

Direct-To-Physician Advertising and Antibiotic Utilization in Upper Respiratory Tract Infection: A Critical Analysis

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Abstract

The pharmaceutical market is one of the biggest and fastest growing industries in the world. Of the many different pharmaceutical sectors that witnessing a rapid growth, antibiotic market is by far the most rapidly growing sector, where the vast majority of the investment is directed. Despite the increase of the investment in research and development in the antibiotics division, which is mainly driven by growth of drug resistant bacteria and the emergence of competitive generic brands, morbidity and mortality continues to rise. The current study reviews the antibiotic market and the ways in which pharmaceutical companies market their products and the pros and cons of the different methods.

Keywords: Antibiotic market; Pharmacoeconomics; Pharmaceutical advertisement

Abbreviations: URTI: Upper Respiratory Tract Infection; DTC: Direct To Consumer Advertisement; DTP: Direct To Physician Advertisement; RSV: Respiratory Syncytial Virus; OPD: Outpatient Department; CSC: Cold Self-Care; GP: General Practitioners; WHO: World Health Organization; SGA&A: Selling, General and Administrative; SA&A: Selling, Advertising and Administrative Expenses; ED: Emergency Department; IT: Information Technology; R&T: Research and Technology

Introduction

Pharmaceutical market is one of the greatly flourishing industries. According to Global Industry Analysts, Inc., it is forecasted that the global market for antibiotics would reach US\$60.3 billion by the 2015. It was suggested that this would be led by intensive research in new areas of treatment, favorable regulatory environment and emergence of new drug classes [1,2]. Moreover, substantial investments are put into R&D in order to develop new types of antibiotics. The growth of the antibiotics market is greatly affected by antibiotic resistance and generic competition. Their research also states that there is a decline in antibiotics prescriptions for respiratory related infections. The growth of resistant is advantageous for pharmaceutical industries to market their more intensive products and invest on the area of research and development. However, it is extremely disadvantageous for patients as the morbidity and mortality grow drastically [3].

The pharmaceutical companies conduct extensive marketing research to finalize the target market, create unique selling proposition, and decide on the brand name, price level, marketing, promotion, and distribution strategy. However, majority of the countries have strict regulations on product testing, product licensing, promotion, pricing, and distribution [4].

The contemporary marketing of antibiotics demonstrates that antibiotics represent 58% of the total cost of medication procedures. Antihistamines, analgesics represents 24% and 10% of the remaining cost; respectively. The drug expenditure for URTI is not consistent with the guidelines and contributes to the increased cost of the illness. In many cases, the physicians prescribe antibiotics that are heavily promoted through the various channels, such as seminars, medical representatives and advertisement. At the same time, the DCT (Direct-

to-consumer) advertisement affects the patients, which request the physicians to prescribe them particular antibiotics for URTI [5,6].

Direct-to-physician advertising is the main chamber for pharmaceutical companies to distribute their knowledge and sales too. Especially given the current focus on using evidence based medicine, it comes with no surprise that all physicians value scientific data that demonstrate safety, efficacy or cost-saving of the prescribed medications. The data are valuable to them when translated into the real practice based on an on-site clinical research, especially, whenever they become part of the research. It is well known that, researchers of independently funded studies are likely to end up with a farewell and trusted view about the situation comparing to those funded by pharmaceutical companies. The later is unlikely to end up with negative recommendations [7].

Beside the best clinical guidelines, as a trend, most physicians base their preferences on the pharmacoeconomic scene. Pharmacoeconomics has become established as a valuable aid to drug reimbursement, pricing and market access decisions for new drugs in many countries. Accordingly, what has been proven to be the most cost-effective or cost-beneficial is more attractive to be prescribed. Delivering the advertisement by cost and clinical data, would bear the attraction and is likely to change the clinical practice to the required direction [8].

It is extremely difficult to approach and convince physicians by simple means such as knowledge sharing, pamphlet distribution, or medical alerts as these will not be helpful in many situations to change the current practices. On the other hand, a medical representative will be able to change the practices from one visit only. A good approach for pharmacists is to increase the awareness among physicians by auditing

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their clinical practice against the global guidelines and provide them with feedback accordingly. Furthermore, the total cost and how much could be the net-saving if malpractices are better to be combined in the study and likely to improve physicians' response. Marketing medications by evidence-based and direct-to physician approaches was found to be useful in reducing poly-pharmacy and leading to appropriate utilization of medications [9].

The Global Nature of the DTP

Information about different types of medicines is fully available via the Internet, books, radio, magazines, word of mouth etc. Spending on pharmaceutical advertising has increased significantly for the last years. Advertising is the main driver of the consumption and purchase of pharmaceuticals. Much of the world drugs are promoted to consumers as well as to prescribing physicians. Huge sums of money are spent on different types of promotion, including advertisements in broadcast media, as well as in print media, sales representatives, samples, sponsorship of different conferences and events of educational nature [10].

There are 3 major components of spending on physician-targeting advertising, DTP advertisement is made via personal visits rendered by representatives of pharmaceutical companies to physician offices (usually, referred to as "detailing" by salespeople), dispensing samples and advertising in journals [11]. It has been found that physician-targeting promotion exerts some influence on physician behaviors. A number of medical professionals think that information from drug companies is biased, but some regard this information as rather useful [12].

