to physician office and hospital outpatient departments that occur in the United States each year.³⁹ Both NAMCS and NHAMCS collect data on the utilization and provision of care. For analysis purposes data were aggregated by quarter-year. Because tegaserod was initially only promoted to female patients, all male patients were excluded.

To estimate the volume of tegaserod prescriptions we used data from IMS Health's National Prescription Audit Plus. National Prescription Audit Plus measures prescriptions of all pharmaceutical products that are sold from the retail pharmacies including independent and chain store pharmacies, mass merchandisers and food stores with pharmacies, mail service pharmacies, and long-term facilities. National Prescription Audit Plus captures more than 70% of the prescriptions nationally and then applies a proprietary method to estimate the nationwide volume.⁴⁰ Data were aggregated into quarterly estimates.

In addition to the influence of pharmaceutical promotion, physicians' awareness of IBS and tegaserod may have been influenced by professional publications. Because this may have affected their diagnoses and prescriptions we determined the number of PubMed citations for constipation, IBS, and tegaserod per quarter for each year and included these data as covariates in certain multivariate models (see below).

Statistical Methods

We first assessed whether DTC advertisement of tegaserod correlated with a change in the overall number of physician visits and IBS diagnoses. To do so we used segmented regression models⁴¹ to assess changes in the level (i.e., the value at the beginning of the time interval) and trend (i.e., the rate of change or slope) in the number of visits for abdominal pain, constipation, or bloating IBS diagnoses over the 25 quarter periods before tegaserod DTC advertising compared to the 11 quarter periods during which tegaserod was directly advertised to consumers. Both regression models included a constant term, a linear time trend (*TIME*, quarters 1 to 36), a binary indicator to assess disruption in the trend line following tegaserod DTC advertising (*DTC*, quarters 26 to 36), and a linear time trend to assess changes in the slope of the trend line following tegaserod DTC marketing (*DTC-Trend*, quarters 26 to 36). The full regression was modeled as:

$$Y_t = \beta_0 + \beta_1 \text{TIME} + \beta_2 \text{DTC} + \beta_3 \text{DTC-TREND}$$

From our initial plot, we noticed patterns of seasonality in prescription drug utilization and expenditures. In other words, observations from a given current quarter were correlated with observations from the preceding year. Accordingly, we used autoregressive integrated moving average (ARIMA) models to control for autocorrelation and seasonality in prescription drug utilization and expenditures in the segmented regression models. Correlograms and partial correlograms were used to determine the appropriate autoregressive and moving average terms for each model. All coefficients were deemed significant at $p < 0.05$.

We next quantified the relationship of various components of DTC and professional promotion expenditures on the number of physician visits for abdominal pain, constipation, and bloating, as well as the number of IBS diagnoses. To do so we modeled the amount of promotional dollars spent in relationship with the sum of quarterly physician visits and IBS diagnoses. For the latter model we included professional citations of IBS as a covariate. For both models we used a Poisson distribution in our regressions to control for skew in the distribution of our count outcome variables. To assess the effect of distributional assumptions on results we also ran each model using a negative binomial distribution. The level of clinical and statistical significance of each model was unchanged (results not shown). While we considered each type of promotion individually, the various forms of promotion directed toward physicians (e.g., samples, journal advertising, detailing) were highly correlated. Therefore, in order to avoid problems with multi-collinearity we also separately examined the relationship between both DTC advertising and a composite sum of all physician directed promotion with visits and diagnoses.

Finally, we quantified the relationship between DTC as well as the various components of professional promotion with the number of tegaserod prescriptions written. To do so we used an ordinary least squares (OLS) regression, which was chosen based on normality of the distribution for our prescription variable and for ease in the interpretation of coefficients. For this model we included professional citations of constipation, IBS, and tegaserod as covariates.

