« HEALTH TECHNOLOGY ASSESSMENT – A REVIEW OF PHYSICIAN PRESCRIBING MODELS AND THE FACTORS INFLUENCING DECISION MAKING »

by

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Title: Health Technology Assessment - A review of Physician prescribing model and the factors influencing decision making.

Abstract/Synopsis

In most industrialised countries, drug expenditure as a percentage of the overall healthcare cost is increasing rapidly. Changing demographics—ageing population with increased morbidity—and a rise in the number of drugs per patient contribute obviously to growing prescription costs. However, the key factor in rising drug expenditure is the greater variety and availability of new, expensive drugs and the higher relative cost of pharmaceuticals. The use of new drugs might explain up to 40 per cent of annual increases in expenditure in Canada, while displacement of old drugs with new drugs at higher costs accounts for over 60 per cent of the rise in the UK (Tamblyn et al. 2003; Walley, Mrazek, and Mossialos, 2005).

Pharmaceuticals are a research and development (R&D)-intensive industrial sector. Innovation and the successful diffusion of new drugs are critical for the financial performance of pharmaceutical companies—as well as the health of patients. In the UK, the pharmaceutical industry R&D represented 36 per cent of sales in 2009, a level approached by only a small number of defence contractors (ONS 2009). Governments are also major influences, both through regulatory and approval agencies—such as the Food and Drug Administration (FDA) in the US and the National Institute for Clinical Excellence (NICE) in the UK—and through budgetary allocations. The diffusion of innovation is thus determined by the strategies of pharmaceutical companies, by government policies, and by the behaviour of medical professionals. This article concentrates on the last, through a detailed review of the literature on doctors' prescribing patterns. Doctors have to strike a balance between using new drugs—and potentially exposing patients to side effects—and delaying the use of new drugs—and depriving

patients of their possible benefits (Jones, Greenfield, and Bradley 2001). The ensuing diffusion process is a complex interaction that reflects attributes of the new drugs as well as characteristics of the potential prescribers and patients.

A variety of factors have been found to influence the prescription of new prescription medicines. These factors are classified into micro-, meso- and macro-level characteristics (Lublóy et al., 2014). Micro-level characteristics include factors such as the socio-demographic and professional characteristics of medical professionals. Meso-level characteristics include the prescribing characteristics of doctors, character. Macro-level characteristics typically refer to government policies. Understanding which factors are important for the uptake of new medicines is important for the following reasons:

Firstly, it facilitates and speeds up the process of diffusion. Numerous new drugs are being researched and developed by pharmaceutical companies each year, but the launch of these product is often delayed. Accelerated adoption of new medicines enables better clinical outcomes as they typically expand therapeutics in areas of yet unmet clinical need. Hence, if budget allows, access to new drugs should be offered quickly and homogeneously to population in need. Therefore, there is a need for a strategy for diffusion of new medicines built upon key determinants of new medicine adoption by the doctors.

Secondly, it may help to promote cost efficiency. Healthcare providers worldwide have limited financial resources. Hence, by adopting new medicines that are cost efficient, the same clinical outcome can be achieved with a lower cost or an improved clinical outcome may be achieved with the same budget. Hence adoption of these cost efficient drugs should be encouraged by the policy makers to enable widest accessibility. Forecasting utilisation, which is not only important

for pharmaceutical companies, but also for healthcare professionals and policy makers in charge of healthcare budget planning.

Lastly, it will also help in the development of targeted detailing and continuing medical education. Detailing and CME aims to promote appropriate use of new drugs, through prescription of the most cost-effective available alternative. There is significant potential for the marketing efforts of pharmaceutical companies to be targeted when the prescribing of new POMs vary among doctors. Identifying and distinguishing doctors who are early or late adopters will enable efficient targeting and subsequent positioning messages, thereby optimising resources.

Diffusion of drugs amongst prescribers is often the last but most crucial step in the drug development process (Landsman et al., 2014) as patients will not be able to benefit from novel medicines if these agents do not reach them (Morris et al., 2011). The process of diffusion of new medicines amongst prescribers is complex (Atun and Sheridan, 2007) and hence understanding the processes involved in the diffusion of new medicines is important and may result in shorter lag-times for patients, i.e. less time between drug discovery and drug access (Morris et al., 2011).

From an economic and social welfare perspective, marketing of pharmaceuticals is a topic of significant importance. It is a domain with a growing amount of academic research that have yielded interesting observations on the outcomes of marketing actions by pharmaceutical companies (Manchanda and Honka, 2005). Within specific therapeutic classes, largescale surveys among physicians have been utilised to describe prescription outcomes. Additionally, the impact of various marketing instruments (such as advertising, detailing, and pricing) have been

examined repeatedly on the basis of factual data collected by specialised syndicated sources such as IMS (see, e.g., DeSarbo et al., 2002; Gönül et al., 2001; Manchanda and Chintagunta, 2004).

However, despite the plethora of research done, much less is known about the lived experience of physicians when adopting new prescription medicines as well as the factors which influences this decision making process (Kahn et al., 1997; Gönül et al., 2001). Studies done to date frequently rely on recorded data of past prescription behaviour. Although these are a valuable source of information, there are several limitations in the use of behavioural data and hence further research would benefit from additional sources of data. First, drug prescribing often takes place in a complex environment with the involvement of a host of stakeholders. Therefore, it is challenging to unravel the impact of all these stakeholders by relying solely on quantitative data alone. Second, even if we were to ignore any system externalities and focus entirely on the prescriber, there is still a challenge that the decision process is one which is partly unconscious; based on heuristics instead of a structured analysis of all relevant information, and may partly also be based on motives which are socially less desirable. These aspects of the decision making process are also not usually studied and analysed through traditional decision making models that are used in conjunction with large scale quantitative data sets. Knapp and Oeltjen (1972) added that most research done on decision making when prescribing is based on information processing, with a focus on drug attributes and outcomes. Hence, the importance of psychosocial factors may be overlooked. Such factors include doctor characteristics (Inman and Pearce, 1993), hospital consultants (Feely et al., 1999), pharmaceutical industry (Peay and Peay, 1988), and patient factors (Cockburn and Pit, 1997), may explain the variation in the prescribing habit among physicians.

There is a crucial need for further research into the conceptual framework of innovation adoption decision making. To bridge this gap, findings from this study will serve to develop a conceptual model whereby the different aspects (from existing theories, models and studies) and multiple perspective on decision making will be integrated. From an industry point of view, this model would also help to inform subsequent marketing programs for novel medicine launch.

In the following chapter, the relevant decision making and adoption of innovation theories will be discussed. In addition, the relevant literature on the factors influencing doctors' uptake of new drugs will be reviewed as well.

Decision theory

Decision theory was suggested by Daniel Albert to be a group of related constructs that either seek to describe or prescribe how a course of action is chosen by individuals or groups of people when they are faced with several alternatives and possess a variable amount of knowledge about the determinance of the outcomes of these alternatives. Decision theory can either be descriptive (how people do behave) or prescriptive (how people should behaviour) and that decisions can also be classified according to the amount of knowledge that the decision maker possess into either decisions of certainty, uncertainty or ignorance. In decisions of certainty, a single well-specified outcome is associated with each alternative course of action. For decisions of uncertainty, alternative course of actions is associated with a well-defined set of possible outcomes, each having a particular probability of happening. In decisions of ignorance, actions can lead to a range of possible outcomes, though the probability of these outcomes occurring is not known. Based on this classification of decision making, prescribing decisions are likely made under conditions of risks and hence would fall under decisions of uncertainty.