Sending sales representatives armed with free samples has become standard practice in marketing campaigns of pharmaceutical companies. Pharmaceutical firms say that such fifteen-minute sales pitches are purely educational. However, advocates of consumers claim the opposite. Sales representatives tend not to have medical backgrounds, so the question is how effective could they be at informing physicians, who have gone through years of scientific training [13].

There are concerns that physicians' practices of prescribing drugs are much affected by promotional efforts made by drug companies. Some stakeholders are much concerned with such practices, so that they even require to place restrictions on DTP advertising, claiming that medical professionals should practice medicine on the basis of unbiased evidence, but not on biased pharmaceutical advertisement. Not all stakeholders are positive about DTP, experts worry that obligation of a drug company's financial arrangement or gift imposes on a healthcare professional the need to prescribe the medicines by that particular pharmaceutical company [14].

According to new updates to the Code on Interactions with Healthcare Professionals 2010, which took effect January 2009, the revised Code prohibits salespeople from providing medical professionals gifts and reminder items like notepads, pens, staplers, pill boxes, clipboards, as well as restaurant meals, although allows them to provide informational presentations [15]. The literature is consistent: all those mugs and calipers, sporting events, vacations and the like, do affect healthcare professionals' behavior [1].

Due to the fact that healthcare providers serve as decision-makers on behalf of patients (consumers) and those who pay (insurers and patients), this marketing effort has historically been always directed at healthcare professionals, via person-to-person promotions, as well as through advertising in specialized journals [16]. Of the components of

advertisement directed at healthcare professionals, it has been found that free sampling produced the biggest positive effect. Prior studies that use surveys of physician and randomized trials have showed that healthcare specialists who distribute such samples are more prone to prescribe those brand name medications. For years (until the early 1980s), prescription drug makers advertised their products only to physicians, who were expected to interpret information of medicine for their patients. As for product sponsors, they produced materials that were given to physicians to pass on to patients if they considered that this would be appropriate for particular patients. The Food and Drug Administration (FDA) oversees the promotion of drug products under the Federal Food, Drug, and Cosmetic Act [8]. This means that drug information should be balanced, truthful, and accurately conveyed. Requirements to DTP advertisements include a brief summary of the drug's contraindications, side effects, precautions, and provide "fair balance" between the risks of the medicine and its benefits [17].

Traditionally prescription drugs were marketed directly towards medical professionals; it proves that physicians maintain their authority to choose a drug. For instance, if teachers provide messages regarding nutrition or sanitation, it can positively affect family practices. Similarly, a health benefit is achieved with little direct cost to the health sector. A health advertising approach, especially when combined with analysis of Hazardous Materials Identification System (HIMIS) data and other sources, can also help to ensure more effective allocation of restricted resources (including financial, human, and pharmaceutical) between primary, secondary and tertiary services. Physicians believe that patients understand that they need to consult a health care expert about treatment appropriate to them. Only a doctor remains a person who possesses full responsibility of deciding whether a drug is right for their patients. However, if the physicians' opinion is affected greatly by such promotional activities, then the patients' health is at great risk and danger [18].

Investment on and impact of DTP

Several Reports showed that DTP advertising in professional journals and selling face-to-face accounted for \$2.7 billion in the first six months of the year 2000. According to a recent study of drug advertising and its effects on revenue received, promotion directed to physicians tends to boost sales of the brand. It has also been found out, that DTP promotions have larger and long-lasting effect on prescription choice than DTC [19].

For instance, pharmaceutical companies in the United States spent \$ 29.6 billion in research and development, whereas \$ 27.7 billion spent on promotional activities. Furthermore, it has been stated that 30% of the promotional activities have not been accounted in this figure, as there have been several unmonitored activities. It is believed that, 10% comes from the undisclosed activities by physicians and 20% comes from the non-surveyed promotions or physicians and unmonitored journals. Accordingly, the predicted real sums of money spent for the promotional activities may reach up to \$ 57 billion. The most critical issue is that 80% of these budgets have been spent on physicians directly by medical representatives. Knowing that, there are 700,000 practicing physicians in the United States in 2006. The pharmaceutical industry spent about \$61,000 per physician for their promotional activities. Therefore, there is a clear evidence that these huge promotional activities have impacted negatively on medication prescription and attitude and have surely impacted positively on the return-on-investment for these companies [13].

It has been found, that direct-to-physician (DTP) advertisement

is closely associated with the volume of prescription: every \$1 million spent on promotion directed at healthcare professionals is connected with an additional 4,100 prescriptions [13]. Thus, this type of advertisement more strongly exerts influence on prescribing, if to compare, for example, with direct-to-customer (DTC) advertisement. It has been calculated, that DTP promotion significantly outweighs spending on DTC promotion. In 2005 only, 14% of total industry expenditures on pharmaceutical advertisement were devoted to such type of promotion. Total spending on advertisement (detailing, advertising in journals, meetings, educational events for doctors, online pharmaceutical advertising) grew from \$11.4 billion to \$29.9 billion from 1996 to 2005. While, the percentage of sales spent on advertising for the industry as a whole increased from 14.2% in 1996 to 18.2% in 2005, some findings suggested that investments in detailing and journals have fallen as a share of the total. DTP advertisement is, therefore, the prevalent strategy in marketing, but there are some medicines in a majority of the top-selling classes that are promoted by such advertising [19].