Results

The pattern of quarterly visits for constipation, bloating, and abdominal pain as well as IBS diagnoses are depicted in Figure 2. In addition, it presents the results from our segmented regression that depicts changes in the level (i.e., number) and trend of visits and IBS diagnoses immediately following the start of tegaserod DTC advertising compared with those before marketing. These results are presented numerically in Table 1. At the beginning of our

observation period (the first quarter of 1997) there were approximately 3.4 million visits [95% CI: (2848795, 3887674)] made to physicians for constipation, bloating, and abdominal pain symptoms and 541,117 IBS diagnoses [95% CI: (316808, 765426)]. From this quarter until the quarter prior to the start of tegaserod marketing there was a non-significant increase of 17,105 additional physician visits and 2,266 IBS diagnoses per quarter. Immediately following the start of DTC marketing of tegaserod, there was a significant 1 million visit [95% CI: (509386, 1644098)] increase in the number of visits made to physicians for constipation, bloating, and abdominal pain and 397,025 additional diagnoses for IBS. In the subsequent 11 quarters there was a reduction in the trend of visits made to physicians for these symptoms and IBS diagnoses: patients made 183,933 ($\beta_1 + \beta_3 = 17,105 + -201,038$) fewer visits to physicians, and physicians made 64,977 ($\beta_1 + \beta_3 = -67,243 + 2,266$) fewer IBS diagnoses each quarter.

Results from our Poisson regressions of advertisement spending on physician visits and IBS diagnoses are shown in Table 2. There was no association between the amount of money spent on DTC advertising for tegaserod and the number of visits made to physicians for constipation, bloating, and abdominal pain nor the number of diagnoses made for IBS. However, we did see evidence of a small, yet statistically significant positive association between physician detailing and the number of visits for abdominal pain, constipation, and bloating: for every 100 million dollars spent detailing physicians, we showed a 0.647% [95% CI: (0.184, 1.111)] increase in visits to physicians for these symptoms. No other physician directed advertisement showed a significant association in our models. Because in administrative data abdominal pain may be a non-specific reason for visit, we also ran segmented regression and Poisson regression models that assessed changes in physician visits for constipation and bloating only. The results did not meaningfully change.

Figure 3 and table 3 shows results from our regressions of tegaserod advertising spending on prescriptions for tegaserod. Both DTC and physician directed advertisements were significantly associated with the amount of prescribing for tegaserod: for every one million dollars spent advertising tegaserod DTC, an additional 1,796 prescriptions [95% CI: (1041, 2549)] were written. Likewise, for every one million dollars spent on physician directed promotion (including physician detailing, sampling, and journal advertising) an additional 5,134 prescriptions [95% CI: (4147, 6120)] were written. Among the components of physician promotion, this association appeared to be predominantly driven by sampling: every one million dollars spent on sampling of tegaserod was associated with an additional 6,774 prescriptions [95% CI: (5447, 8101)] written. Finally, in a model that simultaneously assessed the relationship between DTC advertising and physician promotion on prescriptions, only physician promotion correlated with tegaserod prescribing: for every one million dollars spent on physician promotion (sampling, detailing, and journal advertisements), there was an additional 4108 [95% CI: (2526, 5691)] tegaserod prescriptions written. Thus, physician directed advertising appears to be a more closely tied to tegaserod prescribing than DTC advertising.

Discussion

In the United States drugs are heavily promoted both directly to consumers and to prescribing practitioners. This spending – which is nearly double that spent on research and drug development⁴² – tends to be most concentrated among a select group of highly prevalent, chronic conditions, including acid reflux, hyperlipidemia, erectile dysfunction, and IBS and chronic constipation.²⁵ We sought to determine the relationship between tegaserod promotion and the number of individuals who sought health care for abdominal symptoms, as well as the diagnoses and treatments that they ultimately received. We found that the tegaserod DTCA campaign was associated with an immediate increase in the number of physician visits for abdominal pain, bloating, and constipation as well as the number of diagnoses of IBS. However,

this was short lived: over time this trend reversed and overall there was no association between tegaserod DTCA and the number of visits, IBS diagnoses, nor tegaserod prescriptions. While professional promotion was not associated with the number of IBS diagnoses, it did correlate directly with prescription volume.