Decision makers have also been classified by researchers into either rational or emotional. Rational buyers make an evaluation of all alternatives completely so as to determine the best match between his needs as well as the respective attributes of the products available which fulfil these needs. Theoretically, rational buyers make their purchases with clear goals in mind. Emotional buyers, however, are often influenced by product attributes (or advertising) which may not have anything to do with the need-satisfying properties of the product. Some clarifications have to be made at this point. Rational buying is often regarded as intelligent buying whereby the buyer is assumed to possess the ability and intelligence to evaluate and select products that will completely satisfy his needs. In reality however, there are often a significant proportion of buyers who are rational but are inept. In addition, it should also be noted that there also occasions whereby both rational and emotional motives influence the buyer's decision. An example of this can be seen when physicians prescribe medicine. When selecting the most suitable drug for the treatment of a specific condition, a rational therapeutic approach is often adopted. However, the specific brand of that drug that is ultimately prescribed may be influenced completely by emotional criteria, although the physician's most basic motivation underlying his/her choice of drug should be regarded to be rational whereby there is an expectation for them to select the most cost effective product.

Physician Prescribing Models

Several prescriptive models of prescribing behaviour have been proposed by various researchers, while descriptive studies have been conducted by others. The physicians' ultimate selection of a drug is influenced by numerous interacting variables. Hence, whether the decision is made within the office of a general practitioner or that of a psychiatrist, it always involves a

multiplicity of components and is never simply a decision of symptom and treatment intended to eradicate the symptom.

Variables included in the prescribing process include the patient's clinical and behavioural characteristics, their needs and expectations regarding the medicines used in the treatment and the physician's attitude, expectation and training. In addition, the prescribing decision is also influenced by various organizational and contextual constraints placed upon the features of the treatment. Methods of systems research are suitable for understanding physician prescribing.

Five researchers have examined the physician prescribing decision making process and proposed explanations for it. An experimental study examining the risk-benefit assessment was done by Knapp and Oeltjen (1972) on general practitioners and internist during drug selection. Guided by Rotter's social learning theory, they proposed that the probability of the physician prescribing a drug for a particular case was a function of (1) physician expectancy that a beneficial effect on a patient's condition would occur if the drug were prescribed, (2) the amount of beneficial effect to be gained, (3) the expectancy of drug side-effects, and (4) the magnitude of these side-effects.

Selection of this paradigm was because the components of risk for cognitive decision making was specifically structured and denoted. All physician prescribing studies at that point did not consider how the physician's perception of these components influenced his choice of drugs. Instead, the physician is typically regarded solely as a sociological and/or marketing variable with no reference to decision-making constructs.

Through the use of this analytic framework, the authors observed that 'disease seriousness' and medical specialty are highly related to the perceived risks in the decision to medicate a patient in four hypothetical cases of hypertension. Hemminki (1975) reported that research and the

pressures from pharmaceutical companies are major influences on physician prescribing decision, and proposed a simplified descriptive model of the decision making process for prescribing medicines. She noted that research and pharmaceutical companies are highly dependent on each other, influencing physicians through education, scientific journals, and advertising in accordance to the physician's personal characteristics, his work as well his therapeutic opportunities. Hemminki (1975) suggested that patient demands and expectations are controversial and may be created largely by the doctors themselves.

Using regression analysis of 118 general practitioners who were employed in government service, Lilja (1976) examined the priorities of their decision-making process. Using cases of hypothetical adult diabetes and pneumonia, he noted that the utmost important factor which influence drug selection as the 'high curing effect'. In addition, the second most important factor which influenced antidiabetic drug selection was the low side effect profile. Lilja (1976) also suggested the physician's choice of drug is a habitual one, and hence the habitual process should be taken into consideration when examining how physicians adopt new drugs.

Miller (1974), drawing upon an extensive review, has also constructed a model for depicting the system for adoption of a new drug by a physician. He conceded that aspects of his model cannot be verified with research studies. The model has three major subdivisions: (1) antecedents – factors present in the situation prior to the introduction of innovation; (2) process; and (3) results. Antecedents fall into two major categories, the individual's identity and his perceptions of the situation (cultural and social influences, patients, and organizations).

Miller (1974) defined the drug adoption process as the process from which the physician first hears about a new drug to finally prescribing the drug. He proposed that the process consist of five stages: awareness, interest, evaluation, trial, and adoption. During the awareness stage, the

physicians reads or hears about the new drug but doesn't have complete information about it. The physician then actively seeks information about it during the interest stage and mentally applies the new drug to his situation during the evaluation stage so as to make a decision on whether or not to try the drug. The new drug is then prescribed on a trial basis during the trial stage to determine its value. Finally, in the adoption stage, the new drug is prescribed regularly by the physician for all new and existing patients.

The evidence for the existence of stages in the drug adoption process is derived from studies on the differential use of various sources of information. Although the evidence is not unequivocal, it appears that commercial and formal sources are most influential in the early adoption stages and the more professional and informal sources are used in what corresponds to the later stages of the adoption process. Miller (1974) believed that the model is sufficiently comprehensive to accommodate not only different drugs but other kinds of innovations.

However, Benson (1980) argued that there are two major defects in the various models which limit their usefulness. He noted that most models were based on studies which used physician responses to simulate clinical situations rather than measuring the actual physician prescribing behaviour. Benson (1980) states that such a methodology limits study findings that it is highly problematic to infer that such 'proxy' behaviour measures approximate actual clinical behaviours. Benson (1980) suggested that the second major problem with the existing physician decision making studies is that none of them have attempted examining the influence of all interactive variables simultaneously and hence interpretations which can be formulated from examining the influence of one or two variables is severely restricted.

Review of studies of Physician Prescribing Behaviour

Similar to other consumer purchasing decisions, the prescribers' decision making process for selection of medicine requires input from numerous variables. What is different from the usual consumer purchasing decision are the unique parameters in the physicians' prescribing decision and the considerable degree of responsibility associated with it. Researchers have been examining the factors which motivates physicians into selecting a specific drug and over 100 studies have been done since the late 1940s which examines how specific variables or groups of variables influences prescribing behaviour. On top of these studies, three reviews that collated the results were also written.

The first review was written and published by Worthen in 1974 whereby he examined the effects of six variables which influenced physician prescribing: patients, pharmacists, journals, advertising, sales representatives as well as peer groups. Patients were noted to only have a slight influence on their decision making. Pharmacists exerted significant influence in certain communities but it was a low incidence which did not appear to increase at an appreciable rate. An important source of information for prescribers were the journal articles and these offered the advantage of providing commercial messages and educating physicians to the latest advances in medicine in a scholarly and professional manner. Although printed advertisement ranked high in importance for informing physicians of new products, it may serve more to inform rather than convince. Sales representatives were also noted to be of high importance in updating physicians of product availability as well as other drug data such as dosage forms and schedules. Peers were regarded as a legitimizing channel who influenced prescribing habits by bestowing a form of approval on the physician's usage of certain products.

Examining the effects of peer influence on physician prescribing, a study by Coleman, Menzel and Katz (1959) used social economic techniques to determine the social structure of physician

communities in four Midwestern towns. Through personal interviews, they were able to determine the physicians within the communities who were most often contacted by their colleagues for social purposes, formal consultations or simply an ordinary discussion during the course of a normal work day. After identifying the physicians in this fashion, the researchers were then able to diagram these relationships.

