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IMPACT OF PHARMACEUTICAL MARKETING ON MEDICAL STUDENTS AND PHYSICIAN CLINICAL PRACTICES

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ABSTRACT

The pharmaceutical industry's marketing interactions with the medical field are extensive in both who they target as well as how much they are willing to spend. These interactions have a significant impact on the perceptions of those being marketed to, resulting in increased trust in the pharmaceutical industry and decreased skepticism in the industry's influence over medical decisions. The influence this marketing has over medical decisions has been recurrently shown to be associated with changes in prescribing patterns of physicians. These changes and effects mainly rest on the shoulders of patients, who are subject to increased costs of brand name medications, increased physiologic risk to new medications, as well as increased exposure to opioids amid the opioid epidemic. Policies have been enacted to limit the pharmaceutical industry's interactions with the medical field as well as increase public knowledge of their payments, but these actions have had mixed impacts on the industry's influence over physicians and require further investigation into their effectiveness.

KEYWORDS: Pharmaceutical industries, Medical Student, Residents and Physician clinical practices.

BACKGROUND

This review article discusses the relationship between the pharmaceutical industry and different personnel of the healthcare industry (medical students, residents, physicians, etc.) and how these interactions affect patients downstream. Additionally, this article will delve into the moral dilemmas surrounding these marketing tactics and different responses intended to limit these interactions and their resulting effectiveness.

Pharmaceutical interactions with the healthcare industry are wide and varied in both whom they are interacting with as well as how. Physicians have been surveyed for their perceptions on how pharmaceutical industry interactions affect their them; these surveys have shown that physicians do not believe they are able to be influenced by pharmaceutical marketing.[1] To assess the extent to which these beliefs were pervasive throughout the medical community, medical students and residents were subsequently surveyed as well and found to have similar perceptions as physicians.[2]

Concerning the different types of marketing tactics, from 2015-2017, 67% of US physicians received pharmaceutical industry payments, totaling to 2.18 billion dollars in 2018.[3] The most common payments to physicians are meals; other payments include honoraria, consulting, lectures, and educational events.[3,4] Studies have shown these payments are associated with changes in physician prescription patterns.[1] While these payments were previously behind closed doors, the 2010 Affordable Care Act initiated the Open Payments program or "Sunshine Law", which requires pharmaceutical manufacturers to report all payments over ten dollars made to individual physicians or teaching hospitals.[5] The program began in August 2013 and its information subsequently became open to the public.[5]

The purpose of this review article is to summarize the prior studies evaluating healthcare worker perceptions on their interactions with the pharmaceutical industry. Additionally, it will discuss the more recent objective data obtained from the Open Payments program and additional studies comparing prescription data and costs to patients. Through these discussions, the article will touch on the moral integrity of pharmaceutical marketing, counter arguments made against this data as well as supporting industry interactions, and an evaluation of the effectiveness of the policies taken thus far to limit and alter these marketing tactics.

Evidence in this review article was found via using search terms "pharmaceutical industry and physicians;" "pharmaceutical industry and medical students;" "pharmaceutical industry and residents;" and

"pharmaceutical payments" through public electronic databases such as PubMed, Google Scholar, and Open Access. Publications included PLoS ONE, JAMA, and BMJ. Exclusion and inclusion criteria included primary and secondary sources evaluating pharmaceutical industry interactions with medical students, residents, physicians, and payments to physicians, with opinionated and argumentative articles excluded. Research included surveys of healthcare workers, studies comparing pharmaceutical industry payments and physician prescription rates or costs to patients, and studies evaluating the effectiveness of different policies enacted.

REVIEW: Impact on Medical Students

Extensive studies and surveys have been performed to evaluate the effect of pharmaceutical interaction on medical students. Fitz et al. performed a survey at four medical schools comparing preclinical and clinical students on their knowledge of the pharmaceutical industry, levels of exposure, and opinions on the appropriateness of pharmaceutical interactions.[6] They found that as students progressed from preclinical to clinical studies, their exposure to pharmaceutical representatives increased.[6] A systematic review found similar results, with increases in both cumulative pharmaceutical industry exposures as training progressed as well as month to month exposures between pre-clinical and clinical populations.[7] Additionally, more clinical students believed that it was appropriate for medical students to accept gifts from these representatives (65%) compared to preclinical students (28%).[6,7] This pattern was also consistent for beliefs about gift acceptance by physicians, with over 50% of clinical students believing this was appropriate compared to 30% of preclinical students.[6]