In the three months following the start of the intensive tegaserod DTCA campaign the number of physician visits for abdominal pain, bloating, and/or constipation as well as the number of IBS diagnoses increased substantially (1 million additional visits and 400,000 diagnoses). Additionally, during this period the proportion of patients who presented with these abdominal complaints who were subsequently diagnosed with IBS also increased considerably: from 0.13 (2,266/17,105) in the pre-promotion period to 0.40 (397,025/1,000,000) immediately after promotion. This suggests that beyond increased volume alone, DTCA had an additional link to physician diagnosis patterns. Nonetheless, over time the rates of visits and diagnoses tapered off to pre-promotion levels and overall DTCA was not associated with physician visits nor IBS diagnoses. While there is no simple explanation for this finding, it is possible that the pool of individuals most susceptible to DTCA responded immediately with visits to their physicians. In effect, this may have left a group of individuals who were less responsive to later DTC advertisements.

While we did not specifically assess changes in prescriptions immediately after the start of the tegaserod DTCA, we were surprised to find that over time DTCA expenditures were not associated with prescription volumes. These findings counter a broad literature that suggests DTCA has a strong effect on prescribing behavior.¹¹⁻¹⁵ However, the effects of DTCA may have decreased over time. For instance, in a recent survey of 68 clinicians following over 1,500 office visits the percentage of patients with DTCA related drug inquiries was substantially lower (1.7% in public clinic and 7.2% in private practice visits)⁴³ than had been previously reported (15.8%).⁴⁴ Thus, it is possible that after years of exposure individuals are now less responsive to drug advertisements. Additionally, the effects of DTCA may have previously been over-estimated or overstated, possibly as a result of publication bias. For instance, a marketing analysis of 391 drugs from 1995-1999 found that while the return on \$1 invested in DTCA for individual drugs was as high as \$10.29, the return on investment in DTCA spending for the “median brand” was not statistically significant.⁴⁵ Additionally, results of meta-analyses that include both published and unpublished data suggest that while the effect of DTCA on prescription volume is typically positive, it is generally weak and is in large part determined by the characteristics of the advertised drug and its targeted condition.^{46, 47} Thus, the weak long-term effect of tegaserod DTCA may relate to the fact that tegaserod was not a particularly effective medication: a Cochrane review and meta-analysis estimated that for every 17 patients with IBS treated with tegaserod only one responded.⁴⁸ Similarly, The Oregon Drug Effectiveness Review Project found that for treating chronic constipation tegaserod was no better than other less expensive alternatives.⁴⁹ Thus it is quite plausible that after trying tegaserod many patients perceived it to be ineffective and therefore discontinued its use.

Unlike DTCA, physician promotion of tegaserod was closely associated with prescription volume: every \$1 million spent on physician promotions was associated with an additional 4,100 prescriptions. Others have also found that compared to DTCA, physician promotion more strongly influences prescribing.^{45, 46, 50} Of the components of physician promotion, sampling produced the greatest positive effect. Likewise, prior studies that utilized physician surveys,^{31, 51} administrative databases³² and randomized trials⁵² have demonstrated that physicians who distribute samples are in turn more likely to prescribe those medications. Our finding that journal advertising was inversely associated with prescription volume was unexpected. However, the wide confidence interval suggests that this estimate was imprecise and potentially spurious.

Although a debate of the merits of DTCA and physician promotion is beyond the scope of this study, both positive and negative implications of tegaserod promotion can be imagined. Proponents could argue that given significant associated stigma, many patients with IBS and chronic constipation suffer without seeking health care.^{19, 21} Thus DTC advertisements may have been a powerful source of health information that increased patient awareness and potentially empowered them to discuss their health concerns with their physician.⁹ Conversely, opponents may point out that the tegaserod promotion campaign may have resulted in overuse of a drug that in clinical trials only benefited a select group of patient before adequate information on the associated increased risk in cardiovascular events was available.⁵³ Although in a pooled analysis of short term trial data the risk of serious cardiovascular adverse events for individuals treated with Zelnorm was small (absolute risk increase was 0.09%), when extrapolated across the population the effect may have been considerable.³⁶