A second review on physician prescribing habits was done by Miller in 1974, whereby he observed peer discussions to be important in the adoption of drugs in both small and large cities. In addition, he also reported that physicians have a tendency to use professional sources of information (colleagues in particular) when required to treat difficult conditions whereby effects of drug therapy are less clearly defined. Wealthier patient also has a higher likelihood of being prescribed newer and costlier drugs. When physicians share office, colleagues are often consulted as a source of information for new or unfamiliar drugs. The adoption of new medicines was also positively influenced by attendance at hospital staff meetings. Formularies were also found to exert a significant impact on prescribing decisions.

Miller (1974) also proposed that the adoption of new medicines was influenced by drug attributes such as social reward, therapeutic response consistency, communicability, pharmaceutical attractiveness as well as relative advantage. Factors which negatively impacted physician prescribing were risk and high cost of therapy. In terms of established drugs, factors which influenced the prescribing decision include initial and continuing cost, social reward, time savings, therapeutic response consistency, clarity of results, pharmaceutical attractiveness, length of drug name as well as the manufacturer's name and reputation.

Miller (1974) also observed that physicians who uses new drugs early in the course of treatment and whom may be better prescribers are the specialists and younger scientifically oriented

physicians who share offices and have large practices. These physicians generally also tend to possess a questioning and critical attitude towards prescribing and medical practice. Other factors which correlates with early adoption of new medicines include regular attendance at specialty meetings, receipt of numerous medical journals as well as integration into social networks. Miller (1974) suggested that physicians pass through five phases during the adoption of a drug: awareness, interest, evaluation, trial and adoption. His review concluded that sales representatives serve as an unrivalled source of influence in the initial awareness creation of the drug. Several sources which were important for responding to interest include detailers, journal articles and advertisements, colleagues as well as the Physicians' Desk Reference. During the evaluation phase, various sources of information are utilised by the physician, which includes the Physician's Desk Reference, journal advertisements, house organs, direct mail as well as samples to acquire data on dosage, frequency of administration etc.

The third literature review was published in 1975 by Hemminki, who reported that the quality of prescribing was positively influenced by education. The value of advertising to prescribing was controversial as a positive attitude towards advertising was expected to influence prescribing. Prescribing was found to be positively influenced by colleagues, though the influence from a colleague was noted to be secondary to other factors such as advertising and education. Control and regulatory measures may also exert a positive effect on prescribing. Hemminki also argued that patient and society demands on physicians for medicines may be exaggerated in the case of prescription medicines. He also felt that generalizations cannot be made from the existing studies then which examined the influence of physician characteristics on prescribing behaviour.

On top of these reviews, other articles which examined specific elements associated with physician prescribing were also published between 1975 and 1980.Through a survey of 220

physicians, Lowery et al. (1972) noted that numerous physicians knew little of the cost of antimicrobial agents. A study by Linn and Davis (1972) found that conservation attitudes were significantly more likely in to be found in physicians who had a preference for professional sources of new drug information as opposed to those who would opt for commercial sources. These physicians also have a lower likelihood of accepting medical advice from non-physicians.

In Britain, a study by Mapes and Litt (1977) utilised four criteria to evaluate proper prescribing, which includes appropriateness, economics, effectiveness as well as safety. They noted that the tendency to utilise outmoded prescriptions increases as workload increases and that safety and effectiveness considerations were not entirely independent. Christensen and Wertheimer (1979) examined the sources of information on new medicines in a health maintenance organization and reported that physicians rely on literature sources as their primary means for general information and colleagues for information on new medicines, though they noted that the colleagues were not consistently used among time periods or practice settings. A follow-up study by Hartzema and Christensen looked at 80 family practitioners in a large HMO to examine the variables which influenced prescribing volume. Most of the observed variance were explained by patient panel size and age composition. They also observed that there is a tendency for female patients to select female physicians, and that older physicians tend to have older patients as well. Hence, a physician's age may be a proxy for older panel of patients with chronic diseases.

Applied Management Sciences, in an intensive study for the Food and Drug Administration (FDA), distributed a relatively lengthy 5-page questionnaire to 15,000 physicians in the United States who represented 22 medical specialties. Response was obtained in 73% of the eligible sample of over 10,000 physicians. Significant findings from the study included the following: (1) within national journals, specialty journals received the highest readership among the physicians

(with the Journal of the American Medical Association having the greatest overall readership); (2) the Physician's Desk Reference is the most widely used and consulted source of information; (3) among the drug information materials from pharmaceutical companies, package inserts are the most commonly used; (4) among personal contacts, peer colleagues followed by consultants were most frequently used; (5) textbooks were less commonly used for drug information; (6) national journal articles, meetings and courses are the strong sources of drug information regarded to be trustworthy, current and provided best clinical guidance.

Most recent studies of physician prescribing behaviour were done by Melville (1980) and Shearer (1977). Melville (1980) hypothesized that poor quality prescribing among general practitioners may be associated with low job satisfaction. Through a survey of 124 general practitioners in England and Wales, they noted that low job satisfaction increased the likelihood of prescribing medicines that are considered inappropriate by medical consensus or are likely to cause adverse reactions. Physicians who have poor satisfaction also had a higher tendency to allow ancillary staff to write prescriptions for potentially hazardous drugs. Using a mailed questionnaire, Shearer (1977) looked at the use of drug information sources for various types of drug information. Of the sample of physicians, half practised at a tertiary university hospital while the other half practised at community hospitals. The following findings were reported by the researcher:

This researcher reported the following findings:

1. Compared to their physicians in the community, university hospital physicians tend to sought more drug information.
2. There is a significant difference in the mean reliability scores of information sources between university- and community-affiliated hospitals.

3. Physicians do discriminate between different drug information sources when seeking different types of information.
4. There do not seem to be a significant variation in physicians' use of drug information sources by disease category or duration of which the drug available in the market.
5. Use of various types of drug information differed significantly among clinical, hospital and community pharmacists.

Apparent from the results of studies on physician prescribing behaviour, various drug information sources are utilised by physicians for decision making in different stages of the medicine selection. Researchers have been intrigued by the decision making process which physicians use when selecting a medicine as well as what motivates the physician to decide on a particular drug. The works of Miller (1974) helps to provide a plausible explanation on the process physicians use to decide on a medicine.

Physicians first develop an awareness about a particular medicine through the pharmaceutical company's advertisements or journal articles. Following encounter with clinical situations warranting use of the drug or with increased frequency in reports of the drug, physicians interest is piqued. The medicine then undergoes an evaluation phase when physician decides to consider using it, during which the physician may seek third-party endorsement of the medicine and information on cost versus benefit. Miller (1974) proposed that this is likely the scenario that most physicians follow.

It is noted that different drug information sources are used at different stages of the drug selection process, each offering certain types of information. Problems associated with this process include the frequency of exposure as well as the availability and convenience of the various sources. Availability and convenience are two parameters that are highly valued by

physicians. Thus, first sources of information used are typically those located within their offices. Recognising this, pharmaceutical companies have oriented their advertising and promotional campaigns around the physician's office. Ensuring that free product information is readily available within physicians' office is hence one of the key objectives of pharmaceutical companies. This is accomplished through various means such as direct mail leaflets, journal articles as well as a team of well-trained sales representatives. Though pharmaceutical industry led information program offer the advantage of being free and convenient, a potential risk is the element of bias.

Prescribing studies conducted thus far suggest that every source of information available to physicians are active in the drug selection process. Pharmaceutical companies provide proprietary information containing an accurate description of the drug's characteristics – ingredients, dosages, frequency of administration, side-effects, contraindications, and use. Comparison information on medicines within the same category are available from third-party sources such as journals, specialists, and clinical pharmacists. Competent practitioners are knowledgeable in usage of both sources in their decision making. It is also crucial that medical schools familiarise medical students with the knowledge on various drug information sources available so that these may be used appropriately. Government and third-party insurers should also seek ways to incentivise and compensate practitioners for providing third-party drug information.