Lastly, the portion of the survey evaluating knowledge of the pharmaceutical industry found no difference between preclinical and clinical students.[6] With this, Fitz et al. concluded that it was not difference in knowledge about the industry, but instead the increasing exposure of medical students to the pharmaceutical industry that correlated with improving opinions on gift acceptance by either medical students or physicians.[6] Austad et al. performed a national survey amongst medical students and residents concerning levels of exposure and appropriateness of pharmaceutical gifts and free samples.[8] They found a similar pattern of increasing interactions and exposure to incentives (i.e. meals, gifts, free samples) as students' progress through their training.[8]

This survey additionally evaluated the students and residents for their interpretation of how pharmaceutical representatives may bias the people they interact with.[8] They found that as medical students progressed through their training from first to fourth year and onto residency, the belief that these interactions cause bias significantly reduced.[8] This parallels findings from Fitz et al. and a systematic review in which exposure to pharmaceutical industry was directly correlated with appropriateness of interactions and inversely correlated with perception of bias from interactions.[6,7] Additionally, students and residents felt that gifts from representatives would affect bias others' behavior (42.2%, 51.8%) more than it would their own (33.2%, 36.3%).[8] In a systematic review of medical student perceptions, almost two-thirds of medical students believed they were immune to bias of pharmaceutical industry interactions via gifts or promotion.[7] This phenomenon of believing others are more susceptible to the bias of pharmaceutical industry interactions has been replicated in many surveys from both medical students and physicians and has been dubbed the "Illusion of Unique Invulnerability."[2]

Molina et al. corroborated the concept of "unique invulnerability" in his own national survey across the 37 medical schools in France, finding that 36.8% of surveyed medical students believed a gift from a pharmaceutical representative could influence their own behavior whereas 53.6% believed it could influence the behavior of their colleagues.[2] While evaluating appropriateness, another of Molina et al.'s findings was that of the medical students that specifically did not find receiving small gifts from pharmaceutical representatives appropriate, 76.8% of them had previously received one and 42.6% of those had been within the prior six months.[2] Additionally, 90.7% of the medical students believed that information provided by the pharmaceutical industry in their promotion of drugs was biased, but 61.6% of the students also considered this to be a "useful way of learning about new drugs."[2] This has been replicated in other studies, in which students and residents have found industry-sponsored grand rounds to be educational while also believing that the information presented was biased towards the product the industry was promoting.[8] This stark contrast in personal attitudes and subsequent actions is labeled as "cognitive dissonance" or when people "find themselves doing things that don't fit with what they know.".[9]

Why would medical students and residents actively act against their own beliefs and opinions? An important aspect of the medical field to consider is its hierarchical nature of physicians overseeing residents overseeing medical students as well as the parallels between the medical field and apprenticeships with physicians being the leading authorities. Surveyors evaluated medical students and residents about their superiors' ongoings with the pharmaceutical industry and how this has affected them.[2,8] Austad et. al found that as medical students progressed through their training, superiors were more likely to ask or even require them to attend a pharmaceutical industry-sponsored event, with 4.7% of first year medical students having experienced this compared to 17% of fourth year medical students and residents.[8] One study mentioned much higher rates, with 93% of third-year medical students having reported this experience.[7] Molina et al. also found that 37.5% of medical students "reported having 'often' or 'very often'

been asked by older practitioners or medical teaching staff to meet PRs [pharmaceutical representatives].”[2] Experiencing this establishes interactions with the pharmaceutical industry as the norm by role models within the medical field, thus possibly impacting medical student’s future actions once they reach the same level of training.[7] These hierarchical role-models “lend an implicit seal of approval” of being marketed to by the pharmaceutical industry.[10]

Impact on Residents

Like medical students, many studies have been completed on residents to evaluate their frequency of interactions with the pharmaceutical industry and perceptions. An interesting finding is that unlike medical students in which frequency of contact with the pharmaceutical industry increases as training progresses, Fickweiler et al. found that junior residents were more likely to have interactions with pharmaceutical sales representatives than senior residents.[11] Junior residents were also more likely to feel that these interactions had a valuable teaching role than senior residents in addition to having increased exposure, comparable to the correlation found amongst medical students.[11] Likewise seeming to experience cognitive dissonance, “many residents who considered a promotion inappropriate reported having accepted it nonetheless.”[9,10] The unique invulnerability was also applicable to residents, believing that pharmaceutical industry interactions would bias other physicians’ prescribing practices more than it would bias their own, with 61% of them responding that their own practices were completely immune to the bias.[2,10]