This study had several potential limitations related to the use of administrative data. For example there was no physician level data and one could imagine a number of potentially relevant variables (e.g., formulary status, co-payment, drug prices, etc) that were not measured.⁵⁴ Additionally the specificity of diagnostic codes was unknown, especially for abdominal pain. However, when we restricted analyses to changes in constipation and bloating related visits only the results did not meaningfully change. Second, there were limitations related to the use of IMS data. While it has been a “gold standard” across research studies of this sort, some have argued that because IMS does not capture promotional meetings (which annually total almost \$2 billion) nor phase IV “marketing trials” it may underestimate total promotional expenditures.⁴² This may have biased either estimate towards or away from the null. Furthermore, the Food and Drug Administration recognizes the following three types of DTC advertisements: “reminder advertisements” which call attention to the name of the drug without making claims on its effectiveness; “help-seeking advertisements” which describe symptoms and encourage consumers to consult their physician without mentioning the drug's name; and “product-claims” which reveal both the drug's name and its indication (i.e., “ask your doctor if Zelnorm is right for you.²²”).⁵⁵ However, the IMS data did not differentiate between these types of DTC advertisements nor did it assess the content of physician promotional materials. Third, independent of the tegaserod promotion campaign, general awareness of constipation, irritable bowel syndrome, and tegaserod likely increased over time. While we attempted to control for changes in professional awareness, we could not control for similar changes in the public's awareness. Fourth, although time-series analysis is one of the strongest quasi-experimental designs for assessing interventions, segmented regression assumes a linear trend within each segment.⁴¹ The addition of subsequent time points would have helped to stabilize linear trends.

In conclusion, the initial DTCA of tegaserod was associated with a significant, immediate increase in physician visits for abdominal pain, constipation, and bloating as well as IBS diagnoses. However, over time this trend reversed and in multivariate models neither DTCA nor physician promotion had any overall relationship with visits or diagnoses. Physician promotion (especially detailing) was significantly correlated with tegaserod prescription volume.

Acknowledgments

Grant support: Supported in part by a grants from the National Institutes of Health P30 DK045987, T32 DK 007634, and KL2RR025746

Abbreviations

DTCA

direct to consumer advertising

IBS

IBS irritable bowel syndrome

NAMCS

National Ambulatory Medical Care Survey

NHAMCS

National Hospital Ambulatory Medical Care Survey

References

1. Consumers International. Branding the Cure: A consumer perspective on Corporate Social Responsibility, Drug Promotion, and the Pharmaceutical Industry in Europe. London: 2006.
2. Donohue J. A history of drug advertising: the evolving roles of consumers and consumer protection. *Milbank Q* 2006;84:659–699. [PubMed: 17096638]
3. Rosenthal MB, Berndt ER, Donohue JM, Frank RG, Epstein AM. Promotion of prescription drugs to consumers. *N Engl J Med* 2002;346:498–505. [PubMed: 11844852]
4. Woloshin S, Schwartz LM, Tremmel J, Welch HG. Direct-to-consumer advertisements for prescription drugs: what are Americans being sold? *Lancet* 2001;358:1141–1146. [PubMed: 11597668]
5. Donohue JM, Cevasco M, Rosenthal MB. A decade of direct-to-consumer advertising of prescription drugs. *N Engl J Med* 2007;357:673–681. [PubMed: 17699817]
6. I. M. S. Health Inc.. Total US Promotional Spend by Type, 2007 Top-Line Industry Data. IMS Health Inc.; 2007.
7. Murray E, Lo B, Pollack L, Donelan K, Lee K. Direct-to-consumer advertising: public perceptions of its effects on health behaviors, health care, and the doctor-patient relationship. *J Am Board Fam Pract* 2004;17:6–18. [PubMed: 15014047]
8. Murray E, Lo B, Pollack L, Donelan K, Lee K. Direct-to-consumer advertising: physicians' views of its effects on quality of care and the doctor-patient relationship. *J Am Board Fam Pract* 2003;16:513–524. [PubMed: 14963078]
9. Weissman, JS.; Blumenthal, D.; Silk, AJ.; Zapert, K.; Newman, M.; Leitman, R. Consumers' reports on the health effects of direct-to-consumer drug advertising. *Health Aff; Millwood*: 2003. p. W3-95.
10. Gilbody S, Wilson P, Watt I. Benefits and harms of direct to consumer advertising: a systematic review. *Qual Saf Health Care* 2005;14:246–250. [PubMed: 16076787]
11. Mintzes B, Barer ML, Kravitz RL, Kazanjian A, Bassett K, Lexchin J, Evans RG, Pan R, Marion SA. Influence of direct to consumer pharmaceutical advertising and patients' requests on prescribing decisions: two site cross sectional survey. *BMJ* 2002;324:278–279. [PubMed: 11823361]
12. Zachry WM III, Shepherd MD, Hinich MJ, Wilson JP, Brown CM, Lawson KA. Relationship between direct-to-consumer advertising and physician diagnosing and prescribing. *Am J Health Syst Pharm* 2002;59:42–49. [PubMed: 11813466]
13. Kravitz RL, Epstein RM, Feldman MD, Franz CE, Azari R, Wilkes MS, Hinton L, Franks P. Influence of patients' requests for direct-to-consumer advertised antidepressants: a randomized controlled trial. *JAMA* 2005;293:1995–2002. [PubMed: 15855433]
14. Kaiser Family Foundation. Impact of Direct-to-Consumer Advertising on Prescription Drug Spending. [August 16, 2006]. <http://www.kff.org/rxdrugs/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=14378>
15. United States General Accounting O. Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations. Washington, D.C.: 2002.
16. Sandler RS, Drossman DA. Bowel habits in young adults not seeking health care. *Dig Dis Sci* 1987;32:841–845. [PubMed: 3608732]
17. Sandler RS, Drossman DA, Nathan HP, McKee DC. Symptom complaints and health care seeking behavior in subjects with bowel dysfunction. *Gastroenterology* 1984;87:314–318. [PubMed: 6735075]

