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What influences healthcare providers' prescribing decisions? Results from a national survey

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ABSTRACT

Background: Prior U.S. Food and Drug Administration (FDA) surveys with healthcare providers (HCPs) have focused on attitudes toward direct-to-consumer advertising and have not specifically examined professionally-targeted prescription drug promotion. Similarly, there are no recent national surveys of HCPs examining their interactions with the pharmaceutical industry.

Objectives: The goal of this study was to use a national sample of HCPs to examine exposure to professionally-targeted prescription drug promotions and interactions with industry, and knowledge, attitudes and practices related to FDA approval of prescription drugs.

Methods: An online national survey was conducted with 2000 HCPs representing primary care physicians (PCPs), specialists (SPs), physician assistants (PAs), and nurse practitioners (NPs). The sample was randomly drawn from WebMD's Medscape subscriber network, stratified by HCP group, and designed to yield target numbers of completed surveys in each group. Weights were computed to correct for unequal selection probabilities, differential response rates, and differential coverage and used to generalize completed surveys to a national population of PCPs, SPs, NPs, and PAs.

Results: Exposure and attention to pharmaceutical promotions and contact with industry were significantly associated with reported increase in pharmaceutical industry influence on decisions about prescription drugs. SPs were significantly more likely to prescribe off-label and serve as opinion leaders for the pharmaceutical industry compared to other provider groups.

Conclusions: Findings indicate pharmaceutical promotions directed at HCPs occur in many forms and are disseminated through multiple channels. By using a nationally representative sample of HCPs, this study provides population-level estimates for exposure and attention to prescription drug promotion and contact with industry and evidence for their influence on prescriber decisions. Findings from this study will help to inform FDA of HCP responses to and impacts of prescription drug promotion.

Introduction

In the United States, the pharmaceutical industry spends approximately $60 billion annually on promotional activities to encourage use of their products, with the largest portion of these dollars going towards promotions directed at physicians and other prescribers.[1,2] Interactions with industry often start during the first year of medical school and increase over the course of training.[3–5] Findings from a national survey of medical students and residents conducted in 2011 indicate that despite favoring separation from industry during medical education, most trainees reported receiving gifts from industry and attending industry-sponsored educational sessions.[3] Similarly a 2004 national survey of physicians found that 80% of physicians reported receiving food and drug samples from industry.[6] Concerns about the influence of gifts on prescribers have resulted in voluntary guidelines[7] and, in some states, an outright ban on certain types of gifts.[8,9]

Promotional efforts by pharmaceutical companies, even the provision of small and seemingly inconsequential gifts, have been shown to influence HCP prescribing.[10–13] Studies show that industry marketing of prescription drugs results in less evidence-based prescribing and a

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greater likelihood of prescribing industry-promoted products even when other drugs are available that are equally as effective and have more established safety records.[14–16] A movement away from evidence-based prescribing can result in poorer patient health outcomes.[15]

Physician knowledge about drugs has been shown to correlate more with pharmaceutical marketing materials than with the medical literature[2] and multiple studies have found an association between pharmaceutical sales representatives (PSRs) visits and increased prescribing of the promoted drug.[17–19] The widespread industry practice of distributing drug samples contributes to HCP preferences for marketed, brand-name drugs, less prescribing of generics, fewer recommendations for over-the-counter drugs and higher medication costs.[16,20,21] One study noted that industry marketing increased medication costs by approximately 60%.[21] Similarly, research finds a positive correlation between HCP contact with PSRs and the cost of treatment choices.[4] Pharmaceutical promotion efforts have also been shown to lead to physician requests to add promoted drugs to hospital formularies.[6,20]

Promotional activities for prescription drugs can take many forms including interaction with PSRs[17,18] and medical science liaisons (MSLs),[22] professionally targeted sales aids and advertisements,[23] distribution of drug samples,[18,19] and sponsored continuing medical education.[5] Detailing is an often-used strategy, which allows pharmaceutical manufacturers to educate and promote their products directly to prescribers and often includes providing drug samples and professionally-targeted materials about their products.[6,18,19,24] Industry sources assert that interactions with industry representatives serve an important purpose in educating HCPs about their products, and some HCPs support this assertion.[16,24,25] However, multiple studies have found that data presented in professionally-targeted materials can be misleading in various ways, such as by including insufficient information, unsupported claims, or a failure to disclose limitations of the information provided.[23,26,27]

Research indicates industry-developed materials targeting HCPs sometimes contain extracted data from clinical studies that lack context, exaggerate benefits, minimize risks, and concerns have been raised they may contribute to inappropriately prescribing a drug for unapproved uses.[28,29] Pharmaceutical firms often disseminate published data about unapproved uses of prescription drugs (off-label use). The U.S. Food and Drug Administration (FDA) guidance recommends that firms providing off-label use information should also provide a representative publication that reaches a different conclusion, when such information exists.[30] It is unclear how frequently firms actually disseminate this type of information. Another promotional strategy used by the industry is to recruit physicians to serve as key opinion leaders (KOLs) to speak about off-label uses and to author papers that are ghostwritten by the industry.[31,32] MSLs serve as the pharmaceutical company's clinical or scientific representative and can help facilitate industry relationships with KOLs; they develop collaborative relationships with thought leaders in a given therapeutic area and leverage these relationships to support the company's overall branding strategy and develop new products.[22,33–34] For example, MSLs may invite KOLs to speak at pharma-sponsored events or conduct clinical trials. KOLs are paid by pharmaceutical companies for their services, which may include speaking at meetings, serving as a consultant, or receiving funding for research.[31,32] HCPs that serve as industry KOLs may promote products similar to PSRs, but as fellow physicians, they may be viewed as more credible.