Through the last decade, various third-party information sources such as hospital drug information centres and clinical pharmacists have evolved. Problems which exist today revolves around the convenience and availability of these services to physicians. Pharmaceutical industry has been and continues to be a relatively convenient source of drug information compared to

many other sources. A concerted effort is required among the government, pharmaceutical and medical professions in order to improve convenience and availability of third-party drug information sources for the practitioners.

The same processes are involved for sound decision making, regardless of whether it is for medicines or other convenience items. Decision maker should seek out information on product specifications from manufactures while obtaining information on the usefulness and effectiveness of the product from third party sources who are knowledgeable. Government's responsibility in this process should be to ensure accuracy of the information provided rather than to favour one source while stifling others. It is imperative that professions of pharmacy and medicine educate practitioners about the various information sources with an emphasis on when these should be used. It is also important for a consolidated and concentrated effort towards increasing availability and convenience of third-part drug information sources. With accurate drug information, prescribing decisions may be improved. However, whether or not the system can be remains to be seen.

Diffusion of innovation theory

Multiple factors influence the adoption of innovations by the clinician and healthcare system. Research on the topic noted several themes which come into play, with research evidence being only one of them. Willingness to adopt new medicines for example, is influenced by the physician's sex, specialty, medical school, years since graduation, practice location and practice volume, and the relative proportion of elderly patients in the physician's practice.

One of the better known theoretical frameworks for diffusion of innovation is developed by Rogers (2010), which is useful when determining the adoption of specific innovation as well as

deciding on the components requiring additional effort in order for diffusion to happen. The framework takes into consideration aspects of the innovation, style of communication, steps in decision making as well as the social context.

Rogers (2010) proposed that there are five elements surrounding an innovation which will determine where or not adoption or diffusion of the innovation will take place: relative advantage, compatibility, complexity, trialability as well as observability.

Relative advantage is defined by Rogers (2010) as the degree to which the innovation is perceived to be better than the existing idea it seeks to displace. For medicines, research provides information on the potential benefit and cost-effectiveness of using the new drug over the existing one. However, clinicians' perception on the advantage of the medicine may be more important than the objective data. Beyond just the patient welfare, implementation of evidence-based practice is also driven by an interplay between interests of the patient, clinician and healthcare system. For example, if the balance of power within and between professional groups is altered in a 'negative' way by the proposed innovation, its implementation may not take place easily. However, if the status of clinicians adopting the innovation is elevated or if the innovation brings in more revenue for individuals or the organisation, adoption may take place more readily.

Compatibility of the innovation refers to the degree to which it is perceived as being compatible with existing values, past experiences, and the needs of the potential adopters. For a higher probability of adoption, innovations should address issues that clinicians or others perceive as a problem. For example, new procedures which allow life-threatening diseases to be detected early have a greater likelihood of being adopted. Early screening tests are compatible with medical beliefs that early detection of disease is beneficial. Hence, tests or procedures offering this capacity have a higher likelihood of being adopted. Examples of these in real life include the

rapid adoption of prostate cancer screening test and mammography screening, despite the debate about their effectiveness.

Complexity refers to the degree to which the innovation is perceived by the potential adopters as difficult to understand or use. Innovations which are simple and well defined have a higher likelihood of being adopted. An example includes a proposed change in the patients' drug regimen, which can occur rapidly as it is relatively simple. In contrast, certain preventive activities such as programs which detect and treat patients with hazardous alcohol consumption and smoking did not have a rapid adoption despite the potential health gains. This is partly due to the complexity of these activities and attempts of intervening at primary prevention can be hindered by patient resistance as well as their lack of accuracy in self-reporting risk behaviours. Clinicians may not also have the adequate expertise in consulting skills necessary to achieve change.

Trialability is defined by Rogers (2010) as the degree to which the innovation may be trialed and modified. When the potential medical intervention can be tested by the clinician on a limited basis, it allows them to explore their implementation and acceptability to patients as well as the potential outcomes. Rogers (2010) argued that the enabling a limited cost-benefit trial of the innovation would promote faith towards the validity of the evidence and that it is logistically possible to implement.

Observability is defined as the degree to which results of the innovation is visible to others. Peer discussion is stimulated by the 'visibility' of the innovation, as colleagues of the clinician adopting new procedures often request for information about it. If the application of the innovation is supported and endorsed by respected and influential clinicians, there is usually a positive impact on its adoption rates. The greater the charisma of the individual serving as role

model, the higher the likelihood of having a greater number of other professionals adopting the advocated innovation. Particularly in surgeries, adoption of new techniques often take place very quickly because of the common perception of the disadvantages when 'left behind' for not adopting new technology.

The applicability of the Diffusion of Innovation theory to the pharmaceutical industry was studied by Florentinus (2006). Of the five factors that were mentioned by Rogers (2010), he noted that relative advantage of new drugs was more important as compared to the other factors. Florentinus (2006) argued that when drugs are compared, the other four factors are likely to be very similar and hence are less relevant. For example, when observability of new drugs is assessed, it is very likely that the effects of new drugs would be observed in the same fashion as the previous drug e.g. through regular doctor's visit.

Relative advantage in the perception of primary care physicians may be comprised of various factors and that new drugs often develop their own 'fingerprint' following market authorisation. This unique fingerprint constitutes the key elements which are specific to the drug, which include the research evidence, reported side effects, costs and reimbursement pattern as well as exposure to marketing.

Various communication channels used to inform clinical practice include research publications, databases, mass media, attendance at lectures and workshops, visits from interest groups, as well as videos or audiotapes. Current research suggest that the most effective means of communication remains to be face-to-face exchange, as it provides the opportunity to tailor information to recipients and enable the advocate of change to explore and modify reasons why adoption of the innovation should occur. The effectiveness of interpersonal communication is generally increased when there is high degree of professional resemblance between the person

introducing the innovation and the recipient. Hence this may partially explain why clinical audits undertaken by medical practitioners have a greater likelihood of resulting in adoption of a new practice as compared to those done by an allied health staff. Ager et al. (2011) suggested that change agents within communication channels may be important in influencing diffusion. Rogers (2010) defined change agents as individuals who influences the innovation adopter's decision in a direction that they deem desirable. The Diffusion of innovation theory was applied by Ager et al. (2011) to evidence-based drugs, which includes new evidence-based drugs. They suggested that high quality change agents are able to influence adoption and identified two specific types of change agents i.e. opinion leaders and organisational leaders.

A social system is defined by Rogers (2010) to be a set of interrelated parties with a common goal that are involved in combined problem solving. Primary care physicians' adoption of new medicines may be influenced by a number of items in their social system. For example, Florentinus (2006) suggested that patients may influence their primary care physicians' adoption by requesting new medicines. These requests may be acknowledged and considered by the physicians due to several reasons such as the desire to maintain positive doctor-patient relationship, time constraints as well as the desire to avoid conflict. Liu and Gupta (2012), in their prediction model, similarly described patients' requests to be a key determinant in influencing physicians' adoption of new medicines.