18. Drossman DA, Sandler RS, McKee DC, Lovitz AJ. Bowel patterns among subjects not seeking health care. Use of a questionnaire to identify a population with bowel dysfunction. *Gastroenterology* 1982;83:529–534. [PubMed: 7095360]
19. Cremonini F, Talley NJ. Irritable bowel syndrome: epidemiology, natural history, health care seeking and emerging risk factors. *Gastroenterol Clin North Am* 2005;34:189–204. [PubMed: 15862929]
20. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004;99:750–759. [PubMed: 15089911]
21. Chang L, Toner BB, Fukudo S, Guthrie E, Locke GR, Norton NJ, Sperber AD. Gender, age, society, culture, and the patient's perspective in the functional gastrointestinal disorders. *Gastroenterology* 2006;130:1435–1446. [PubMed: 16678557]
22. [July 2, 2006]. www.zelnorm.com/
23. Prescription Drug Advertising Break-Through: IAG Research reveals the best prescription drug advertising from this past TV season. IAG Research. 2006 [December 21, 2008]. http://www.iagr.net/ne_press/pr_112906.jsp
24. New York American Marketing Association. EFFIE Awards. Brief of Effectiveness. Zelnorm: “Tummies.”. [December 21, 2008]. http://s3.amazonaws.com/effie_assets/2005/573/2005_573_pdf_1.pdf
25. Medical Marketing and Media Changing Channels. [July 16, 2006]. <http://offlinehbpl.hbpl.co.uk/Misc/MMM/Features/APR05%2034-42%20DTC%20OUTLOOK.pdf>
26. IMS Health. Integrated Promotional Services and CMR. Fairfield, Conn.: Promotional data.
27. Gönül FF, Carter F, Petrova E, Srinivasan K. Promotion of Prescription Drugs and Its Impact on Physicians' Choice Behavior. *J Marketing* 2001;65:79–90.
28. Watkins C, Moore L, Harvey I, Carthy P, Robinson E, Brawn R. Characteristics of general practitioners who frequently see drug industry representatives: national cross sectional study. *BMJ* 2003;326:1178–1179. [PubMed: 12775618]
29. Lexchin J. Doctors and detailers: therapeutic education or pharmaceutical promotion? *Int. J Health Serv* 1989;19:663–679.
30. Caudill TS, Johnson MS, Rich EC, McKinney WP. Physicians, pharmaceutical sales representatives, and the cost of prescribing. *Arch Fam Med* 1996;5:201–206. [PubMed: 8769907]
31. Morelli D, Koenigsberg MR. Sample medication dispensing in a residency practice. *J Fam Pract* 1992;34:42–48. [PubMed: 1728653]
32. Symm B, Averitt M, Forjuoh SN, Preece C. Effects of using free sample medications on the prescribing practices of family physicians. *J Am Board Fam Med* 2006;19:443–449. [PubMed: 16951293]
33. Avorn J, Chen M, Hartley R. Scientific versus commercial sources of influence on the prescribing behavior of physicians. *Am J Med* 1982;73:4–8. [PubMed: 7091173]
34. Peay MY, Peay ER. The role of commercial sources in the adoption of a new drug. *Soc Sci Med* 1988;26:1183–1189. [PubMed: 2905075]
35. Orlowski JP, Wateska L. The effects of pharmaceutical firm enticements on physician prescribing patterns. There's no such thing as a free lunch. *Chest* 1992;102:270–273. [PubMed: 1623766]
36. U.S. Food and Drug Administration. FDA Announces Discontinued Marketing of GI Drug, Zelnorm, for Safety Reasons. [September 1, 2008]. <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01597.html>
37. Donohue JM, Berndt ER, Rosenthal M, Epstein AM, Frank RG. Effects of pharmaceutical promotion on adherence to the treatment guidelines for depression. *Med Care* 2004;42:1176–1185. [PubMed: 15550797]
38. Ling DC, Berndt ER, Kyle MK. Deregulating Direct-to-Consumer Marketing of Prescription Drugs: Effects on Prescription and Over-the-Counter Product Sales*. *The Journal of Law and Economics* 2002;45:691–723.
39. Statistics NCfH. Health, United States, 2005, with chartbook on trends in the health of Americans. US Department of Health and Human Services, CDC, National Center for Health Statistics; 2005.
40. IMS Health. National Prescription Audit Plus Basic Data Report. Plymouth Meeting, PA: 2006.

41. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27:299–309. [PubMed: 12174032]
42. Gagnon MA, Lexchin J. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLoS Med* 2008;5:e1. [PubMed: 18177202]
43. Parnes B, Smith PC, Gilroy C, Quintela J, Emsermann CB, Dickinson LM, Westfall JM. Lack of impact of direct-to-consumer advertising on the physician-patient encounter in primary care: a SNOCAP report. *Ann Fam Med* 2009;7:41–6. [PubMed: 19139448]
44. Mintzes B, Barer ML, Kravitz RL, Bassett K, Lexchin J, Kazanjian A, Evans RG, Pan R, Marion SA. How does direct-to-consumer advertising (DTCA) affect prescribing? A survey in primary care environments with and without legal DTCA. *Cmaj* 2003;169:405–12. [PubMed: 12952801]
45. Neslin, SA. Return on Investment Analysis of Pharmaceutical Promotion (RAPP): An Independent Study. [November 21, 2008]. <http://www.rxpromoi.org/rapp/index.html>
46. Kremer STM, Bijmolt THA, Leeflang PSH, Wieringa JE. Generalizations on the effectiveness of pharmaceutical promotional expenditures. *International Journal of Research in Marketing* 2008;25:234–246.
47. Singh T, Smith D. Direct-to-consumer prescription drug advertising: a study of consumer attitudes and behavioral intentions. *Journal of Consumer Marketing* 2005;22:369–378.
48. Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. *Cochrane Database Syst Rev*. 2007CD003960
49. Gartlehner, G.; Jonas, DE.; Morgan, LC.; Ringel, Y.; Hansen, RA.; Bryant, CM. T. C. Drug Class Review on Constipation Drugs. 2007 [September 1, 2008]. <http://www.ohsu.edu/drugeffectiveness/reports/final.cfm>
50. Narayanan S, Desiraju R, Chintagunta PK. Return on Investment Implications for Pharmaceutical Promotional Expenditures: The Role of Marketing-Mix Interactions. *Journal of Marketing* 2004;68:90–105.
51. Chew LD, O'Young TS, Hazlet TK, Bradley KA, Maynard C, Lessler DS. A physician survey of the effect of drug sample availability on physicians' behavior. *J Gen Intern Med* 2000;15:478–483. [PubMed: 10940134]
52. Adair RF, Holmgren LR. Do drug samples influence resident prescribing behavior? A randomized trial. *Am J Med* 2005;118:881–884. [PubMed: 16084181]
53. Hollon MF. Direct-to-consumer advertising: a haphazard approach to health promotion. *JAMA* 2005;293:2030–2033. [PubMed: 15855439]
54. Taubes G. Epidemiology faces its limits. *Science* 1995;269:164–169. [PubMed: 7618077]
55. Lyles A. Direct Marketing of Pharmaceuticals to Consumers. *Annual review of public health* 2002;23:73–91.