Despite training and expertise in their field, HCPs, like most people, may have cognitive biases in the type of information they attend to at any given time. They may be persuaded by leading experts and strong statements in professional pieces and may not have the time to ascertain the accuracy of such information.[35,36] FDA's goal is to help ensure that information disseminated about prescription drugs is truthful, balanced, and accurately communicated. FDA's Office of Prescription Drug Promotion has a robust social science research program that examines issues of relevance to direct-to-consumer (DTC) and HCP-directed promotional prescription drug materials.[37] Prior FDA surveys with HCPs have focused on attitudes about DTC advertising[38] and have not examined professionally targeted promotions in depth. In addition, the most recent national surveys examining industry interactions with physicians and medical trainees were conducted in 2004[6] and 2011[3], respectively. To our knowledge, there have been no national surveys of HCPs examining these issues in nearly a decade. To address these gaps, FDA conducted a national survey with HCPs in 2019 to examine exposure to professionally targeted prescription drug promotions and interactions with industry and their influence on prescribing decisions.

A secondary goal of the survey was to examine HCPs' knowledge and practices related to FDA policies around prescription drugs, and emerging issues related to prescribing, including the use of accelerated approval prescription drugs[1] and biosimilars[2] to inform future Agency activities. While accelerated approval pathways make medications available more quickly, understanding the standards for approval and their limitations is critical for prescribing decisions. The few surveys conducted with specialty physicians indicate most misunderstand the standards used for accelerated approval.[39,40] Similarly, previous surveys conducted with specialty physicians indicate significant knowledge gaps regarding biosimilars,[41,42] which may be exacerbated by dissemination of misinformation.[43] Biosimilars meet the Agency's rigorous approval standards and were created with a streamlined approval process and intended to spur competition and reduce costs of biological therapies.[44,45] However, HCP acceptance and uptake of biosimilars has been slow.[46] As discussed previously, HCPs rely on industry materials to educate themselves about prescription drugs, which may not always accurately depict information.

Methods

Study design and sample

An online national survey was conducted with 2000 HCPs representing primary care physicians (PCPs, n = 700), specialists (SPs, n = 600), physician assistants (PAs, n = 350), and nurse practitioners (NPs, n = 350). The sample was randomly drawn from WebMD's Medscape subscriber network, stratified by HCP group, and designed to yield target numbers of completed interviews in each group. The Medscape subscriber network includes over 600,000 American Medical Association (AMA) validated physicians, including PCPs and SPs, and more than 165,000 NPs and PAs.[3] Sample selection was *not* limited to HCPs that opted in to participate in market research surveys. All HCPs in relevant practitioner groups had an equal probability of receiving the initial email about the study. Eligible HCPs had to practice in an office-based setting and spend at least 50% of their time providing patient care. PCPs and SPs were required to be AMA-validated U.S. physicians (MDs and DOs). PCPs were from family practice, general practice, or internal medicine specialties and SPs were from cardiology, dermatology, endocrinology, neurology, obstetrics/gynecology, oncology, ophthalmology, psychiatry, rheumatology, and urology, all specialties that have

[1] Accelerated Approval regulations allow FDA to approve drugs for serious conditions that fill an unmet medical need using a surrogate or intermediate clinical endpoint to assess substantial evidence of drug effectiveness. This saves time and enables faster approvals for these drugs (https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval).

[2] Biosimilars are biologics that have as no clinically meaningful difference from an existing FDA-approved reference product; U.S. Food and Drug Administration. *Biosimilars*. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars.

[3] Physicians are matched against AMA data (https://www.mmslists.com/ama-physicians-list). NP/PAs are matched against the National Provider Identifier (NPI) registry (https://npiregistry.cms.hhs.gov/) and IQVIA's One Key data for additional matching and validation.

included recent promotion for prescription products. NPs and PAs were required to have prescribing authority (restricted or unrestricted) in their state and included a mix of primary care and specialists. For completion of the survey, PCPs, NPs, and PAs were provided a honorarium of $50 and SPs were provided a honorarium of $60. The study was approved by institutional review boards of each author's institution. The survey was administered between October and November 2019.

Survey development and testing

The investigators collaborated in developing the survey and used a multi-stage design and development process. This included an expert review, cognitive interviews and usability testing, and a pretest. Recommendations emerging from the expert review focused on ways to reduce respondent burden and jargon language, harmonize response scales (where possible) for consistency, and on adding demographic and practice characteristic measures from other national provider surveys. Cognitive and usability testing of the online survey was conducted with nine HCPs from the four provider groups included in the study. This testing assessed comprehension and appropriateness of response options, as well as overall respondent experience using the online instrument. As a final check of the content and usability of the instrument, a pretest with a small sample (n = 25) of HCPs from the target provider groups was conducted online. Frequency distributions of the quantitative data were reviewed to identify any questions with high item nonresponse. Pretest data also provided support for removing one item and developing close-ended responses for a previously open-ended question.

Measures

Exposure to promotions. Exposure to pharmaceutical promotion was measured through three questions (*When you read through journals, how often do you notice pharmaceutical promotions?; When you visit these reference websites, how often do you notice prescription drug promotions?; When you watch television, how often do you notice ads for prescription drugs?*) using a 5-point Likert-type scale. The three questions were summed to create an overall measure of exposure to pharmaceutical promotion for use in the regression model. Cronbach's alpha was 0.53.[4]

Attention to promotions. Attention to pharmaceutical promotion was measured by asking HCPs to rate how closely they read advertisements in journals *(When you notice a prescription drug advertisement for a new product, how closely do you usually read it?; When you notice a prescription drug advertisement related to your practice, how closely do you usually read it?)* and in medical websites *(When you notice a prescription drug promotion on a reference website, how closely do you usually read it?)*[5] using a 5-point Likert-type scale. Responses to the three questions were summed to create an overall measure of attention to pharmaceutical promotion for use in the regression model. Cronbach's alpha was 0.75.

Contact with industry. Frequency of contact with the pharmaceutical industry was assessed across multiple channels or venues (in-person practice visits, attendance at industry-sponsored conferences and dinners, and online contact). Factor analysis using principle component analyses was conducted to create a global measure of contact with the pharmaceutical industry. Factor loadings for the four items ranged between, 0.60 to 0.70.

Influence of information sources. HCPs rated the influence of nine different information sources on informing their decisions about prescription drugs using a 4-point Likert-type scale. These sources included, (1) colleagues/peers, (2) key experts in the field presenting at conferences, (3) online community of HCPs, (4) sponsored conference sessions, (5) sales aids with product information from pharmaceutical sales representatives (PSRs), (6) dinner talks sponsored by pharmaceutical companies, (7) commercial drug websites, (8) journal advertisements, and (9) direct-to-consumer advertisements.