To compare this bias over prescription knowledge, Austad et al. performed a survey of medical students and residents to evaluate their frequency of pharmaceutical representative contact, use of promotional information, and evidence-based prescribing choices.[12] They found 20% of residents used pharmaceutical sales representatives for promotional drug information as compared to 7.9% of first-year medical students.[12]

When comparing prescription practices with questions that provided both evidence- based and marketed-drug answers for different medical conditions, significantly more residents chose marketed-drug answers for the medical conditions of hypertension and diabetes as compared to medical students.[12] For both medical students and residents, increased frequency of pharmaceutical industry contact (as calculated via an “industry relations index”) was associated with lower odds of choosing an evidence-based medication, with a stronger effect for residents.[12] These results established an association between increased industry contact (i.e. promotional drug information) and changes in prescription behavior away from evidence-based patterns.[12]

Impact on Physicians

Beginning with exposure as a medical student and continuing with prescribing practice bias in residency, the effects on physicians have been evaluated as well, concerning both their perceptions and objective prescribing patterns. Like medical students and residents, physicians consider themselves immune to pharmaceutical industry influence and their colleagues more susceptible.[11] Exposure to pharmaceutical representatives via acceptance of drug samples was associated with more positive views of the industry and a strong correlation was found between amount of gifts received and belief that pharmaceutical representative interactions do not bias physician prescribing patterns.[11]

One study evaluated physicians ability to distinguish accurate and inaccurate information about promoted medications during sponsored lectures, during which a majority of physicians failed to do so.[11] This suggests that physicians are often not aware of the extent to which their perceptions and knowledge is affected by their interactions with the pharmaceutical industry.[10]

Lieb et al. further evaluated physician perceptions on their ability to be influenced by pharmaceutical sales representatives via a national survey in Germany and compared this against their prescribing practices.[13] They found that 45% of physicians believed that they could rarely or never be influenced by pharmaceutical representatives.[13]

Additionally, 43.3% of physicians felt they frequently or always received adequate and accurate information from representatives; of these physicians that believed this, 46% admitted that their prescribing practices were occasionally or frequently biased.[13] Upon evaluation of their prescribing practices, the physicians that believed they received accurate information from representatives had higher prescribing costs on off-patent branded medications per patient and lower rates of generic medication prescription.[13] These results show the association between trust in accuracy of pharmaceutical information and increased brand-name prescription patterns.

Several studies have evaluated the effect of pharmaceutical industry payments to physicians and prescription habits. DeJong et al. compared payments via the Open Payments program and prescriptions via Medicare Part D information for four different drug classes (statins, cardioselective beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and selective serotonin and serotonin- norepinephrine reuptake inhibitors).[14] They specifically looked for payments promoting brand-name medications and respective subsequent prescription rates.[14] Results showed that the most common payment (95% of all payments) was in the form of a sponsored meal with a mean value of less than twenty dollars.[14] Physicians that received payments for the promoted medication had higher average prescription volume for

the promoted medication in each of the four drug classes.[14] Additionally, as the amount of payments for the promoted medication increased, so did the prescription of that brand name medication for each of the four drug classes, implying a dose- dependent relationship.[14] Despite the relatively small payments, this study shows even these have a significant association with differing prescription rates.