The second item within the social system which influences the diffusion of news drugs is the marketing efforts directed at physicians i.e. physicians' interaction with the pharmaceutical industry (Florentinus, 2006). Pharmaceutical companies possess the most amount of information about new drugs since they have been studying it extensively as opposed the potential adopter who would have limited information, which fuels uncertainty. Marketing efforts by

pharmaceutical companies hence serve as a means to transfer information to doctors, often through highlighting benefits of the new drug. Targeted detailing is a specific tool which is often used by pharmaceutical companies whereby sales representatives of the company visit the primary care doctor to discuss research evidence of the new drug. The influence of marketing efforts and specifically detailing on new drug adoption is similarly described by Liu and Gupta (2012).

Florentinus (2006) suggested that prescription decisions are also influenced by interaction with local community pharmacists. Makowsky et al. (2013) noted the evolving role of pharmacists in healthcare from being supplying drug passively to becoming an active supervisor of drug prescriptions and even prescribing drugs. Hence it is argued that the enhanced that primary care doctors' prescribing is influenced by the enhanced involvement of community pharmacists, which in turn influences the adoption of new drugs. High quality pharmacotherapeutic audit meetings is a specific tool which may influence adoption. These are meetings which are between pharmacists and primary care physicians whereby first-choice prescription patterns are discussed with the goal of improving prescribing quality (Eimers et al., 2008). Florentinus (2006) suggested that information from industry may be discussed in these settings, sometimes with the presence of industry representatives. However, Eimers et al. (2008) noted that presence of industry counterparts at such meetings is currently not desirable and advised against.

Prescribing decisions are also influenced by interaction with academia, whereby medical education from academia keeps the primary care physicians abreast and updated on current medical developments. Continuous medical education is identified by Mascarenhas et al. (2007) as an important factor for physicians when adopting new drugs. Academic detailing is a specific tool by academia to influence adoption of new drugs, which is a process by which academia or

occasionally non-profit educational research centres provide pharmacists and primary care physicians with the latest research evidence (Fischer and Avorn, 2012). Academia detailing aims to improve prescribing behaviour by influencing it to be more evidence-based (Fischer and Avorn, 2012) and hence exerts a direct influence on the prescribing habits of primary care physicians (Chhina et al., 2013).

Roger's diffusion model (2010) postulates that there are five steps in the decision making process:

- The clinician acquires knowledge about the proposed innovation
- The clinician is then persuaded about the advantages of the innovation
- The clinician then engages in activities leading up to a decision of whether to accept or reject the innovation e.g. reading, attending workshops, communication with individuals with experience in the field.
- The innovation is then incorporated into the clinician's daily activities
- The clinician then seeks out reinforcement about the innovation decision i.e. discussion and comparison with peers.

Progression through the decision process occurs at a different rate for individuals and organisations, depending on whether they are an innovator, early or late adopter. Characteristic to the innovators are their tolerance for a high level of uncertainty. Florentinus (2006) investigated if adoption of new drugs were influenced by specific characteristics of primary care physicians i.e. their innovativeness. He observed that not all primary care physicians who were early adopters of a first drug adopted a second one early as well. He further suggested that there were no specific patterns in early adoption and that this process is highly drug-dependent.

Contrast to Florentinus (2006) however, Liu and Gupta (2012) described in their diffusion model of new drug adoption that there are specific adopter characteristics among physicians, such as previous prescription volume in the disease category, which exerts a direct influence on the adoption process directly. Similar findings were noted by Ager et al. (2011), who also noted that prior knowledge about a drug and the related underling theories were positively related to the adoption of that drug.

Sanson-Fisher (2004) argued that systems which have the highest likelihood of responding quickly and easily to innovations are the ones with a culture of creativity and innovation as well as a relatively flat hierarchical system, with a strong leadership team committed towards effecting change. However, healthcare systems generally have a hierarchical model, with each professional group having a separate organisational structure. In addition, the system is more often than not bureaucratic, with social norms which hinders any rapid change. Nevertheless, it is still possible for clinicians within the system to change certain aspects of their clinical activities relatively quickly, with relatively fewer restraints in terms of determining the choice of care.

Factors influencing adoption of new medicine

Several characteristics which are found to be crucial in the adoption process are identified in 35 eligible studies, which seem to predict the uptake of new medicine consistently. The key characteristics of these studies are summarised in the table below:

Author (s) and year	Sample	Method

Álvárez and Hernández 2005	32 healthcare centres, 313321 inhabitants, Spain	Multiple linear regressions
Behan et al. 2005	126991 inhabitants, 134 full-time equivalent GPs, Australia	Comparison of means (Student's t-test)
Bourke and Roper 2012	616 GPs and all their prescriptions, Ireland	Survival analysis
Coleman et al. 1966	125 GPs (prescriptions and interviews) and 103 SPs (interviews), four small cities in Illinois, US	Elementary statistics
Corrigan and Glass 2005	4216 doctors, US	Analysis of covariance (ANCOVA) model
Dybdahl et al. 2004	191 practices, 470000 inhabitants, Denmark	Pearson's correlation coefficient
Dybdahl et al. 2005	191 practices, 470000 inhabitants, Denmark	Multiple linear regressions

Dybdahl et al. 2011	68 GPs, Denmark	Univariate and multivariate linear regressions
Florentinus el al 2007	86 GPs, 13997 patients, the Netherlands	Logistic multilevel model
García et al. 2000	74 GPs and SPs (paediatrics), Spain	Univariate and multivariate linear regressions
Garjón et al. 2012	1248 doctors, Spain	Survival analysis
Glass 2003	1876 doctors, US	Comparison of means (Fischer's least significant difference method)
Glass 2004	2108 clinical trial investigators, US	Multiple linear regressions
Glass and	3646 doctors, US	Binomial logistic

Rosenthal 2004		regression
Glass and Rosenthal 2005	2287 clinical trial investigators, US	Ordinary least squares (OLS) and binomial logistic regression
Glass and Dalton 2006	484 phase IV clinical trial investigators, US	Binomial logistic regression
Greving et al. 2006	70 GPs, 9470 hypertensive patients, the Netherlands	Multilevel logistic regressions
JP Griffin and TD Griffin 1993	10 developed countries	Descriptive statistics
Groves et al. 2010	925 doctors and all their prescriptions, Canada	Correlation analysis with t-tests
Helin-Salmivaara et al. 2005	2558 doctors, 507262 prescriptions from the same therapeutic class, Finland	General linear mixed model

Huskamp et al. 2013	30369 doctors, US	Cox's proportional hazard model
Inman and Pearce 1993	3346 GPs, England	Descriptive statistics
Iyengar et al. 2011	185 doctors, US	Discrete-time hazard model
Kozyrskyj et al. 2007	12 million patients and 2000 doctors, Canada	Polytomous logistic regression
Lin et al. 2011	155 SPs (psychiatry) affiliated with 12 healthcare centres, Taiwan	Cox's proportional hazard model
Liu et al. 2011	41488 patients, 4429681 prescriptions, Taiwan	Logit model
Liu and Gupta 2012	2129 doctors, US	Discrete-time hazard model
Manchanda et al. 2008	466 doctors, Manhattan (New York City), US	Discrete-time hazard model

Mark et al. 2002	187 doctors, 752 patients, prescriptions from medical records, US	Bivariate and multivariate probit regression analysis
Mizik and Jacobson 2004	74075 doctors, US	Dynamic fixed effects distributed lag regression
Ohlsson et al. 2009	73547 doctors, 32011 patients, Sweden	Generalised estimation equations and alternating logistic
Steffensen et al. 1999	319 GPs, 193876 prescriptions, Denmark	Multiple logistic regression
Ruof et al. 2002	72 GPs, 28 SPs (neurology), Germany	Sperman's rank correlation coefficient
Tamblyn et al. 2003	1661 doctors, 669867 elderly patients, Canada	Multivariate logistic and conditional Poisson

		regressions
Van den Bulte and Lilien 2001	121 GPs, four small cities in Illinois, US	Discrete-time hazard model