Pharmaceutical industry influence. This is a global measure of industry influence on HCP decisions about prescription drugs and combines ratings of five information sources (see *influence of information sources* measure above) commonly used by industry to educate and promote their products to HCPs. The five sources include: sponsored *conference sessions, sales aids with product information from PSRs, dinner talks* sponsored *by pharmaceutical companies, commercial drug websites, and journal advertisements.* HCPs rated the influence of these source individually on informing their decisions about prescription drugs using a 4-point Likert-type scale. The five items were subsequently combined to create the global measure for use in the regression. Chronbach's alpha was 0.83.

KOL activities. HCPs were asked if they participated in activities during the last 24 months that could be associated with being an industry KOL.[31,32] The three activities (*gave talk/made conference presentation on behalf of a pharmaceutical company, served as a consultant for a pharmaceutical company,* and *participated as an investigator in a clinical trial or other research study* funded *by a pharmaceutical company)*represented a sensitive measure of involvement, including not only talks, but also other regular interactions that involved renumeration from the pharmaceutical industry. These three items were combined to create a KOL summary score for use in the regression model. Cronbach's alpha was 0.70. HCPs were also asked if their colleagues participated in these activities.

Importance of prescribing FDA approved product. HCPs were asked to rate the importance of prescribing a drug that is FDA-approved for that particular indication using a 4-point Likert-type scale. They could also select *It depends* as a response. Participants were also asked how often they prescribed a drug for a condition for which it is not approved using a 4-point Likert-type scale. They could also select, *Do not know* as a response for this question.

Understanding of FDA policies and emerging issues related to prescribing were assessed through both close-ended and open-ended questions. Investigators developed coding sheets for open-ended questions, which included two or three key codes. Responses that did not fit these codes could be coded as, *other* or *don't know/unsure* as appropriate. Two coders used the coding sheets to code responses to the three open-ended questions. To ensure consistency across coders, the investigators had both coders code a pre-selected random sample of 20% of the responses for each of the three questions and conducted reliability testing. Inter-rater reliability using Cohen's Kappa was calculated for key codes for each question, which are described below.

Prescription drug approval. HCPs were presented with three statements and asked to check the statement that best described their understanding of how FDA regulates prescription drug promotion. Participants also had the option to select "I'm not sure how FDA regulates prescription drug promotion." HCPs were also asked an open-ended question, *Can you describe your understanding of what FDA approval of prescription drugs means?* Three key codes were used for this open-ended question: (1) Process (mentions aspects of the process involved in the approval, such as clinical trials, testing, review, evaluation, etc.); (2) Drug safety (mentions outcomes of approval, such as drug safety, benefits, and efficacy for specific indications, conditions); and (3) Process and Drug Safety (mentions both the process and drug safety as described previously). Cohen's Kappa ranged from 0.84 to

[4] Given the low alpha for the three questions, we compared regression models using the individual items and the overall exposure measure. The results of the two regression models were very similar. For parsimony, we present regression model findings using the overall exposure measure in the results section.

[5] Cognitive testing findings indicated that HCPs were exposed to many journal ads, but primarily paid attention to journal ads about new prescription drugs and drugs related to their practice. Thus, questions about attention to journal ads were designed to be specific to these areas. There were no parallel findings about ads on medical reference websites and the attention question was more general.

0.97.

Accelerated approval. HCPs were asked: *In your own words, what is an accelerated approval drug?* Three key codes were used for this open-ended question: (1) Serious (mentions serious or life-threatening condition, fills an unmet medical need); (2) Effective (mentions outcome such as, effective, beneficial, reduces/minimizes risk); and (3) Limited testing (mentions limited testing, fewer clinical trials, and trials waived). Cohen's Kappa for the key codes ranged from 0.81 to 0.94. As a follow-up question, HCPs were asked to rate their comfort in prescribing an accelerated approval drug, using a 4-point Likert-type scale. They could also select "I'm not sure what an accelerated approval drug is."

Biosimilars. To examine knowledge of biosimilars, HCPs were asked: Now we want to understand your perspective on "biosimilar." In your own words, what is a "*biosimilar*"*?* Three key codes were used for this open-ended question: (1) Structure and Function (mentions drugs that are biologically similar in their makeup or action/function); (2) Clinical Outcomes (mentions drugs that have similar outcomes, effects or comparable clinical outcomes); and (3) Biologic (mentions drugs that are similar to a biologic, biologic product, or to a reference product). Cohen's Kappa for these codes ranged from 0.91 to 0.98. HCPs also rated their comfort in prescribing biosimilar products using a 4-point Likert-type scale.

Demographics and practice characteristics. Provider characteristics (age, gender, race/ethnicity, and HCP group and physician specialty) were collected through the screening instrument. Practice characteristics (practice type, years in practice, number of prescriptions written, and patients seen in a typical week) were included in the survey.

Data collection

Selected HCP samples were initially sent a pre-notification letter by email 2 days prior to launching the web survey. After 2 days, HCP samples received a recruitment email about the survey, which included a link to the eligibility screener. HCPs who met the eligibility requirements were invited to participate in the survey within 24 h of completing the screener. Non-respondents received weekly email reminders. The 2000 targeted surveys by HCP group were completed in 3 weeks, and data collection was terminated for each HCP group as they met their sample quota requirements.

The online platform used by WebMD was able to detect when a person opened the email and about 75% of the emails were never opened by the practitioner. In the literature, there is a distinction between "noncontact" versus "refusal" as components of nonresponse, with the former being no contact established with the sample person, and the latter being a refusal of the sample person to participate in the study after being invited and understanding the study purpose and incentives offered.[47] Not opening an email does not necessarily imply complete noncontact, as the recipient may have read the subject line or possibly a portion of the email itself. If a "refusal" occurs in this case, it is a highly passive refusal based on limited psychological engagement with the email. Studies have found that noncontact rates are correlated with factors increasing or decreasing the propensity of being at home, such as employment/unemployment and age.[48] Refusal rates, on the other hand, are more complex and are based on a wide range of socioeconomic factors mediating potential attitudes toward the survey.[49] In the context of the current survey, a failure to open the email is treated as noncontact, which may be correlated with the practitioners' busy schedules and work habits, whereas refusals may be mediated by attitudes toward the survey content.