Fleischman et al. used these databases to evaluate payments to physicians for two drug classes (oral anticoagulants and non-insulin diabetes drugs) and their prescription patterns in the physician's respective hospital referral regions.[5] They found that the number of payments to physicians was associated with increased prescription of the promoted medications within the two drug classes in respective hospital referral regions.[5] For one payment of 13 dollars, there was an associated increase of 94 days of promoted oral anticoagulant prescriptions filled and 107 days of non-insulin diabetes drug prescriptions filled.[5] Again, in spite of the payment being low, each payment is associated with over three months of additional prescription filled. Yeh et al. evaluated all payments to Massachusetts physicians and their prescription patterns for one drug class (statins).4 They also found that the most frequent payment was in the form of sponsored meals (71.1%), with other significant payments being grants and educational training.[4] For every 1000 dollars of payments to physicians, there was a 0.1% increase in brand-name drug prescription for this drug class.[4] Of note, these payments were for all sponsored medications and were not restricted to the specific sponsored medication like DeJong et al., which is believed to have diluted the results.[4,14] Additionally, educational training payments were associated with a 4.8% increase in brand-name prescribing in this drug class.[4] These results show that in addition to an association between prescription patterns and small payments (i.e. 13 dollars), there is also an association with large payments (i.e. 1000 dollars).[4,14] Perlis et al. evaluated payments to physicians across various specialties and subsequent prescription costs to patients.15 They found that there were "clear linear dose-response relationships" between the two variables, with increasing payments associated with increasing cost per patient.[15] These relationships were consistent across all specialties except one.[15] The cost for the patient comes in the form of being prescribed more expensive and branded medications.[15] Overall, these results suggest that increased interactions with the pharmaceutical industry via payments results in increased prescription of more expensive and branded medications, resulting in increasing cost to patients.

These results are similar to those by Watkins et al. as found by a national survey performed in the United Kingdom comparing general practitioner interactions with the pharmaceutical industry and prescription costs.[16] They found that general practitioners that were considered to be "high cost prescribing" were more likely to see pharmaceutical sales representatives more often.[16] They also found that more general practitioners that were considered to be "low cost prescribing" never or rarely read promotional information from pharmaceutical companies.[16]

This supports the relationship of increased prescription costs associated with increased pharmaceutical industry interaction.[16]

Systematic reviews on the topic of physician interactions with the pharmaceutical industry have confirmed the prevalence of the above results. Mitchell et al. evaluated 36 studies, of which 30 found positive associations between pharmaceutical industry payments to physicians and prescription patterns; the remaining six studies have mixed positive and null results for their associations, with no reported inverse results.[3] These studies additionally showed the association between increased prescription of promoted drugs and increased contact with the pharmaceutical industry.[3] Brax et al. expands on this in their systematic review and meta-analysis, in which a single visit from a drug representative had a significant effect on a general practitioner's prescription practice via increased prescription of the promoted drug; this effect increased after a second visit from the representative.[1]

Another aspect of pharmaceutical industry interaction that must be addressed is the allotment of free samples to physicians and its effects on prescription patterns. Hurley et al. addresses this by evaluating dermatologist prescription patterns nationwide against a control academic medical center (AMC) that does not receive free samples.[17]

Dermatology was chosen as the specialty given their high rates of prescribing medications with free samples compared to other specialties, especially for the medical conditions of acne and rosacea.[17] They found that in 2005, of Dermatologists' most commonly prescribed five medications, four of the medications were the most commonly prescribed medications with free sample; in 2010, there was an overlap of three medications, all of which were different from 2005.[17] Additionally, of the top fifteen most prescribed medications nationally by dermatologists for acne, there was an overlap of twelve medications with the most sampled medications.[17] This implies there is a preference for medications with free samples when they are available.[17]

In comparison, the top ten medications prescribed by dermatologists at the AMC had only one medication overlap with dermatologists nationwide who have access to free samples.[17] At the AMC, 83% of dermatology prescriptions for acne or rosacea were generic medications whereas nationally, 79% of prescriptions for the same conditions are brand-name.[17] When comparing the cost of these medications, the mean estimated cost for each patient visit was $465 nationally and $200 at the

academic medical center; it is estimated that an average of $60 can be saved per prescription if a brand name dermatologic medication is switched to generic.[17] Using this AMC as a control due to lack of free samples, there is a significant contrast in most commonly prescribed medications with national practices paralleling available free samples.[17] Additionally, the rates of prescribed branded medications and subsequent patient costs reflect the consequences of these differences.

The relationship between presence of free samples and prescription patterns have been evaluated in prior studies. Clinicians who did not have access to free samples for hypertension medication were more likely to prescribe a first line hypertension medication; those with access to samples for hypertension medication were less likely to prescribe the first-line hypertension medication of a thiazide diuretic.[1] When considering the specific medication of temazepam, clinicians who had received a sample of the medication were more likely to have prescribed it than those who had not received the sample, as well as were more likely to continue prescribing it compared to alternatives.[1] These results imply an immediate effect of preference for prescribing the free samples as well as long-term effects of continuing to prescribe that same medication.