Supporter of DTP

Pharmaceutical companies, the supporters of DTP, claim that such promotion results in greater compliance, improve the quality of care received by patients and, unlike DTC, physician-targeted advertising does not confuse consumers about drugs, does not encourage inappropriate prescribing and treatment and use of medications. DTC advertisements do not communicate information about benefits and risks equally well. Besides, many doctors view information conveyed via DTC advertising as harmful as physicians believe that DTC promotion causes patients to think that the medicine works better than it really does, and many physicians feel some pressure to prescribe something when patients mentioned DTC advertisement.

As advertising is ultimately the provision of information, it can be seen that the direct advertising of pharmaceuticals to physicians can provide more comprehensive, detailed, and current information regarding new products, new uses, and the risks and benefits of specific pharmaceutical agents. The direct advertising constitutes an information-sharing relationship, and arming physicians with better information can only serve to assist them in their quest to achieve the best results for their patients [20]. Furthermore, direct-to-physician advertising is actually far more preferable to direct-to-consumer advertising in terms of ensuring that proper decisions are being made, and that malpractice potentials are being reduced or avoided through the increased knowledge and competence of the decision makers [4,16].

DTP as a source of malpractice

While concerns have been raised about direct and even indirect financial relationships between pharmaceutical companies, drug representatives and physicians, it has also been noted that physicians can depend on the information provided by drug representatives to make decisions based on the most current available information [20]. At the same time, not all or even most physicians recognize the level of influence that the information provided by pharmaceutical companies in regards to their products can have on the prescription habits of physicians, though these influences have been measured and reported in numerous studies [21]. Promoting physician awareness of pharmaceutical advertising as a means of gathering relevant information and then consciously applying this information could help them make more effective decisions and provide greater clarity and transparency in the pharmaceutical representative/physician relationship, both of which could lead to greater levels of health promotion in patients and therefore reduced incidence and accusations of malpractice.

Direct-to-physician advertising need not only be utilized in the promotion of more effective pharmaceutical use in terms of encouraging prescription use, but also when it comes to preventing misuse of prescriptions. Off-label prescribing has been a major concern in the medical community and advertising off-label uses has been strictly prohibited by law, and thus any direct-to-physician advertising would necessarily be directed towards encouraging the proper and approved use of pharmacological agents, which would necessarily discourage off-label uses and prescriptions [22]. In this manner, direct-to-physician advertising works to limit potential malpractice claims and accusations as well as truly negative events from both ends, promoting the effective and proper use of medications and defining the limits of use to ensure that medications are not prescribed for situations that they are not suited to. This relates directly to one of the most pressing ways in which direct-to-physician advertising can reduce malpractice: the presentation of research.

Pharmaceutical advertising that appears in medical journals affects malpractice potentials in two primary ways. First, the advertising itself typically contains detailed information about the specific pharmacological agents being advertised, including the results of evaluational research conducted in clinical trials and practice, providing in a concise and widely-read and -disseminated form all of the information that a physician needs to make a responsible and effective decision based on the information that is currently available [23]. Second, the pharmaceutical advertising published in medical journals is a major source of the revenue that these journals need in order to remain operational, and so in a slightly indirect manner the pharmaceutical industry and the direct-to-physician advertising engages in are responsible for maintaining adequate levels of information flowing within the medical community, which has a profound impact on health promotion and the ability of physicians to reduce malpractice potential through the adoption of best practices [13].

Cost Analysis in DTP

Cost control is an important feature of medical practice for patients and medical institutions alike, and ineffective prescription, over-prescription, or other unintentional misuses of pharmacological and inefficiencies in prescription practices can lead to overspending and reductions in the cost-effectiveness of medications. Some studies have found that direct-to-physician advertising by pharmacological companies actually lowers prescription costs for physicians, a finding which has several implications [24]. First, it can be seen that pharmacological advertising includes information that is at least tangentially related to prescription costs, to a high enough degree to affect physician thinking and decision-making in regards to the writing of prescriptions. Second, the specific findings in regards to this observed cost reductions are not especially wide-spread and could likely be made more significant and more prevalent if a more direct and conscious effort to provide cost analyses in pharmaceutical advertising was made by the pharmaceutical companies [24].

Interestingly, a study of general practice physician outcomes and trends in England found no statistically significant correlation between prescription costs and the quality of patient outcomes; that is, lower prescriptions costs were not consistently associated with a higher overall quality of care and health promotion, nor were they associated with lower qualities of care [5,13,18]. This suggests that there are a multitude of factors involved in the relationship between prescription cost and health promotion when it comes to pharmaceuticals, with direct implications on direct-to-physician advertising. If advertising

has been associated with lower prescription costs but these lower costs are not associated with higher levels of care quality, health promotion, and ultimate outcomes, though, this advertising is not as effective as it potentially could be. To make matters even more pressing, other research has demonstrated that there might actually be a negative correlation between exposure to direct-to-physician advertising and the overall quality of prescribing behaviors in some physicians [24]. Though this finding has only emerged in a very small number of studies from a rather large body of research that has examined the issue, it is enough to suggest that more direct attention needs to be paid to associating cost effectiveness with quality outcomes in direct-to-physician advertising, maximizing the potential for increasing health promotion through this method of information provision.