Table 1 presents sample contact, screener eligibility and response rates. Response rates were calculated based on the American Association for Public Opinion Research standards.[50] While response rates were low across HCP groups, we note this was a quota-based sampling design and procedures used in these studies typically result in lower response rates.[51] In the current study, screening and survey data collection was terminated as each HCP group met their sample quota requirements. In addition, we note that the interview response rates (number of completed interviews divided by eligible screeners) were all very high.

Table 1
Email contacts, screener eligibility and final response rates.

Status of sample unit	PCPs	SPs	PAs	NPs
Total emails sent (T)	39,767	26,570	9184	8371
Total sample contacted (C)	8752	6319	2227	2304
Eligible Screeners (E)	769	647	373	365
Screener Eligibility Rate (ScrERate)	69.0%	73.0%	64.5%	65.7%
Screener Eligible Response Rate (ScrRR)	2.8%	3.3%	6.3%	6.7%
Completed Interviews (CI)	700	600	350	350
Interview Response Rate (CIRR=CI/E)	91.3%	92.8%	93.8%	95.9%
Final Total Response Rate (RR = ScrRR*CIRR)	2.6%	3.1%	5.9%	6.4%

Nonresponse bias analysis and weighting procedures

Nonresponse bias analysis was conducted to compare respondents and non-respondents on known characteristics for both the screener and survey. A high cutoff ($p < 0.20$) was used to test for significant differences for response rate bias considerations, as it is better to err on the side of assuming too many differences rather than too few differences. Using a high cutoff also helps identify variables that would be good candidates for use in weighting adjustments. At this level, significant differences in response were found in primary specialty, geographic region, race, and age groups. However, the differences observed in response rates were not generally large and raking to the National Ambulatory Medical Care Survey (NAMCS) and the American Community Survey (ACS)[6] totals (by specialty for PCPs and SPs, and by Census Region for all four practitioner subgroups) corrected for any differences observed in the screener nonresponse analysis. For the survey, weights were computed for each completed interview to correct for unequal selection probabilities, differential response rates, and differential coverage. The weights were used to generalize the completed interviews to a national population of PCPs, SPs, NPs, and PAs. Weights were developed for gender, age groups and the four U.S. Census Regions based on external totals from national surveys (NAMCS and ACS). In addition, external totals were used to develop weights for specialty and practice size for PCPs and SPs. There were no external control totals for these dimensions for PAs and NPs. NAMCS estimates were used as benchmarks for PCPs and SPs and ACS was used for benchmarks for PAs and NPs.

Data analysis

All estimates were based on weighted estimates utilizing the final calibrated weights unless otherwise noted. All standard errors were computed using the weights and the replicate weights. All tests (Chi-square, t-tests) reflected degrees of freedom accurate for the replicate variances. The analysis then utilized weights and replicate weights to appropriately account for the effects of the complex sample design and estimation procedures. The replicate control totals allow for the computation of an unbiased sampling error, including the independent

[6] We used the NAMCS restricted dataset, which provides detailed information on the physician sample, including specialty, age, race/ethnicity, census region, practice type, practice size (# of physicians, # of PAs, # of NPs), and other variables (https://www.cdc.gov/nchs/data/ahcd/Availability_of_NAMCS_and_NHAMCS_Restricted_Data.pdf). The ACS Public Use Microdata Sample (PUMS) provides demographic and geographic estimates by profession. Totals for age, race/ethnicity, and census region for both PAs and NPs were downloaded from the ACS PUMS website (https://www.census.gov/programs-surveys/acs/microdata.html) by searching on occupational code and and NAICS code. Both data sources provide national estimates on the four HCPs groups.

sampling error inherent in the control totals used for the study (from NAMCS and ACS).

Analyses were conducted using SPSS Version 25 complex samples module and utilized Taylor Series variance computations to account correctly for weighting and the sample design. A subset of the analyses was conducted in SAS version 9.4 using the jackknife variance estimator and the replicate weights developed for the sample. These analyses were conducted to identify any systematic differences in variances and procedures between the two software packages. The SPSS Taylor Series calculations appear valid to a reasonable level of approximation. Data were analyzed using descriptive statistics, including percentages, means, and confidence intervals (CI). Chi-square and the Benjamini-Hochberg (BH) procedure were used to examine differences in survey measures across the four HCP groups. BH allows for a larger number of significant results than the very strict Bonferroni procedure by controlling a false discovery rate rather than an omnibus overall Type I error rate, and it has acquired general acceptance in the research community.[52,53] Cronbach's alpha was used to assess the scale reliability for items. Linear regression was used to examine the association between pharmaceutical industry influence on decisions about prescription drugs and predictors such as, exposure and attention to pharmaceutical promotion and frequency of contact with pharmaceutical representatives. Ordinal regression was conducted to examine the association between prescribing off-label and predictors such as, beliefs about importance of prescribing FDA-approved drugs and being an industry KOL. All regression models included provider characteristics (age, gender, race/ethnicity and HCP group) and practice type as covariates.

Results

Characteristics of survey respondents

Table 2 presents characteristics of survey respondents across the four HCP groups. Both unweighted and weighted frequencies are presented. The weighted data show that while most of the PCPs and SPs were male, the NPs and PAs were mostly female. Most respondents across HCP groups were White and practiced in a solo or group practice. A little more than half the PCPs and SPs were in practice for more than 20 years, but this was not the case for PAs and NPs, whose years in practice were quite varied. The age groups across the four HCP groups were diverse, as were the number of patients HCPs saw and the number of prescriptions written in a typical week.