From the literature, certain characteristics seem constant across different medicine types, although contradictions do exist in some cases. It is also noteworthy that certain variables may be found to be significant by some studies, others would find no evidence of predictive power for that variable. A summary of the characteristics influencing diffusion of pharmaceutical innovations is as below:

Prescriber Characteristics	Patient Characteristics
- gender - age - training location - board certification - clinical and therapeutic area - hospital affiliation - clinical trial participation - prescribing characteristics - total prescribing volume - portfolio width - prescribing volume of drugs by the same pharmaceutical company as the new drug	- age - gender - socioeconomic characteristics - income - education - health insurance - race / ethnicity - marital status - health

- prescribing volume in the therapeutic class of the new drug	
Practice Characteristics	Drug Characteristics
- solo / group - location (urban / rural) - size - number of patients - prescribing volume - number of diagnostic and therapeutic activities - composition of employee - private / public	- medical characteristics - unmet clinical need - suboptimal response to existing therapies - improvement over existing therapies - relative therapeutic / economic advantage - safety versus perceived risk - perceived efficacy - cost - marketing budget of the pharmaceutical company

Adoption of new drugs occur early in some doctors, whereas it happens later or never in others. It has been implicitly assumed that there are some doctors with a greater tendency to adopt new drugs regardless of the drug type. Several factors have been associated with early adoption behaviour, which includes the doctor's age, gender and personality as well as the practice characteristics (Coleman, Menzel, and Katz 1959; Williamson 1975b; Strickland-Hodge and

Jepson 1982; Weiss et al. 1990; Prosser and Walley 2003). It is also thought that early adopters have a significant influence on the adoption of new drugs by other doctors.

From the prescription-based literature, it does not appear that there is an existence of 'pure' early prescribers and adopters. There are no groups of doctors or patients that are adopters or users of all newly introduced drugs that were potentially relevant. One of the first quantitative study which explicitly questioned the assumption that doctors can be grouped into different adopter categories based on specific characteristics that are shared was done by Steffensen, Sörensen, and Olesen's (1999). They found that across drug groups, early adoption was not found to be consistent. Both characteristics of the doctor and drug influenced the shape and slope of the diffusion curve. Similarly, a study by Dybdahl et al. (2004) on general practitioners' adoption of new medicine found that there was a poor association between their adoption of one group of drugs with another. The early adoption of new drugs by doctors were not a personal trait that was independent of drug type. In 2006, the adoption of five new drugs by general practitioners were examined by Florentinus et al. With a sample size of close to a hundred general practitioners, they found that a huge portion of early new drug prescriptions were attributed to a small group of 'innovative' general practitioners. They noted that the early prescriptions were highly drug dependent whereby the doctors who heavily prescribed one drug were not as heavy prescribers of the other four drugs, with also a strong variation across the general practitioners. Similar conclusions were reached in a study by Kozyrskyj, Raymond and Racher (2007).

However, a study by Bourke and Roper (2012) noted contrasting findings. Examining across six drugs, they found a consistent and significant signed effects with relation to portfolio. Doctors with a wider prescription portfolio tend to be those with shorter adoption time. Doctors who had an early adoption of one of the six new drugs also shown significantly faster early adoption of

one of the other five drugs. Although the authors argued that doctors who demonstrated a track record of early adoption generally tend to be early adopters of any new drug, this was disproved by scrutinizing the sample whereby it is noted that none of the doctors had adopted all six drugs within six months of their introduction. Across the six study drugs, portfolio width was the only variable (out of more than ten) which demonstrated a consistent prediction on early adoption. Although the authors favoured the idea of 'early adopters', their findings instead supported the notion that early adoption by doctors was dependent heavily on the new drugs in question.

In conclusion, from the prescribing data, there is inconsistencies in new drug update whereby depending on the study drug, prescribers who are heavy and early adopters on a particular new drug may be late or even non-adopters of another. It appears that the individual merits of new drugs are considered by doctors. Adoption also appears to be influenced by personal and patient related characteristics.

Prescriber characteristics

Gender: Early adoption of new drugs seem to be significantly influenced by gender. Compared to female prescribers, male prescribers appear to have a much higher likelihood of adopting new medicines, the findings of which appears to be consistent across different drug types. Inman and Pearce (1993) examined British doctors through a large scale quantitative study and noted that utilization of new drugs was much higher among the male doctors compared to female doctors. In the group of doctors with the highest new drug prescriptions, only 9% of them were women. Similar conclusions were reach by subsequent studies (Steffensen, Sörensen, and Olesen 1999; Tamblyn et al. 2003; Helin-Salmivaara et al. 2005; Groves et al. 2010). Studies by Bensing, van den Brink-Muinen, and de Bakker 1993; Tamblyn et al. 2003 suggested that the most likely

reason behind the difference in initiation of new medicines between male and female doctors were due to the differences in their confidence levels.

Age: Uptake of new medicines seem to be associated with age. From qualitative research, there is a clear association that early prescribers tend to be younger compared to the majority of the other doctors (Coleman, Katz, and Menzel 1966; Weiss et al. 1990; M. Y. Peay and E. R. Peay 1994). Similar conclusions were reached by quantitative studies (Tamblyn et al. 2003; Glass and Rosenthal 2004; Groves et al. 2010). In a recent study by Bourke and Roper (2012) examining the adoption of six study drugs among general practitioners, they found that age of the doctor exerted a small but statistically significant positive impact on the time to adoption in four of the drugs. Studies by other researchers (Lurie, Rich, and Simpson 1990; Tamblyn et al. 2003) suggested that the most likely younger doctors had a higher likelihood of adopting new medicines early was because of their propensity towards more aggressive intervention in addition to the targeted marketing practices. Older doctors also tend to have more established prescribing practices. However, other studies have shown contrasting findings whereby some of these noted that early prescribers tend to be older (Kozyrskyj, Raymond, and Racher 2007; Groves et al. 2010) while others did not find any correlation between the prescriber age with the early adoption of new drugs. Nevertheless, it does seem that younger prescribers in general would favor early adoption of new medicines as compared to the older prescribers.

Training location: The impact of training location on the uptake of new drugs were assessed by four quantitative studies. Except for Grove et al. (2010), all the other studies found that early adoption of new drugs were significantly influenced by the training location. From the perspective of the British (Inman and Pearce 1993) and North American (Kozyrskyj, Raymond, and Racher 2007), doctors with overseas qualifications tend to prescribe more new drugs. In

addition, the study by Tamblyn et al. (2003) also note that higher usage of new drugs was seen among the doctors (both specialists and general practitioners) that had graduated from the most newly formed medical schools. It is also likely that aspects of the training location in all three studies which were not measured had also influenced new drug uptake. This includes the basic pharmacological training, policies regarding the detailing of drugs, pharmaceutical industry's relative contribution towards training and research as well as the practices of attending doctors (who are influential educationally) during the formative training years (Tamblyn et al. 2003). Hence all the literature does point towards a significant influence of the doctors' training location towards new drug uptake.

Board certification: Both quantitative (Glass and Rosenthal 2004) and qualitative (Weiss et al. 1990) studies have noted a consistent association between board certification and adoption of new drugs, although other researchers did not (Majumdar et al. 2001; Corrigan and Glass 2005).