Well-informed physicians are capable of making better and more consistent decisions; this fact is essentially self-evident and is of paramount importance in developing and effectively utilizing direct-to-physician advertising by pharmaceutical companies. Less self-evident but equally important is the observation made in current research that well-informed physicians are more capable of controlling prescription costs in a much more consistent manner than other patient and clinical settings [25]. In a comparison of physicians to adjusted clinical groups and other group settings in medical centers, it was found that physicians achieved lower prescription costs than other settings with the same basic level of health promotion and quality of care, meaning that cost benefits can be achieved for patients and for medical institutions by both making sure that physicians remain well-informed in regards to pharmacological practices and opportunities and that they are given the necessary latitude in decision-making to take full advantage of the knowledge they obtain from various sources. Direct-to-physician advertising can be a significant and meaningful source of this information if it is properly designed and developed, providing clear and concise assessments of costs and needs that might warrant certain prescriptions at higher costs, or even suggesting alternatives that might be cheaper and still appropriate in certain situations.

The increasing prominence of direct-to-consumer advertising by pharmacological companies has implications that encourage the presenting of cost analyses in direct-to-physician, as well. Though there are both benefits and risks to direct-to-consumer advertising, one of the most consistent features of this advertising that has been noted is the lack of true need and benefit appraisal by consumers when considering pharmacological treatments [15,16]. Physicians are in a much better position to make such appraisals, but are often less directly aware of and concerned with costs than patients. Including cost analysis information in direct-to-physician advertising would help to rectify this difference in awareness and focus and lead to even more effective considerations and decisions by physicians in regards to the cost benefits of utilizing certain prescriptions.

Direct cost: The international expenditure

It is essential to us to understand the global figures of antibiotic expenditure on direct costs to be able to evaluate our situation and estimate the size of cost-saving. Furthermore, the gathered data will be shown to physicians during the DTP process to compare and contrast the situations with best practices.

Sixty percent of outpatient episodes and 48% of emergency department episodes resulted in an antibiotic prescription being filled. In outpatient settings, episodes in which secondary diagnoses of either otitis media or acute sinusitis were found accounted for less than 6% of the episodes that resulted in an antibiotic prescription being filled.

The most frequently filled antibiotic was amoxicillin, although second- and third-generation cephalosporins were the second most frequently occurring antibiotic class. Twenty-three percent and nine percent of outpatient and emergency department episodes, respectively, resulted in a prescription filled for antihistamines. In outpatient episodes, antibiotics account for 23% of the total cost of care. In emergency department visits, antibiotics account for 8% of the cost of URTIs. Antibiotics cost, on average, \$9.91 for each episode of care in outpatient office visits. An estimate of the cost of antibiotics for URTIs in a year for the Kentucky Medicaid program is \$1.62 million [26].

In 1976, in Canada, some direct costs were estimated, including physicians' fees, hospitalization, antibiotics, "cold remedies", and pharmacists' prescription fees for URTIs. It was found that the total cost ranged from \$141 million to \$211 million per year [27]. Although the incidence of URTI is very high, there is no peer reviewed articles discussed this. A small number of articles, however, have discussed the cost of some specific types of URTI separately. In 1998, the estimated cost of otitis media was roughly \$4 billion in the United State and \$600 million in Canada. In 2000, nearly 98% of RSV infection-related hospitalizations occurred in children <5 years old. There were approximately 86,000 hospitalizations, 1.7 million office visits, 402,000 emergency room visits and 236,000 hospital outpatient visits for children <5 years old that were attributable to RSV infection. The total annual direct medical costs for all RSV infection-related hospitalizations (\$US394 million) and other medical encounters (\$US258 million) for children <5 years old were estimated at \$US652 million in 2000. Thus, otitis media was a major cost driver for physician visits. RSV infection-related hospitalizations dramatically increased from 1993 to 2000, but average costs per hospitalization were relatively stable [28]. In this study, 74% of the children received an antibiotic prescription to cure their upper respiratory tract infection. According to Koda-Kimble (2009), 65% of the visiting patients with upper respiratory infection should not be given an antibiotic as viral infections contribute to the majority of the cases [29]. Accordingly, the cost of these infections could have been at least halved and distributed to other required services or medications.

In Taiwan, among the 10 diseases with the highest number of outpatient department (OPD) visits were due to upper respiratory diseases. Acute upper respiratory infections (URTIs) and acute nasopharyngitis were the two diseases with the highest number of OPD visits. Drug expenditure for acute URTIs is about 6% of total expenditure for drugs. Medications suitable for URTIs patients' self-care accounted for 42.8% of the total cost of prescribed drugs for these illnesses, and treatment medications unsuitable for patients' self-care accounted for 48.6%. Other medications used for URTIs could not be grouped into these categories. The total expenditure for acute nasopharyngitis was about 1.3% of total expenditure for drugs. Medications suitable for self-care in patients with nasopharyngitis accounted for 51.8% of the total cost of medication prescribed for this illness, and medications unsuitable for patients' self-care accounted for 36.8% [9].