Exposure and attention to pharmaceutical promotions and contact with industry

HCPs reported exposure to pharmaceutical promotion was significantly higher for medical journals (Mean = 3.79, CI = 3.73–3.84) compared to television (Mean = 3.48, CI = 3.42–3.54) (BH adjusted $p < 0.01$). Reported exposure was significantly lower for medical reference websites (Mean = 2.64, CI = 2.59–2.70) compared to both television and medical journals (BH adjusted $p < 0.01$). HCPs reported significantly greater attention to a prescription drug ad in a journal when it related to their practice (Mean = 3.79, CI = 3.74–3.84) or to a new product (Mean = 3.14, CI = 3.09–3.20) compared to an ad on a medical reference website (Mean = 2.34, CI = 2.27–2.40) (BH adjusted $p < 0.01$).[7]

Contact with industry occurred through multiple channels and provided opportunities for receiving prescription drug information. Seventy-five percent of HCPs indicated their practice allowed visits from PSRs, with approximately 53% HCPs reporting a PSR visit once a week or more. Specialists (82%) were more likely to report their practice allowed PSR visits compared to PCPs (70%), PAs (75%) and NPs (70%), BH adjusted, $p < 0.01$. HCPs reported that PSRs brought brochures for patients and HCPs (80%), drug samples (79%), food/beverage (69%), and sales aids/electronic visuals containing product information (42%) during the past 12 months. Forty percent of HCPs also reported contact with PSRs through electronic detailing during the past 12 months. Eighty percent of HCPs reported attending one or more professional conference sessions sponsored by a pharmaceutical company during the last 24 months. On average, HCPs reported attending two to three pharmaceutical sponsored dinner meetings with medical experts each year. Attendance at pharmaceutical sponsored dinner meetings was significantly lower for PCPs (Mean = 2.15, CI = 1.82–2.48) compared to SPs (Mean = 2.53, CI = 2.12–2.93), BH adjusted $p < 0.05$), PAs (Mean = 2.71, CI = 2.25–3.16) BH adjusted $p < 0.01$), and NPs (Mean = 2.54, CI = 2.22–2.87, BH adjusted $p < 0.01$).

Influence on decisions about prescription drugs

Overall, HCPs reported that colleagues and key experts in the field presenting at conferences were the most influential on their decisions about prescription drugs. PAs and NPs generally reported significantly greater influence from most sources compared to the two physician groups (see Table 3).

The findings from the linear regression model (Table 4) indicated a significant positive association between the outcome measure, pharmaceutical industry influence on decisions about prescription drugs and predictors, exposure and attention to pharmaceutical promotions and the pharma contact factor score. Being a physician was significantly negatively associated with pharmaceutical influence on decisions compared to the reference group and pairwise comparisons were conducted using the BH procedure to examine differences across HCP groups. Results indicated NPs (Mean = 11.88 CI = 11.50–12.26, $p < .01$) reported significantly higher pharmaceutical industry influence compared to both PCPs (Mean = 10.74, CI = 10.37–11.11) and SPs (Mean = 11.10, CI = 10.76–11.45). Similarly, PAs (Mean = 11.66, CI = 11.27–12.04) reported significantly higher industry influence compared to PCPs (p-value <0.01) and were marginally significantly higher compared to SPs (p-value < 0.06). The values for pharmaceutical industry influence ranged from a minimum of 5 to a maximum 20, with an overall mean of 11.26 (CI = 11.07–11.45) across all HCP groups. While there were some statistically significant differences across provider groups, the differences were not large or meaningfully different. Overall the findings suggest industry influenced decisions about prescription drugs for all HCP groups.

Influences on off-label prescribing

Over 80% of all HCPs reported it was "very important" or "somewhat

[7] For the three exposure and attention items, we analyzed the ordinal indices of responses (e.g. the index of ""1" for the response "Never" and the index of ""5" for the response "Every time"), and for each respondent we calculated the difference in these indices between each pair of items. To test whether the average responses to a given pair of items would differ, we conducted a *t*-test of whether the average difference in numeric indices for each pair of items is zero. To account for the testing of multiple pairs of items, we determined significance based on the BH adjustment for controlling the false discovery rate among the set of tests at $p = 0.05$.

Table 2
Characteristics of survey respondents.

	Unweighted n = 2000				Weighted n = 348,269			
	PCPs	SPs	PAs	NPs	PCPs	SPs	PAs	NPs
Total	**700**	**600**	**350**	**350**	**104,576**	**107,408**	**59,539**	**76,746**
Gender								
Male	60%	66%	25%	8%	66%	70%	28%	10%
Female	40%	34%	75%	92%	34%	30%	72%	90%
Race/Hispanic Identity								
Hispanic	8%	5%	6%	3%	7%	6%	6%	4%
Non-Hispanic White	65%	66%	82%	81%	66%	70%	82%	80%
Non-Hispanic Black	2%	2%	3%	6%	3%	2%	2%	6%
Non-Hispanic Asian	20%	23%	5%	5%	20%	18%	6%	6%
Non-Hispanic Other	5%	5%	3%	5%	4%	4%	3%	5%
Age								
Less than 35 years	13%	11%	33%	18%	4%	2%	42%	23%
35–44 years	29%	30%	35%	30%	21%	19%	28%	26%
45–54 years	26%	26%	17%	21%	31%	31%	16%	21%
55–64 years	21%	23%	12%	23%	30%	28%	10%	22%
65 years or older	10%	12%	3%	8%	15%	20%	4%	8%
Type of Practice								
Private solo or group practice	60%	78%	62%	50%	72%	82%	61%	52%
Freestanding clinic/urgent care center	9%	6%	13%	13%	7%	5%	13%	12%
Non-Federal Government clinic (state, county, maternal health, etc.)	5%	4%	4%	7%	4%	2%	4%	7%
Federal Government-operated clinics (Veterans Affairs, etc.)	3%	2%	5%	4%	2%	2%	5%	4%
Health maintenance organization or other prepaid practice	6%	3%	3%	6%	3%	2%	4%	6%
Community health center (FQHC, federally funded clinics, etc.)	9%	3%	7%	13%	5%	4%	7%	13%
Other	7%	5%	6%	8%	6%	3%	6%	8%
Number of years in practice								
Less than 5	15%	12%	29%	26%	7%	5%	33%	27%
5 to 10	21%	22%	27%	28%	13%	13%	27%	29%
11 to 15	13%	13%	15%	14%	13%	11%	13%	13%
16 to 20	14%	13%	13%	11%	15%	18%	12%	10%
More than 20	37%	39%	16%	22%	53%	53%	16%	21%
Number of Prescriptions in a Typical Week								
Fewer than 35 prescriptions	13%	33%	24%	29%	16%	33%	25%	29%
35 to 65 prescriptions	21%	29%	29%	30%	20%	25%	28%	29%
66 to 125 prescriptions	27%	22%	26%	22%	26%	24%	28%	22%
More than 125 prescriptions	39%	15%	21%	19%	38%	18%	19%	20%
Number of Patients in a Typical Week								
Fewer than 40 visits	9%	8%	11%	16%	13%	11%	11%	17%
40 to 79 visits	33%	36%	42%	51%	34%	36%	41%	50%
80 to 119 visits	40%	31%	35%	23%	35%	28%	35%	23%
120 or more visits	18%	26%	13%	10%	18%	26%	14%	11%

Table 3
Influence of information source on decisions about prescriptions drugs and participation in KOL activities (N = 2000).