Clinical and therapeutic area: Several qualitative studies have suggested that doctors have a greater likelihood of prescribing new drugs in clinical and therapeutic areas which they have greater familiarity or are particularly interested in (Coleman, Katz, and Menzel 1966; Jacoby, Smith, and Eccles 2003; Prosser and Walley 2003; Tobin et al. 2008). Adoption of new drugs was reported to be faster among the specialists in secondary care as opposed to general practitioners in primary care (Fendrick, Hirth, and Chernew 1996). Contrary to these findings however, Dybdahl et a. (2011) did not observe a clear association between the prescribing of new drugs with general practitioners' self-rated clinical interest. These mixed findings were similarly reported in several quantitative studies. Studies done by Majumdar et al. (2001), Ruof et al. (2002), Glass and Rosenthal (2004), and HelinSalmivaara et al. (2005) supported the notion that adoption of new drugs were more likely among the specialists as compared to the general

practitioners. However, Kozyrskyj, Raymond, and Racher (2007) found mixed evidence. However, a study done by Groves et al. (2010) found instead that adoption of new drugs was more likely among the general practitioners compared to the specialists. On the whole, it appears that the process of new drug adoption is influenced by the clinical and therapeutic area, with specialists having a greater likelihood to adopt special-purpose new drugs while early adoption of new drugs that are used for a spectrum of therapies were more likely among the general practitioners.

Hospital affiliation: Many qualitative studies have evaluated the influence of hospital affiliation with the adoption of new drugs (Strickland-Hodge and Jepson 1988; Feely et al. 1999; Jones, Greenfield, and Bradley 2001; Jones et al. 2001; McGettigan et al. 2001; Prosser, Almond, and Walley 2003; Tobin et al. 2008). Doctors who are affiliated to hospitals are generally restricted by the hospital formularies (Glass and Rosenthal 2004). However, on the other hand, they are also exposed to influence by specialist, which appears to outweigh the restrictions imposed by the hospital formulary (Kozyrskyj, Raymond, and Racher 2007).

Clinical trial participation: According to both qualitative (Denig et al. 1991) and quantitative studies (Corrigan and Glass 2005), participation in clinical trials appear to increase the early adoption of new drugs. This is likely due to increased proximity to research and a better understanding of the evidence base (Chauhan and Mason 2008).

Prescribing characteristics: The adoption of new drug process seems to be significantly influenced by prescribing characteristics. Doctors that have a high patient load and flow seems to keep a keen eye for new drugs, likely because of the need to address any unmet clinical needs of their patients. This appears to appear regardless of the therapeutic novelty, with a greater likelihood for early adoption of new drugs seen in those with higher total prescribing volume and

higher portfolio width (Glass and Rosenthal 2004). Bourke and Roper (2012) noted that such doctors have a greater awareness of alternative options and have a tendency for early adoption of new drugs. In the context of first-in-class drugs, Glass and Rosenthal (2004) doctors with a higher prescribing volume of drugs from the same pharmaceutical company as the new drug had a greater likelihood of adopting it earlier. This may be attributed towards the increased marketing efforts towards the doctor as well as the doctors' confidence and trust towards the company and their sales representatives. For all other new drugs, Glass and Rosenthal (2004) found that the likelihood of early adoption were increased among those doctors were a higher prescribing volume of the therapeutic class of the new drug. Prescription of new but non-novel drugs were thought to be due to the failure of existing drugs to fulfil the clinical needs of the patients. For non-prescribers of a therapeutic class of drugs, they are either not convinced of the clinical value of the therapeutic class or they may not have suitable patients for that therapeutic class.

Patient Characteristics

New drug uptake appears to be influenced by various patient characteristics such as age, gender, socioeconomic status as well as their existing comorbidities. Although the amount of empirical evidence is vast, there is a huge variation in the early receivers' characteristics between different drugs, the therapeutic goal as well as the drugs' target hence. Hence it is not possible to provide an exhaustive review of the literature.

Age: Age of the patient influences the doctors' likelihood of prescribing new drugs, whereby they are generally less likely to prescribe new drugs for elderly patients as geriatric patients generally have a higher likelihood of developing adverse effects (Tamblyn et al. 2003; Álvárez and Hernández 2005). Hence doctors are typically more likely to prescribe new drugs to the younger patients (Mark et al. 2002; Hansen et al. 2004; Greving et al. 2006; Ohlsson, Chaix, and

Merlo 2009). An exception would include drugs that are designed for geriatric patients, such as those for the management of Alzheimer's disease or arthritis for example (Florentinus et al. 2005a, 2005b, 2006; Helin-Salmivaara et al. 2005).

Although the likelihood of doctors starting new medicines may be influenced by the patient's gender, the main gender target group is usually determined by the therapeutic goals as well as the drug characteristics (Mark et al. 2002; Florentinus et al. 2005a, 2005b, 2006; Roer at al. 2010).

Socioeconomic characteristics (income, education, and health insurance): Patients' socioeconomic status reflects their social and economic position relative to other people, taking into consideration their education, income and occupation (Winkleby et al. 1992). Based on a huge body of registry-base literature, it is suggestive that regardless of the medical considerations, doctors' prescribing behaviour are influenced by the patients' socioeconomic status (Mamdani et al. 2002; Roer et al. 2010). New drugs are generally received by patients with high income, partially also due to their ability to afford out-of-pocket treatments (Kozyrskyj, Raymond, and Racher 2007; Ohlsson, Chaix, and Merlo 2009). Patients with private insurance also have a higher likelihood of receiving new drugs early (Florentinus et al. 2005a). In terms of the education level, elderly patients with higher levels of formal education have a greater likelihood of receiving new drugs as compared to those with lower levels of formal education. This was regardless of gender, age, residential area type, comorbidity, as well as the number of drugs used (Haider et al. 2008). Although the literature is generally homogenous with regards to a higher likelihood of patients with higher socioeconomic status receiving new drug early, there are some studies which did not find any association (Hansen et al. 2004).

Race / ethnicity: There seem to be some correlation between race/ethnicity with the uptake of new drugs, wan example including the higher likelihood of the non-African-Americans receiving

new drugs as compared to the African-Americans and Hispanics (Mark et al. 2002; Daumit et al. 2003; Van Dorn et al. 2006; Wang et al. 2006).

Marital status: Although new drug uptake may be influenced by the patients' marital status, the pattern was noted to vary from drug to drug. New-generation antidepressants were found to be more likely prescribed to single patients as compared to those married or cohabiting patients (Hansen et al. 2004) whereas new drugs for the management of high cholesterol had a higher likelihood of being prescribed to married or cohabiting patients as compared to single patients (Ohlsson, Chaix, and Merlo 2009).

Health: Uptake of new drugs seem to be significantly influenced by a patient's health status, which includes the patient's self-reported health, presence of comorbidities, prior use of certain medication as well as a poor response existing treatment (Florentinus et al. 2005a, 2005b; Greving et al. 2006; Kozyrskyj, Raymond, and Racher 2007). The patient's individual contexts are considered earnestly by doctors, with patient convenience seemingly influencing the uptake of new drugs and also promoting earlier adoption in patients with conditions in desperate disease stages.

Practice Characteristics

Solo / group: The early adoption of new drugs appears to be accelerated in group/partnership practices, partly due to the continuous professional stimulation as well as other social factors. Circulation of medical notes due to shared responsibility for patients enable cross-fertilisation of therapeutic information (Williamson 1975b). An efficient channel for Information transfer and evaluation is provided through personal contact with colleagues. In addition, there is also the

chance that doctors may become conformist in their prescribing habits as a result of working closely together (Williamson 1975b).