In a cost-effective study, a Cold Self-Care (CSC) Center was established in a prepaid ambulatory care setting serving 21,500 subscribers and their dependents. After CSC establishment, a decrease in visits to practitioners for common colds was demonstrated. The operating cost ratio of an outpatient visit as compared to a CSC visit was 14.7/1. Savings over a two-year period are estimated at over \$46,000, representing an average estimated ratio of \$.09 cost per dollar saved per member per year [30].

Since sinusitis is a self-limiting disease in 40 to 50 percent of

patients, the expensive, newer-generation antibiotics should not be used as first-line therapy. First-line antibiotics such as amoxicillin or trimethoprim-sulfamethoxazole are as effective in the treatment of sinusitis as the more expensive antibiotics. However, the use of trimethoprim-sulfamethoxazole is now debatable. Little evidence supports the use of adjunctive treatments such as nasal corticosteroids and systemic decongestants.

Generally, most studies showed that inappropriate prescribing for upper respiratory tract infections is the norm not the exception, with significant cost and health consequences. It will become a problematic issue for us to convince physician that the norm is wrong. However, this justifies, if exists, why should also our physicians practice the same norm.

Indirect cost: The international expenditure

Indirect costs for upper respiratory drug infections were estimated by including the following potential costs to the patient: prescription charges transport costs and cost of time in travelling to and from the surgery and/or pharmacy together with the time spent at these places. Antibiotic containing prescription charges were £2.80 at the time of the study. Patient travel costs were estimated at £0.37 per journey, which was the flat rate fare for a single journey by public at the time of the study. A monetary value for patients' time was taken from the Department of Transport estimate of the value of leisure time, which was £1.53 per hour in 1987. The time taken for a return journey to the practice or pharmacy was estimated to be 40 minutes. Estimates for the time spent at the practice or pharmacy were 25 minutes and 10 minutes, respectively [31].

By having the awareness increased regarding the viral infections, the majority of these costs can be reduced, saving the patients' and healthcare providers' budget. Most of the GP clinics receive one hundred patients daily on average. Seventy percent of them would have URTI, as a rough estimation. Accordingly, the indirect costs of antibiotic prescribed for URTI is: £2.80 per prescription multiplied by 70 patients equals to £196 daily. Since URTI represents the major number of these cases, saving the indirect costs can impact hugely on the overall net costs of the healthcare provider.

Antibiotics are well known to cause harms at several degrees. At the level of URTI, the utilized antibiotics may cause gastrointestinal disturbances, headache, and colon related problems. In these cases patients come back to the treating physicians and require more medications or physicians will prescribe the required medications in combination at the first visit. The second is more common. Both scenarios contribute to the overall costs and may duplicate the net cost per visit. In some particular antibiotic, if combined with non appropriate prescription, serious neurological and haematological symptoms may occur which require admission and emergency treatment. Although it is rare, if happens will raise the cost significantly not only at the level of the general practitioner, but rather at the level of general hospitals. One of these serious events is called antibiotic-induced-colitis, which results from the excessive uses of antibiotics that in turn induce imbalance of the normal flora of the colon. Although colitis is very common nowadays, it is not known whether resulted from antibiotic use or from other environmental causes [29].

Another intangible concerning cost is the cost of resistance. Clinically, if the patient receives an antibiotic several times to treat the same bacteria or organism, resistance may develop. Having said that, the cost of next alternative is usually higher than the cost of the first

choice, which in turn would add further financial burden to the total health cost. Furthermore, cross tolerance between different groups of antibiotics may emerge, leading to a persistent resistance and loss of lives [9,32]. The indirect costs are not accounted in our study. However, it must be discussed in the DTP, as they may contribute the morbidity and mortality of our patients. Comparing to the global trend, our indirect costs should be raising and we should elaborate on them in separate studies.

Models Utilized Alongside DTP

After detailed examination of various models and practices on the practice of how to influence physician perception and attitude toward prescribing particular medications and not others, we can spot out clearly that money, cost, and personal relationships were the main contributors for the success of the pharmaceutical industries when contacting physicians.

The most utilized model is the medical representative model. One of the main reasons why should the medical representative model succeeded is the optimal employment of the DTP approach and money expenditure. They take the opportunity to discuss the hot issues with the physician in private and convince them appropriately. They are usually well prepared and equipped with the necessary medical brochures, pamphlets, gifts and clinical studies. However, legalized bribes may offset this model significantly. Unfortunately, they are the source of the malpractices either intentionally or unintentionally. Therefore, controlling the medical representative in a positive way could be influential and help to save the cost of the total expenditure [33].