	PCPs	SPs	PAs	NPs
% Reporting somewhat/very influential on informing decisions about prescription drugs				
Colleagues[1]	86[b]	86[b]	94[a]	95[a]
Key experts in the field presenting at confer ences[2]	79[b]	84	87[a]	87[a]
Online community of HCPs[1]	50[b]	49[b]	60[a]	66[a]
Sponsored conference sessions[3]	42[d]	48[c]	53[e]	60[a]
Sales aids with product info. from PSR[2]	41[b]	42	51[c]	50[a]
Dinner talk sponsored by pharm. company[1]	43[b]	48[b]	58[a]	60[a]
Commercial drug website	24	25	30	29
Journal advertisements	31	32	35	37
Direct-to-consumer advertisements	18	14	20	21
% Reporting participating in KOL Activities in last 24 Months[4]				
Gave talk/presented at a conference on behalf of a pharmaceutical company	2	12	1	3
Consultant for a pharmaceutical company	2	8	3	3
Investigator in clinical trial/other research funded by a pharmaceutical company	4	12	4	4
% Reporting colleague participating in KOL activities in last 24 months[4]				
Gave talk/presented at a conference on behalf of a pharmaceutical company	33	54	29	32
Consultant for a pharmaceutical company	20	43	18	21
Investigator in clinical trial/other research funded by a pharm. company	19	43	16	20

[1]a > b, BH, p <0.01.
[2]a>b, BH, p <0.05.
[3]a >d; a >c; d > e, BH, p < 0.01.
[4]Specialists were significantly more likely to report "yes" for self and colleague for all KOL activities compared to other three HCP groups (BH, p < 0.01).

Table 4
General linear regression model of pharmaceutical industry influence on prescriber decisions[a] (N = 2000).

Predictors	Adjusted coefficients (SE)	P-value
Pharma contact factor score	1.406 (0.104)	<0.001
Attention to pharmaceutical promotion	0.410 (0.037)	<0.001
Exposure to pharmaceutical promotion	0.176 (0.023)	<0.001
HCP Group: PCPs	−0.678 (0.216)	0.002
HCP Group: SPs	−0.599 (0.236)	0.011
HCP Group: PAs	−0.138 (0.216)	0.521
HCP Group: NPs	0.000[b]	
Gender: Male	−0.317 (0.165)	0.055
Gender: Female	0.000[b]	
Practice Type: Solo/group practice	0.096 (0.283)	0.735
Practice Type: Clinics/Urgent care centers	0.006 (0.348)	0.987
Practice Type: Non-federal gov't. clinics	0.164 (0.401)	0.683
Practice Type: Federal gov't. clinics	0.061 (0.471)	0.897
Practice Type: HMOs	0.005 (0.433)	0.992
Practice Type: Comm. health centers	−0.045 (0.370)	0.903
Practice Type: Other	0.000[b]	
Race/ethnicity: Hispanic	0.106 (0.428)	0.805
Race/ethnicity: Non-HS White	−0.193 (0.327)	0.555
Race/ethnicity: Non-HS Asian	0.298 (0.369)	0.419
Race/ethnicity: Non-HS Black	0.683 (0.514)	0.184
Race/ethnicity: Non-HS Other	0.000[b]	
Age	−0.001 (0.006)	0.825

[a] R-square for this model is 0.445. The outcome variablefor this model is pharmaceutical industry influence, which is a global measure of industry influence on HCP decisions about prescription drugs. The global measure combines ratings of five different sources or channels (*sponsored conference sessions, sales aids with product information from PSRs, dinner talks sponsored by pharmaceutical companies, commercial drug websites, and journal advertisements*) commonly used by industry to educate and promote their products to HCPs and ranges in value from a minimum 5 to a maximum of 20.

[b] This is the reference category.

important" to them to prescribe a drug that is FDA-approved for that particular indication. Approximately 37% reported they never or rarely prescribed a drug for a condition for which it is not approved (a.k.a., off-label prescribing) and 63% reported prescribing off-label sometimes or often.

Specialists reported prescribing drugs for off-label uses significantly more often (BH, $p < 0.01$) compared to the other three HCP groups (see Fig. 1) and also reported greater participation in activities that could be construed as industry KOL activities for themselves (BH adjusted $p < 0.01$) and their colleagues (BH adjusted $p < 0.01$) compared to other HCP groups. The most frequent KOL activities reported by specialists were giving a talk or making a conference presentation on behalf of a pharmaceutical company and participating as an investigator in a clinical trial or other research study funded by a pharmaceutical company, 12% for both activities (see Table 3).

Findings from the ordinal regression model indicated that off-label prescribing was significantly, negatively associated with beliefs about the importance of prescribing a drug for its indication, and positively associated with being a pharmaceutical industry opinion leader and being a physician (see Table 5). Pairwise comparisons between HCP groups using the BH procedure indicated that SPs ($p < 0.01$) were significantly different from PCPs, PAs, and NPs (see Fig. 1).

Understanding of FDA policies and emerging issues related to prescribing

Participants were presented with four statements and asked to select the statement that best described their understanding of how FDA regulates prescription drug promotion. Findings indicated that only 20% of all HCP participants correctly recognized the statement (*FDA regulates prescription drug promotion, but does not generally require review before release*) about FDA regulation of prescription drugs.