Counterarguments

Limitations mentioned for a number of studies is the inability to prove causality between pharmaceutical payments to physicians and their subsequent prescription habits. Many mention the possibility of reverse causality: that the pharmaceutical industry targets physicians who are already high prescribers of the drug because they want them to continue their high prescription rates.[3,4,18] Mitchell et al. addresses this in their systematic review, referencing three studies that evaluated pharmaceutical payments and subsequent prescriptions via time-series analysis, each finding increases in prescription practices after payment.[3] Additionally, they refer to 25 studies that evaluated changes in prescription rates/costs compared to changes in physician payment values, all of which had significant results supporting a dose-response relationship.[3] These studies evaluated several different medication classes and medical specialties, emphasizing the broad scope of these effects.[3] While these do not disprove this counterargument, they do strengthen the argument that there is most likely a causal relationship with pharmaceutical industry payments prompting increased prescription rates.

An additional claim that should be considered is one made by physicians themselves in response to their interactions with the pharmaceutical industry, specifically in reference to free samples. This argument claims that these free samples and use of promoted medications is beneficial to the patients, as it improves medication access to patients who would otherwise not be able to afford it for their own benefit.[19] Cutrona et al. extensively evaluates this counterargument in two studies concerning adult and pediatric patient populations.[19,20] Both studies analyzed national patient demographic information to evaluate for household income, insurance status, and free sample receipt.[19,20] The adult patient population study found that low-income patients (family income of less than 200% of the poverty line) whose insurance status was uninsured for part or all of the year were less likely than high-income or insured patients to receive free samples.[19] Of all free-sample recipients, 82.1% of them were insured for the entire year, whereas 17.9% had lapses in or no insurance; concerning income, "the poor were the least likely to receive free samples."[19]

When these results were compared with additional variables including number of prescription medications received and site of medical care, the result of this additional analysis found that people who were uninsured were more likely to receive free samples as compared to those who were insured.[19] These added variables were considered to be measures of access to health care, as those who are uninsured were less likely to report having received any medication prescriptions at all or have a usual site for medical care.[19] Cutrona et al. concluded that the initial results of high-income, insured patients being more likely to receive free samples was confounded by an overarching problem within healthcare: access.[19] However, free samples were not an effective solution to this problem and did not bridge the healthcare access disparity as physicians claimed.[19] The patients did not have the access to healthcare to reap the benefits of the free samples, thus "selectively direct[ing] free samples to the affluent."[19]

Cutrona et al.'s study in the pediatric population found similar results.[20] Children with family income under 200% of the poverty level or uninsured for part or all of the year were less likely to receive free samples compared to children with family incomes over 400% of the poverty level or continuously insured.[20] Access to health care was a confounding variable for children as well, as children who had more medications prescribed to them and had visited medical providers more often were more likely to receive a free sample; "greater use of health care services was associated with greater odds of sample receipt."[20] Pediatric free samples, similar to adult free samples, fail to overcome the overarching failures of access to healthcare.[20]

Moral Dilemmas

As mentioned in prior studies, physician's prescribing habits and patterns have been shown to consistently be affected and altered by the extent of pharmaceutical industry contact and marketing in the form of payments and free samples. These results imply that physician prescribing habits are not independent of the influence of the pharmaceutical industry, inconsistently follow evidence-based guidelines, and are not solely for the benefit of the patient.[1,2,3,21] In fact, these influenced decisions may come at the cost of patients, both within

the monetary cost of the medications themselves by prescribing branded medications over generics and the physiologic effect of these medications if other safer and more effective medications exist.[3,4]

Mitchell et al. explored the association between pharmaceutical industry payments in 2013 and prescription of medications filled for treatment of chronic myeloid leukemia (CML), a blood cancer, in 2014.[22] For the three medications they evaluated for this diagnosis, payments in 2013 for two of the medications (dasatinib and nilotinib) were associated with increased prescriptions filled in 2014, whereas payments for the last medication imatinib was associated with a decrease in prescriptions in 2014.[22] They explain that the same pharmaceutical company that owned the patent for nilotinib also owned the patent for imatinib; however, the patent for branded imatinib was going to expire in 2015 and be replaced by a generic, so the company was most likely promoting their new medication of nilotinib and de-promoting imatinib, as they were no longer going to be able to reap the benefits of the branded version in the future.[22] These results support the theory that pharmaceutical company payments influence physician prescribing patterns. They also add to this theory that this influence can either be promotion to increase prescription but also de-promotion of medications.[22]