Another model to stand against the growing burden of antibiotic resistance is that both scientists and economists should work together in creating new business models in order to market old and new antibiotics to the market appropriately. There are several opportunities to re-engineer the marketing process throughout the value-chain, from drug manufacturing to post-marketing stage. This allows better utilization and appropriate uses for the right patient. Moreover, there are much more issues to be discussed and considered, such as necessity of medical trials, pre-clinical and clinical testing, regulatory approvals, reimbursements, and so on. In many ways, they could be the bottlenecks of the organization and further marketing of antibiotics.

A good model was suggested by Katz and Martin (1995), states that the scientific output is interrelated on the quality and frequency of collaboration between the medical team members [34]. In case there is a positive relationships and good collaboration, there is a great chance that the work would be more productive and include more creative approaches. However, with the weak collaboration, the productivity could gradually decrease. Plus, majority of the people would tend to collaborate with the highly medical productive members than lower medical productive members.

Auditing and reporting model is widely utilized in medicine and medications worldwide, especially by pharmacists. It is one of the unique ways to deliver the message of clinical malpractices in a scientific way, aiming to change for better clinical practices. The advantage of this approach is that you can figure out the performance of the clinics by real statistics, compare it to the published data and guidelines, and then report it and discuss it with the medical practitioners in charge. This would keep very limited rooms for rejecting the malpractices, compared with the usual convincing approach. Usually, pharmacists are rejected when they report repeated drug-related problems to

physicians. Several reasons could contribute to the rejection, including the feeling of knowledge superiority, as the main factor. At the opposition, the medical representatives are able to convey the required messages easily and smoothly utilizing summaries of the latest medical news for the latest medical researchers. Of course is not only this, but other indirect enforcements are used such as financial supports and gifts. The later could be perceived as non-ethical by authoritative bodies. Learning from medical representatives, clinical pharmacists worldwide started to audit and report to convince with no financial supports or gifts successfully. This approach has been reported to be useful to reduce the net costs and health injuries resulted from the clinical malpractices [35].

An extremely important factor in this equation is to include the cost in auditing model, especially when convincing the government medical physicians. In many times, the medical consequences of using the antibiotics are overseen. Resistance and death of the useful colon bacteria are not countable and not possible to measure. Long term medical consequences, however, would be seen instead. Thus, if the medication costs are included, it could give a clear and tangible clue of the current performance. Mentioning the cost can always be helpful improve the medical practice.

The Scientific Model: The Hybrid DTP Model

In order for a model to be comprehensive, it should take into consideration all the contributing factors mentioned above, namely: cost, clinical trial, face-to-face interview and good relationships. Although gifts may affect the practices drastically, it is unethical to use gifts by all the means in clinical studies and is considered to be a malpractice. Thus, all types of gifts should not be included nor distributed and a modified medical representative model shall be implemented, which should include the establishment of good relationships with physicians, evaluation of the conduct by an official clinical trial, and then finally Direct-to-physician advertising based on the results of a study (Figure 1). The collaboration of the marketing department, physicians and pharmacists could provide the consultations for implementation of the practice changes, improvement of the performance, decrease of the over-abuse of the antibiotics and other related medications.

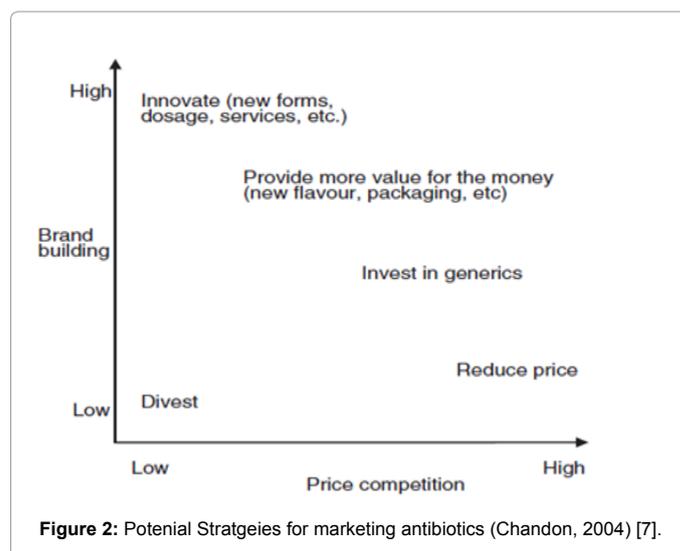
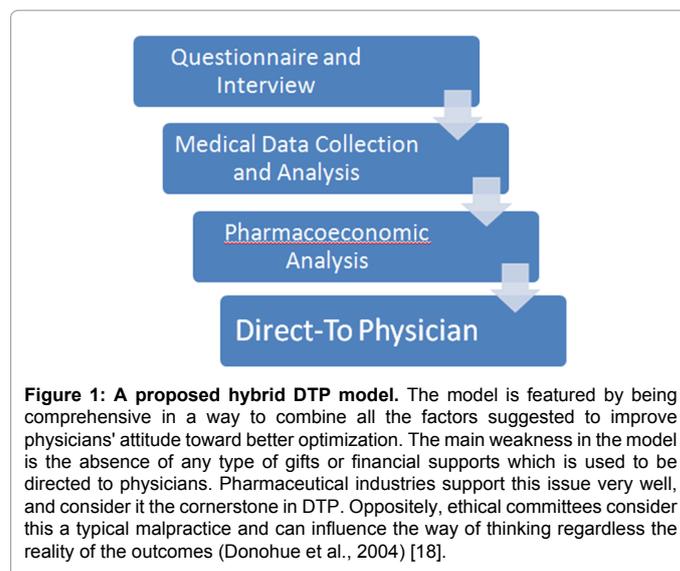
Antibiotic Marketing Overview

Marketing strategies

Exploring the available marketing strategy will help us to formulate the best DTP approach based on the best supportive researches. According to Chandon [7], there are several types of marketing antibiotics, such as making innovative design, dosage, services, adding more value, making generic brands, reducing price, and divesting (Figure 2) [7].