Figure 1. Conceptual Model

Figure 2. Gastroenterological Related Diagnoses and Office Visits

Figure 3. Monthly tegaserod Advertising and Prescribing Patterns

Table 1

Segmented Regression Results

	Coefficient	95% CI
Physician visits for constipation, Bloating, and abdominal Paining		
Baseline Visits (β_0)	3,368,235***	(2,848,795; 3,887,674)
Trend (β_1)	17,105	(-23,128; 57,338)
drc (β_2)	1,076,742***	(509,386; 1,644,098)
DTC Trend (β_3)	-201,038***	(-281,970; -120,106)
Physician diagnoses for Irritable Bowel Syndrome		
Baseline Diagnoses (β_0)	541,117***	(316,808; 765,426)
Trend (β_1)	2,266	(-10,854; 15,386)
DTC (β_2)	397,025*	(3,909; 790,141)
DTC Trend (β_3)	-67,243***	(-104,577; -29,908)

* Significant at $p < 0.05$

** Significant at $p < 0.01$

*** Significant at $p < 0.001$

Baseline: number of visits or diagnoses during the first quarter of 1997

Trend (B1): number of additional visits to physicians or IBS diagnoses per quarter *prior* to the start of the DTC marketing campaign

DTC (B2): number of additional visits to physicians or IBS diagnoses *during* the first quarter of the marketing campaign

DTC trend: number of visits or diagnoses per quarter following the start of the DTC marketing campaign

Table 2
Predicted Advertising Effect on Quarterly Physician Visits (Model 2A) and IBS Diagnoses (Model 2B)

	Coefficient	95% CI
Physician Visits for Constipation, Bloating, and Abdominal Pain^I		
DTC Advertising	-0.00027	(-0.00202, 0.00149)
Physician Directed Advertising	0.00057	(-0.00221, 0.00335)
Physician Detailing	0.00647**	(0.00184, 0.01111)
Sampling	-0.00190	(-0.00625, 0.00245)
Journal Advertising	0.07974	(-0.02500, 0.18448)
IBS Diagnoses^I		
DTC Advertising	-0.00014	(-0.00438, 0.00410)
Physician Directed Advertising	-0.00026	(-0.00640, 0.00588)
Physician Detailing	0.00620	(-0.00524, 0.01764)
Sampling	-0.00290	(-0.01331, 0.00752)
Journal Advertising	0.05786	(-0.19806, 0.31378)

^I Modeled using a Poisson distribution with advertising in millions of dollars.

* p < 0.05

** p < 0.01

*** p < 0.001

Table 3
Ordinary Least Squared Regression of Marketing on Monthly tegaserod Prescribing (Model 3)

	Coefficient	95% CI
Univariate Model of Each Individual Predictor		
DTC Advertising	1,796 ^{***}	(1,041; 2,549)
Physician Directed Advertising	5,134 ^{***}	(4,147; 6,120)
Physician Detailing	19.09	(-5,850; 5,888)
Sampling	6,774 ^{***}	(5,447; 8,101)
Journal Advertising	-195,537 ^{***}	(-235,363; -155,710)
Multivariate Model Combining All Predictors		
Intercept	-68,124 ^{**}	(-105,112; -31,136)
DTC Advertising	192	(-734; 1,118)
Physician Directed Advertising	4,108 ^{***}	(2,526; 5,691)
IBS Citations in Scientific Journals	1,770 ^{**}	(808; 2,731)

*
p < 0.05

**
p < 0.01

p < 0.001