When considering how pharmaceutical industry influence over medications specifically affects patients, Cole et al. examined these same three medications for the treatment of CML and the incidence of hospitalizations and emergency room visits during their use as well as overall costs to compare their safety and costs for patients.[23] They found that the risk of hospitalization or emergency room visit was higher for dasatinib in comparison to imatinib within the first year of use and cumulative use; the results for nilotinib were also higher than imatinib, but not statistically significant.[23] Cole et al. states that nilotinib's incidence of hospitalizations and ER visits increased later in the evaluation period and approached that of dasatinib, suggesting the need to evaluate the safety events for long-term periods.[23] Concerning cost, patients who used dasatinib or nilotinib had higher all-cause health care expenditures, approximating almost twenty thousand dollars more in the first year of use in comparison to those who used imatinib.[23] These results support the relative safety of imatinib to its counterpart of dasatinib (with more research needed for nilotinib) and relative reduced cost of imatinib compared to either counterpart.[23] The pharmaceutical industry's ability to influence physician's prescription patterns for these medications puts patients at increased risk of hospitalization and emergency room visits as well as almost twenty thousand dollars more monetary cost.[23]

Another drug class with significant patient effects that should be considered is opioids. The rise in opioid-related deaths has been a developing epidemic within the United States, with 40% of these deaths associated with prescription opioids.[18] Additionally, the role of prescription opioids has been found to be significant, as they are often the first opioid encountered in those who develop opiate-use disorders.[18] 1 in 12 physicians and 1 in 5 family medicine physicians received opioid marketing in the United States from 2013 to 2015.[24] Hadland et al. explored how this marketing in the form of pharmaceutical industry payments to physicians may influence prescription rates by applying a time lag between payments and prescription rates.[18] They found that nationally, the pharmaceutical industry provided over 9 million dollars of non-research opioid-related payments to physicians in 2014.[18] For each meal payment to a physician in 2014, there was an associated increase in opioid prescription claims in 2015.[18] When comparing physicians who did and did not receive payments, receiving opioid-related payments in 2014 was associated with 9.3% more opioid prescription claims in 2015 compared to physicians who did not receive opioid-related payments.[18] Given the integral contribution of prescription opioids to opioid-use disorders and opioid-related deaths, the association between increased opioid prescriptions and pharmaceutical industry payment is harrowing and does not reflect well on the industry.

Hadland et al. also evaluated the relationship between pharmaceutical industry payments to physicians and county-level opioid-related mortality, including a time lag between payments and deaths.[24] They found that mortality from opioid-related overdose increased in relation to an increase in three separate variables: marketing dollars per physician, number of payments per physician, and number of physicians receiving the marketing.[24] The number of payments per physician was shown to have the greatest effect associated with mortality from opioid-related overdose.[24] These results show a direct association between the pharmaceutical industry payments and opioid-related mortality and calls into question the intentions of the industry and the extent of their involvement in the opioid epidemic. The industry's continued marketing of opioids may counter other changes enacted to decrease opioid prescription and their subsequent morbid consequences.[24]

Continuing the theme of direct medication harms to patients, Cutrona et al. touches on the possible safety risk that pediatric free samples have, as they do not have child-proof packaging, information on pediatric dosing, instructions to keep the medication out of the reach of children, or instructions on what to do in case of accidental child overdose.[20] Additionally, one of the top fifteen most distributed pediatric free samples, Elidel (pimecrolimus), was found to have been distributed to over 38,000 children under the age of two despite having a black box warning that states that the medication should not be used for children under two years of age.[20] Pediatric free samples pose a risk to pediatric patients via physical packaging safety risks as well the

medication's indications given its physiologic effects.[20]

Policies and their Effectiveness

Addressing the effects of the pharmaceutical industry on the healthcare industry has been multifold given the extensive ways that the industry has integrated its influence. For medical students, addressing this includes increased education on pharmaceutical industry interactions and policies restricting such interactions. Per the systematic review by Austad et al., most medical students did not feel they had received adequate education on this topic with 11% of preclinical students feeling they had received adequate instruction.[7] In a separate survey, only 21.6% of fourth-year students and 27.6% of residents felt "very prepared" to perceive possible conflicts of interest with the pharmaceutical industry.[8] Another survey found that 76% of the 5992 students surveyed had never received education on the pharmaceutical industry's relationship with physicians and their marketing strategies.[2] This is corroborated by Sierles et al., who found that 82.9% of the 803 students had not been educated on this topic and 77.9% believed they should be.[21] The effectiveness of education has had mixed results; two schools that had a two-hour optional class on the topic did not find that this intervention had a significant effect on student behaviors with the industry, whereas a separate study found that students who had received education had altered perceptions of the industry, believing interactions were less appropriate and were more skeptical of them.[2,21]