When asked to describe their understanding of FDA approval of prescription drugs in an open-ended question, approximately 53% of participants mentioned both the process of approval (e.g., review, clinical trials, testing) and drug safety (e.g., outcomes of approval, such as drug safety, efficacy). Approximately 17% of participants mentioned only the process or only drug safety. The remaining 13% mentioned comments that were coded as "other" or "do not know."

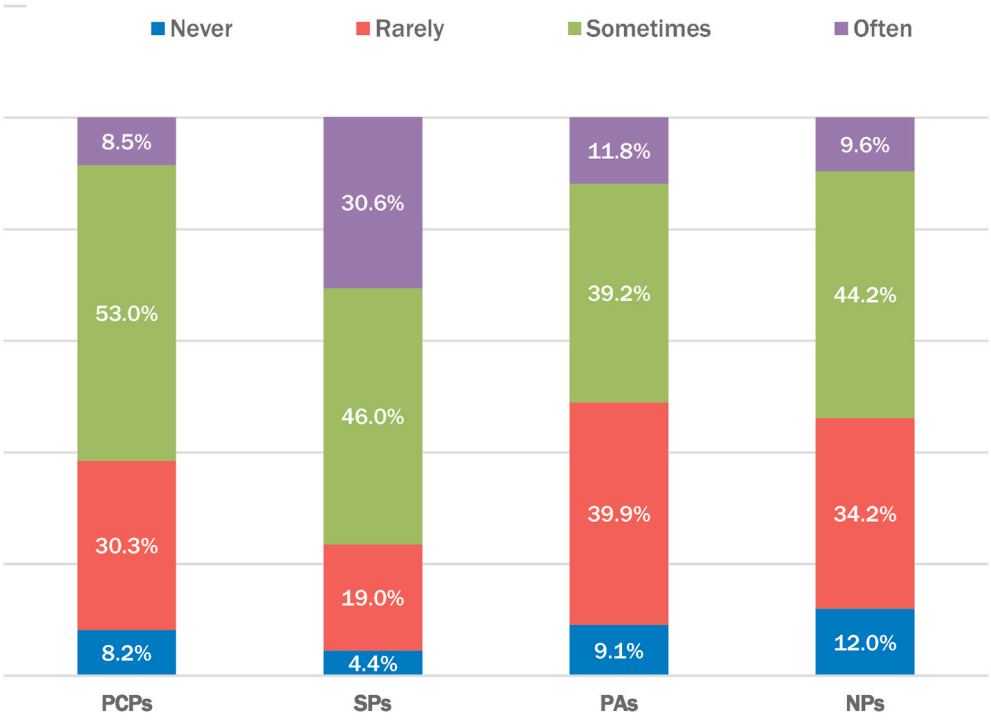

Fig. 1. Off-label prescribing frequency by HCP group.
Percentages in bar graphs reflect distribution of responses options (never, rarely, sometimes, and often) for the question, *How often do you prescribe a drug for a condition for which it is not approved?*.

Table 5
Ordinal regression model of off-label prescribing[a] (N = 2000).

Predictors	Adjusted coefficients (SE)	95% Confidence interval	P-value
Important to prescribe FDA-approved drug	−1.264 (0.088)	−1.436–−1.092	<0.001
Industry opinion leader score	0.244 (0.115)	0.019–0.470	<0.050
Race/ethnicity: Hispanic	−0.123 (0.325)	−0.761 – 0.514	0.704
Race/ethnicity: Non-HS White	0.280 (0.231)	−0.172 – 0.733	0.224
Race/ethnicity: Non-HS Asian	−0.309 (0.274)	−0.847 – 0.229	0.260
Race/ethnicity: Non-HS Black	−0.211 (0.473)	−1.139 – 0.717	0.656
Race/ethnicity: Non-HS Other	0.000[b]		
Practice Type: Solo/group practice	0.148 (0.208)	−0.260 – 0.556	0.477
Practice Type: Clinics/ Urgent care centers	−0.309 (0.248)	−0.795 – 0.177	0.212
Practice Type: Non-federal gov't. clinics	−0.336 (0.305)	−0.935 – 0.263	0.271
Practice Type: Federal gov't. clinics	−0.023 (0.328)	−0.666 – 0.619	0.943
Practice Type: HMOs	0.241 (0.337)	−0.419 – 0.902	0.473
Practice Type: Comm. health centers	0.400 (0.287)	−0.164 – 0.963	0.164
Practice Type: Other	0.000[b]		
HCP Group: PCPs	0.331 (0.160)	−0.018 – 0.644	0.038
HCP Group: SPs	1.231 (0.185)	0.868–1.594	<0.001
HCP Group: PAs	0.011 (0.165)	−0.312 – 0.334	0.947
HCP Group: NPs	0.000[b]		
Gender: Male	0.110 (0.127)	−0.360 – 0.140	0.387
Gender: Female	0.000[b]		
Age	−0.009 (0.005)	−0.018 – 0.000	0.062

[a] The outcome variable is frequency of off-label prescribing.
[b] This is the reference category.

Analysis of the open-ended question about what is an accelerated approval drug indicated slightly different emphasis across the HCP groups. PCPs (29%), PAs (28%), and NPs (26%) were significantly more likely to have responses that were coded as "effective" (e.g., shown positive outcomes and minimal risk) when describing an accelerated approval drug compared to SPs (17%, BH, $p < 0.05$). SPs were significantly more likely to have responses coded as "serious" (e.g., drug approved for a life-threatening condition) compared to PAs (26%). PAs (6%) and NPs (6%) were significantly more likely to have responses that were coded as "limited testing" (e.g., limited testing, fewer clinical trials, and trials waived) (BH, $p < 0.05$) compared to PCPs (3%) and SPs (2%). Findings from the close-ended question indicated that PAs (40%) and NPs (41%) were significantly more likely to report they did not know what an accelerated approval drug was or were not at all comfortable prescribing an accelerated approval drug (BH, $p < 0.01$) compared to either SPs (24%) and PCPs (30%). In contrast, over 70% of PCPs and SPs reported they were somewhat or very comfortable prescribing an accelerated approval drug.