According to the author, making innovative antibiotics, such as new forms, attractive design, additional services, etc. are the best for building brand recognition and loyalty. At the same time, investing in generic products and reducing price would lead to the best price competition in the market. In case of URTI antibiotics, the price competition is one of the main since there are many strong competitors in global and domestic level.

Moreover, the pharmaceutical companies would use different marketing strategies, such as re-center marketing on value creation within disease states; take an integrated multi-stakeholder, multi-channel approach; incorporate value creation early in the product development cycle; accelerate reallocation of marketing resources



and align capabilities to support future market needs; and effectively measure and manage marketing return on investment [36].

Usage of the modern technologies

Currently, it is possible to purchase antibiotics online. The main advantages are: convenience, lower price, avoidance of embarrassment and being able to buy products that would not otherwise be available without prescription. The WHO, has found that medicines purchased online from illegal sites that mask their physical address were fake in about 50% of cases. A study by the European Alliance for Access to Safe Medicines reported that 62% of prescription products ordered from the internet were fake, substandard or unapproved generic medicines [37].

At this point, the consumer is less protected from purchasing counterfeit products; however, it allows the pharmaceutical companies to communicate with the potential clients with less governmental restrictions and could be one of the potential market niches for future development. On the other hand, the Internet technologies become one of the marketing tools of the pharmaceutical companies. Considering

the fact that physicians use modern internet technologies to conduct the research on the antibiotics or be constantly updated about the industry news and procedures, the pharmaceutical companies use various tools to communicate with them. Therefore, the pharmaceutical companies implement e-conferencing, online events, electronic sampling, specialized service portals for physicians, such as MdLinx or Physicians interactive [1].

Currently, pharmaceutical companies use modern web technologies (Twitter, Facebook, blogs, etc) for advertising purposes and approximately spend \$ 1 billion on DTC tools. For example, although GlaxoSmithKline's blog site and AstraZeneca's community Facebook page indicate that they are intended for US residents/customers only, non-US users have no access restrictions. Furthermore, Pfizer's mobile applications are intended for Canadian and French audiences; Novartis targets Canadian and Korean audiences; and Roche advertises to French patients [38]. This way of modern marketing may not affect the attitudes of physicians greatly comparing to DTP.

Marketing antibiotics by cost

According to TNS Media Intelligence, the total promotional spending had increased in 2009 in comparison to 2008 by 0.7 % and comprised \$3,384.5 billion (Table 1). Pfizer was the No. 1 pharma advertiser of 2009, with spend up 37% to \$1.1 billion on strong support for brands like Lipitor, Viagra, Pristiq and Chantix. That puts the company head and shoulders above No. 2 industry spender AstraZeneca, which also increased DTC spend 37% in 2009 but spent a mere \$371 million. Lilly was in third place, with spending down 11% to \$350 million, and Merck took fourth place with spending down 16% to \$345 million [2].

While analyzing the data for the period of 1975 to 2005, it becomes clear that majority of the largest pharmaceutical companies have greater expenditures on advertising and administrative expenses (SF&A) than on R&D (Figure 3). The pharmaceutical companies spent \$20.5 billion on promotional activities in 2008. There were \$12 billion spent on detailing information for physicians, nurse practitioners, and physicians' assistants. Approximately \$3.4 billion were spent on sponsoring professional meetings and events. \$0.4 billion were spent on the advertisement in the specialized journals. The rest, \$4.7 billion were spent on DOC advertisement. According to Pharmaceutical Research and Manufacturers of America, the domestic sales of pharmaceuticals and medicines totaled \$189 billion in 2008 and domestic spending on R&D totaled \$38 billion [9,13].

Promotional activities of the advertising had contributed to the cost of the antibiotics, which led to the increase of the inappropriate over-prescription of antibiotics. Moreover, the promotion had other negative aspect to the use of antibiotics for URTI. By misleading both physicians and patients, the promotional activities could also contribute

Total Promotional Spending 2008 vs. 2009 Drug Companies			
	2008	2009	%CHG
Television	\$2,147.90	\$2,105.30	-2.00%
Radio	\$9.90	\$196	49.50%
Outdoor	\$2.40	\$2.90	17.20%
Newspaper	\$80.90	\$103.60	21.90%
Magazine	\$1,057.70	\$932.20	-13.50%
Internet	\$62.90	\$220.90	71.50%
Total	\$3,361.70	\$3,384.50	0.70%

Table 1: Total Promotional spending by different drug companies (Word of DTC Marketing, 2010). The table illustrates how much pharmaceutical companies spend on promotional activities.