Policies restricting medical student interaction with the pharmaceutical industry have been evaluated for their efficacy. Sierles et al. performed a survey of eight medical schools, of which two of the schools had affiliated hospitals with policies restricting pharmaceutical interactions.[21] The students at these two medical schools had significantly lower exposure and higher skeptical perceptions of industry interactions.[21] Yeh et al. evaluated medical students nationally on their interactions with the pharmaceutical industry and compared this against the measure of how restrictive their respective medical school's policies concerning these interactions were.[25] They found that students who went to medical schools with more restrictive policies were 50-70% less likely to interact with marketing representatives and less likely to have received a gift from a marketing representative.[25] However, these results were confounded by the school's NIH funding level; when this was controlled for, the association between strict policies and frequency of student interactions was no longer significant.[25] They suggest that schools with more NIH funding may have more experience with enacting these policies and that this enactment requires a significant amount of resources.[25] The results of this study suggest that these policies may not be the sole association with altered medical student interactions with the pharmaceutical industry and that further studies into this subject are warranted.

These policies and their effects on medical students have been evaluated long-term as well. International studies on graduates of medical schools with strict restricting policies have found that after graduation, they have fewer interactions with the pharmaceutical industry, accept fewer marketing gifts, and have more skeptical perceptions.[2] King et al. evaluated physician prescribing habits for three psychiatric drug classes compared with prior exposure to pharmaceutical industry conflict of interest policies in their respective medical schools.[26] They found that physicians who attended medical school at the time of a gift restriction policy were less likely to prescribe newly marketed medications in two of the three drug classes compared to physicians that had not been exposed to the policy.[26] Physicians were compared to other physicians who attended the same medical school before and after enactment of gift restriction and found that those who attended after enactment of the restrictive policy were less likely to prescribe the marketed medication lisdexamfetamine.[26] Additionally, physicians that would have been exposed to the restrictive policy for longer duration in medical school had lower odds of prescribing the marketed medication lisdexamfetamine.[26] These results imply that restrictive policies, while not confirmed to be associated with altered medical student interactions with the pharmaceutical industry, do have long-term associations with differing physician prescribing habits as well as a possible dose-dependent relationship.[26]

Furthermore, the influence of physicians and their prescription patterns has been addressed via the implementation of hospital restrictive policies. Larkin et al. compared prescription data at several academic centers prior to and after enacting restrictive pharmaceutical representative visits as well as against centers that did not have any policies.[27] They found that during the pre-intervention period, the intervention and control groups between-group difference was not significant and close to 0.27 After the intervention of restrictive policies was initiated, these trends diverged and there was an average of 1.67% decrease in prescription of marketed drugs and 0.84% increase in prescription of not-marketed drugs in the intervention group.[27] These changes were observed in 6 of 8 different drug classes.[27] Of the 11 academic medical centers with this intervention, 8 had significant results; of the 8 control centers, there were nonsignificant results at 7.27 These results support the theory that policies restricting pharmaceutical representative interactions with physicians are associated with decreased prescription of the medications those representatives are marketing, therefore decreasing their influence. Other studies have corroborated these results, with restrictive policies increasing prescriptions for generic, non-marketed, and evidence based prescriptions.[15] It is important to note that physicians being exposed to hospital-wide restrictive policies affects medical students and residents as well, given the hierarchical nature of the medical field and repeated reports from students being

asked by superiors to attend pharmaceutical industry promoted events.[2,7,10]