Approximately, 31% of participants selected "I am not sure" when asked an open-ended question about their understanding of biosimilar. Of those who provided a response to this question, 73% of responses were coded as structure and function (e.g., drugs that are biologically similar in their makeup or action/function), 15% were coded as a clinical outcome (e.g., drugs that have similar outcomes, effects or comparable clinical outcomes), and 11% were coded as biologic (drugs that are similar to a biologic, biologic product, or to a reference product). Following the open-ended question, participants that did not check "do not know" were asked how comfortable they were prescribing biosimilar products. Findings indicated that 39% of PCPs and SPs reported they were very or moderately comfortable prescribing biosimilar products, and significantly more comfortable compared to PAs (26%) and NPs (27%), (BH, $p < 0.01$).

Discussion

This study found that HCPs were exposed to professionally-directed promotion from numerous sources and had interactions with the pharmaceutical industry across multiple venues, including sponsored conferences and dinners as well as in-person practice visits. Similarly, HCPs reported receiving patient brochures, drug samples, sales aids, or electronic visuals about the manufacturer's products as well as food/beverages. Study findings suggest these factors contribute to an increase in pharmaceutical industry influence on HCP decisions about prescription drugs. Findings indicated that physicians reported lower levels of pharmaceutical industry influence compared NPs and PAs. However, the differences between provider groups were not meaningfully different, and the findings suggest all HCPs were influenced by industry. Other studies have found that physicians believe they are not susceptible to pharmaceutical industry marketing strategies and believe their colleagues are more susceptible.[54,55] Some research also indicates physicians may be unable to distinguish between promotional information and scientific evidence.[23,55,56] Thus, findings may suggest a genuine lack of understanding of what is promotional information.

Interestingly, HCPs reported that colleagues and key experts in the field presenting at conferences were the most influential on their decisions about prescription drugs. It is worthwhile noting that depending on the specific colleague or expert presenting at a conference, the pharmaceutical industry may still be influencing HCP decisions by helping to craft the messaging delivered by these experts. Similarly, having colleagues that may be industry KOLs might also lead to unsuspected industry influence. Although findings suggest limited participation in activities that reflect potential industry KOL activities (including the relatively common activity of leading a clinical trial) overall, specialists were significantly more likely to report they participated in KOL activities and their colleagues participated in such activities compared to other HCP groups. This may suggest that the pharmaceutical industry targets specialists to serve as KOLs. Other research also finds that some specialists, such as cardiologists, are twice as likely to receive payments for professional services compared to PCPs.[6] However, given that we measured potential KOL activities in aggregate, it is possible that our findings reflect the fact that specialists are more likely targeted to lead clinical trials in their area of expertise.

The findings regarding off-label use are consistent with prior studies.[57] Although most HCPs had prescribed drugs for off-label use at some point, specialists prescribed off-label significantly more often than other HCP groups. The findings from the ordinal regression indicated that off-label prescribing was significantly negatively associated with beliefs about the importance of prescribing an FDA-approved drug for its indication, and positively associated with being a physician and an industry KOL.

Findings indicated that the majority of HCPs had some understanding of the process and outcomes of FDA approval of prescription drugs. However, few HCPs understood how FDA regulates prescription drug promotion. The survey also identified other knowledge gaps. Most PCPs and SPs reported they were comfortable prescribing an accelerated approval drug, but most could not fully describe the key characteristics of these drugs. Similarly, HCPs had some awareness of the key properties of biosimilar products but most were not comfortable prescribing them. Overall, NPs and PAs were less comfortable prescribing biosimilar products and accelerated approval drugs compared to the two physician groups. Knowledge gaps regarding accelerated approval drugs and biosimilars, as shown in this and other studies[40–42] highlight the need to educate HCPs on FDA's accelerated approval pathway, which provides earlier access to novel therapies, as well as on the various aspects of biosimilars. A key factor in gaining the acceptance of biosimilars is educating HCPs on the rigorous approval standards required of biosimilars by the FDA.

Limitations

As with all research studies, the current study has limitations. First, the screener and survey response rates were low. A nonresponse bias analysis found some differences at the 20% significance level. To address the low response, raking to national survey totals (by specialty for PCPs and SPs, and by Census Region for all four practitioner subgroups) corrected for differences observed in the nonresponse analysis for the screener. For the survey, weights were computed for each completed interview to correct for unequal selection probabilities, differential response rates, and differential coverage. The weights were used to generalize the completed interviews to a national population of PCPs, SPs, NPs, and PAs. Weights were developed for gender, age groups and the four U.S. Census Regions based on external totals from national surveys. In addition, external totals were used to develop weights for specialty and practice size for PCPs and SPs. A second issue was that two states (Vermont and Maine) have restrictions on payments to providers for market research. To ensure the sample was nationally representative, samples were drawn from Vermont and Maine, but HCPs were not offered incentives to complete the survey. The lack of incentives resulted in no completed surveys in Vermont and one completed survey in Maine. However, the raking to control totals (including Census Region) mitigated the very small bias from not having completed surveys in these two states.

Finally, as with most self-reported data, there is the potential for social desirability bias. In particular, HCPs may have underreported the influence of the pharmaceutical industry as an information source. As discussed earlier, other studies have found self-report biases about susceptibility to pharmaceutical marketing among physicians.[10,55]

Conclusions

Study findings indicate that pharmaceutical promotions directed at HCPs about prescription drugs occur in many forms and are disseminated through a variety of channels. By using a nationally representative sample of HCPs, this study provides population-level estimates for exposure and attention to prescription drug promotion and contact with industry and some evidence for their influence on prescriber decisions. The findings from this study will help to inform FDA of HCP responses to and impacts of prescription drug promotion, as well as HCP knowledge of important topics such as FDA approval, accelerated approval, and biosimilar products.

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CRediT authorship contribution statement

Simani M. Price: Writing - original draft, Formal analysis, Methodology. **Amie C. O'Donoghue:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Lou Rizzo:** Writing - original draft, Formal analysis. **Saloni Sapru:** Writing - review & editing, Visualization. **Kathryn J. Aikin:** Conceptualization, Methodology, Writing - review & editing.

Declaration of competing interest

The authors have no competing interests.

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Appendix A. Supplementary data

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