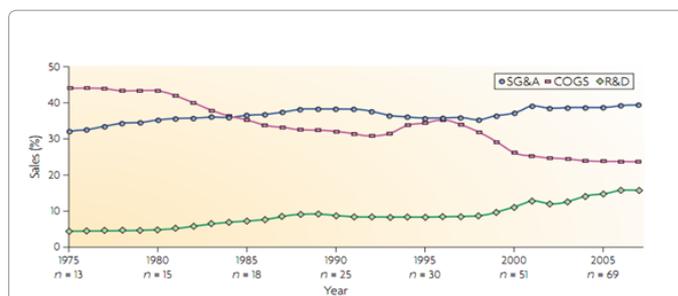


Figure 3: Trends in resource allocation (Word of DTC Marketing, 2010). The graph demonstrates the trends in expenditures for promotions trends in resource allocation to SG&A, R&D and cogs in the pharmaceutical industry: 1975–2007 (Word of Direct to Consumer Marketing, 2010).

to the increased usage of particular antibiotics [13]. Therefore, for us to conduct a simple free-of-money DTP will be much more challenging to be able to stand against this huge amount of money.

Antibiotics accounted 8% or \$7.58 of the cost of URTI in emergency department (ED) visits. However, the additional costs in ED episodes were higher than in outpatient office. The results indicate that a substantial proportion of resources in Medicaid are being used for non indicated and ineffective treatments for URTIs [39-41]. Analysis of the frequency of antibiotic prescription by facility revealed two peaks in distribution, with one group prescribing to about 90% of URTI patients and the second appearing to prescribe to about 40% of patients [3,28]. The former were represented mainly by hospitals and the latter by physician offices. This will give us a rough estimate on our situation and to prepare our DTP accordingly.

A study of 19 campaigns to reduce usage of antibiotics in cases of cold and flu, showed that use of antibiotics fell by 27% in France between 2000 and 2007 and by 36% in Belgium between 1999 and 2006. However, it was not noticeable in the USA where the public campaigns had to compete with extensive pharmaceutical advertising of \$ 4.2 billion on DTC and \$7.2 on direct promotions to doctors. Thus, it made difficult to “deliver messages and monitor outcomes [42]. This study is very promising as it supports our hypothesis, in which that physicians' opinion can be re-directed by non-financial means.

Marketing antibiotics by research collaboration

There is a great interest among researchers and scientists in the notion of research collaboration. This allows uniting diverse researchers into one group in order to contribute to the large scientific project. For example, our study is brought to evaluate the clinical situation of the clinic and investigate whether DTP is an effective approach to change the malpractices. This is especially important in collaborating universities and industries. Considering the fact that modern technologies had eliminated geographical and communication barriers, this could also lead to the international collaboration of the researchers from different parts of the world to work on a specific project and enabling cost-saving.

In general, research collaboration could take many forms, such as making partnerships with the Universities, faculty members, different researchers, or specialists in their discipline. The main idea of such partnership is shared responsibility, rights, and contribution to the project all of the members are working for. Moreover, the presence of the representatives of different areas, such as IT, biology, chemistry, marketing, and so on could provide unexpected results due to the diversity of the group members. Of course, each of the participants

should realize the responsibilities at different levels, co-authorship, and benefits regarding the research collaboration.

Philbin et al.[43], provides the conceptual model for performance measurement of the research collaboration process. According to the Model, there should be cooperation between research and technology (R&T) [43]. According to the author, the technical, business, and social activities are transformed into sustainability and knowledge sharing, which lead to the improvement of the project. Moreover, it becomes a goal-oriented measurement tool that could be used both in the management and improvement of R&T collaborations.

When taking into consideration the marketing of antibiotics, the research collaboration could be a very effective model in developing modern approaches and technologies. Such type of collaboration could be done with the Universities, individual researchers, marketers, IT specialists, sociologists, psychologists, chemists, and so on. The diversity of the project members would greatly contribute to the project outcomes.

If applying research collaboration in marketing of antibiotics, the research group could identify the target market, social interests of the target group, and possible incentives to build brand awareness of the people. At the same time, the psychologists and sociologists could provide detailed information about people, their possible interests, and ways to attract them. The chemists group could provide consultations about the peculiarities of the antibiotics and their usage. Lastly, the IT specialists working with other specialists could develop attractive and user-friendly Internet based applications.

For instance, the majority of people know about harmful effects of antibiotics and try to avoid them unless necessary; however, there are some individuals who request antibiotics from their physician right after the first appearance of cold or flu symptoms. Despite the fact that they could be healed without antibiotics, they consume antibiotics since they believe that they would recover quicker.

Summary

Antibiotics have been marketed by several strategies directed to physician and customer. This has led a huge expenditure in the promotional activities of the pharmaceutical companies, which in turns necessitate the importance to target and cover a particular market. The evaluation of costs involved varies significantly from one country to another and it depends on many factors. The research collaboration could be used for developing new product or renewing the existing product, with the increased importance of interdisciplinary fields, the collaborative research could integrate with the real life to produce the best required benefits.

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