In order to address the possible conflict of interest of pharmaceutical payments to physicians, the Open Payments policy was passed in 2010 in the hopes that exposure of the payments would limit the conflict.[5] Guo et al. examines the effectiveness of the Open Payments policy by comparing changes in payments to physicians before and after the policy's enactment as well as against control states that had already passed payment disclosure policies (Massachusetts, Vermont, and Minnesota).[28] They found that the payment disclosure policy had an insignificant effect on overall monthly payments from pharmaceutical companies to physicians.[28] However, for specific physician-drug pairs, the average payment for expensive drugs increased by 8.94% and decreased by 0.66% for less-expensive drugs; for physicians that were considered "heavy prescribers" of a medication, there was a larger increase in payment to them compared to "lighter prescribers."[28] When calculating disparity of payments among physicians, Guo et al. found that this increased by 4% after enacting the payment disclosure policy.[28] Despite there being no change in overall monthly payments, there were adjustments to where these monthly payments went, specifically increasing for more expensive drugs and decreasing for less-expensive drugs.[28] Additionally, the payments targeted "heavy" prescribers of marketed medications more than "light" prescribers.[28] These results suggest that pharmaceutical companies adjusted their payment targets to increase marketing of more expensive medications as well as targeting physicians that already prescribe those medications more frequently.[28] This is concerning, as it also implies that the Open Payments policy does not address the conflict-of-interest concern as initially intended. Further evaluation of how this policy has affected pharmaceutical company payments to physicians is warranted in order to reflect on the effectiveness of this intervention.

CONCLUSIONS

Overall, medical student exposure to the pharmaceutical industry increases as they progress through their training.[6,8] This increased exposure is correlated with decreased perception that interactions with the industry cause bias and increased belief that interactions via gifts and promotion are appropriate despite no proof of improved knowledge of how the pharmaceutical industry functions.[6] Additionally, medical students often believe that they are less likely to be biased by these interactions than fellow students, believing themselves to be uniquely invulnerable.[2] For those that don't believe certain interactions with the industry are appropriate, many medical students find themselves performing those interactions anyway in situations of cognitive dissonance.[2,8,9] It has been suggested that this may be a result of superior physicians encouraging or even requiring medical students to participate in these interactions.[2,7,8] Residents have been shown to have similar perceptions of the pharmaceutical industry as medical students.[2,9,10] However, these two roles have significant differences in their level of responsibility. Unlike medical students, residents are able to write orders and prescribe medications to patients, allowing for any influence that pharmaceutical representatives have to directly impact patients via biasing of prescription patterns away from evidence-based choices and encouraging use of marketed-drugs instead.[12]

Physicians have very similar perceptions and downfalls as medical students and residents with increasing trust in the pharmaceutical industry associated with increased interaction and feelings of unique invulnerability.[13] The effects of these perceptions and interactions have been extensively evaluated via comparisons between payments and subsequent prescribing patterns, resulting in mounting evidence of a positive association between the two.[4,5,14,15] Additionally, studies have shown an association between both physician payments and free sample access and higher prescription costs to patients.[17]

While none of these studies can claim causation, the pervasive positive association between pharmaceutical industry payments and physician prescription patterns via time series analysis as well as dose-dependent results are highly suggestive of causation.[3] Concerning the possible benefit of free samples in the fight against healthcare inequity, lack of healthcare access unfortunately funnels free samples towards those that have insurance and restricts their ability to benefit those who most need it.[19] With free samples affecting physician prescription rates and not benefiting the patients that need it the most, their negative effects outweigh their positives.[17,19]

The main bearers of the consequences of the pharmaceutical industry's influence are the patients. In addition to the increased cost to patients, new medications that the pharmaceutical industry are marketing have unexplored long-term effects that may be more detrimental to patients than generic or previously explored medications, calling into question the moral integrity of this marketing.[22,23] Another considerable moral dilemma is the pharmaceutical industry's involvement in the opioid epidemic, as the industry contributes a significant amount of marketing payments per year for opioids with significant positive associations with increased physician opioid prescription and opioid-related mortality.[18,24]

Many policies have been passed to limit or alter pharmaceutical industry interactions with those in the medical field. The effectiveness of these policies have been minimally evaluated with varying results.[25] For medical students, increased education has had varying effects on their perceptions of the pharmaceutical industry and restricting policies for medical students have been shown to have the confounding variable of

NIH funding.[2,21,25] These policies may have positive long-term effects by instilling skepticism of the industry.[26] Policies restricting pharmaceutical industry visits for physicians have been shown to be fairly effective.[27] Concerning the Open Payments program and its effects, results show that payments may have been adjusted to target physicians who are more likely to prescribe those medications.[28] Overall, there is room for additional studies to be performed on the effectiveness of medical school policies and the Open Payments program.

Guarantor

The corresponding author is a guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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