However, there is ambiguity in the empirical studies with regards to the impact of group/partnership practice on the uptake of new drugs. The classic study by Coleman, Menzel and Katz (1959) reported that the adoption of new drugs takes place 2.3 months earlier with doctors that are practicing in partnerships as compared to those who practise alone. A similar conclusion was reached by Williamson (1975b) whereby he demonstrated that the speed difference in evaluating information had a direct consequence on the adoption time, which is partly accounted for by contact time with peers.

A questionnaire study by Weiss et al.'s (1990) concluded that a powerful variable which distinguished between doctors that innovate and those that don't is membership in a group practice. These findings were also supported by a registry-based study (Steffensen, Sörensen, and Olesen 1990), although another had suggested that the difference was negligible once practice size was adjusted for (Dybdahl et al. 2004). Dybdahl et al. (2004) argued that practices with a larger number of patients would naturally have a greater probability of having patients who are suitable candidates for the new drug and that this would have been the same conclusion that Steffensen, Sörensen, and Olesen (1990) would have drawn if practice size was adjusted for.

M. Y. Peay and E. R. Peay (1988, 1994) did not support the note that there was a difference in new drug uptake between doctors who practised in partnership as opposed to their counterparts who have solo practices. Contract to what other researchers found, Florentinus et al. (2006) found that new drugs were prescribed more by doctors with their own practice as compared to those working within group practices and suggested that it was because these doctors tend to have more interactions with specialists as compared to other generalists and that the hospital tend

to exert a greater influence over the adoption process (M. Y. Peay and E. R. Peay 1994; Prosser, Almond, and Walley 2003). There is a need to adjust for practice size in new medicine adoption studies as it allows us to determine whether early adoption of new drugs is due to the high patient number or because of the continuous professional stimulation. Based on previous empirical data, the former contention seems more likely whereby new drugs are adopted early by group practices as they have a greater likelihood of meeting patients who have a new for the new drugs.

Location (urban / rural): New drop adoption may be influenced by the practice location whereby adoption tend to take place earlier among urban practices as compared to rural practices. This may be due to the personal characteristics of doctors who opt to practice in rural areas, or may also be due to the lesser opportunity for peer-to-peer profession interactions as compared to their urban colleagues, which have been suggested by many researchers to be a factor which is important in influencing the decision for initiating new treatments (Coleman, Menzel, and Katz 1959; Williamson 1975b; M. Y. Peay and E. R. Peay 1994; Jones, Greenfield, and Bradley 2001; McGettigan et al. 2001). The lower rates of new drug uptake among doctors in rural practices may also be due to differences in the intensity of visits by pharmaceutical sales representatives due to their geographical inaccessibility (Tamblyn et al. 2003). A questionnaire study by Cutts and Tett 2003 also found that doctors practising in rural areas were less likely to prescribe new drugs as compared to their urban colleagues, with the prescribing data reflecting the doctors' self-reported behaviour (Tamblyn et al. 2003; Bourke and Roper 2012). Similarly, a study by Contrary to these findings however, a mail survey performed by Buban, Link and Doucette (2001) on oncologist did not find that their adoption of new medicines were influenced by practice location, which suggested reassuringly of the efficiency in dissemination of information. In addition, four other quantitative studies done also did not find an increased uptake of new

drugs among doctors in urban areas (Majumdar et al. 2001; Álvárez and Hernández 2005; Behan, Cutts, and Tett 2005; Ohlsson, Chaix, and Merlo 2009).

On the extreme end of the spectrum however, Groves et al. (2010) found that doctors that were regarded to be heavy prescribers of new drugs have a higher likelihood of practising in rural areas, which they attribute the higher patient and elderly patient loads. There were also numerous other studies which supported the findings of Groves et al., suggesting the availability of effective means for dissemination of information across geographical boundaries (Majumdar et al. 2001; Álvárez and Hernández 2005; Behan, Cutts, and Tett 2005; Ohlsson, Chaix, and Merlo 2009). Through the use of modern communication technology, doctors working in rural areas are likely able be as updated as urban doctors with plentiful opportunities for continuing education and professional interaction with colleagues. They would also likely have full access to information from pharmaceutical companies.

Size (number of patients and prescribing volume): The size of practice can potentially be measured by the number of patients, which is also an indicator of the likelihood of early new drug adoption. Practices with a greater number of patients tend to have a higher likelihood of adopting new drugs early (Strickland-Hodge and Jepson 1982; Weiss et al. 1990). Although these findings were supported by some quantitative studies (Steffensen, Sörensen, and Olesen 1999), there were also others with differing observations (Álvárez and Hernández 2005). Three explanations were provided by Strickland-Hodge and Jepson (1982) with regards to the association between the size of patients with uptake of new drugs. They suggested that practices with higher patient numbers would naturally have a greater probability of having patients' whose conditions are targeted by the new drugs. Secondly, they also proposed that doctors that were perceived to be more innovative increases their likelihood of attracting more patients. They also

argued that when doctors were busy with patient management, they have a higher tendency of taking favourable drug information for granted and do not spend a lot of time critically evaluating drug advertisements.

No association was found at the practice level between high prescribing volume and the early adoption of new drugs (Glass and Rosenthal 2004; Ohlsson, Chaix, and Merlo 2009). This was supported by Dybdahl et al. (2005), who also observed only few associations that were weak and inconsistent between the early uptake of new drugs with previous prescribing of drugs that were of the same therapeutic class. Hence it was concluded that the size of practice does not significantly influence the uptake of new drugs, regardless of whether it is measured by prescribing volume or number of patients. Although this conclusion is counterintuitive and at odds with the literature on individual doctors' prescribing characteristics, it may be due to the cancelling effect of individual doctors' innovative and conservative behaviours when summed up at the practice level.

Number of diagnostic and therapeutic activities: There is a positive association between the early uptake of new drugs with a high volume of diagnostic and therapeutic activity (Steffensen, Sörensen, and Olesen 1999; Álvárez and Hernández 2005), which was at least so for the general practitioners if not the specialists (Tamblyn et al. 2003). This may be because a high volume of diagnostic and therapeutic activity is an indication of the severity of the patients' health, which triggers the need for early adoption of new drugs.

Composition of employees: It was observed that medical practices which employed both specialists and general practitioners tend to adopt new drugs earlier as opposed to those which employed general practitioners only (Ohlsson, Chaix, and Merlo 2009). Similar findings were

observed by Bourke and Roper (2012) among practices which employed the help of a secretary or nurse.

Private/public: Ohlsson, Chaix, and Merlo (2009) found that adoption of new drugs tends to happen earlier among the private medical practices as opposed to the public healthcare practices.

Drug Characteristics

Majority of the drug characteristics can only be measured qualitatively. This includes the perceived safety and efficacy of new drugs as well as the patients' suboptimal response to existing pharmacotherapy agents. Cost of the new drug as well as the pharmaceutical company's marketing budget are the only two characteristics of drug that can be measured quantitatively.

Medical characteristics: Early adoption of new drugs are influenced by various medical characteristics such as whether the new drug fulfils an unmet clinical need, whether it offers any improvement relative advantage (either therapeutic or economic) over existing therapies.

Safety versus perceived risk: Safety profile of the new drug is typically a primary concern for physicians considering early adoption. This includes the adverse effect profile of the new drug as well as if there are any clinically significant drug-drug interactions with other medications prescribed to the patient. The impact of perceived risk is also emphasized by several researchers, and it is found that drugs with higher perceived risks are typically associated with longer time to adoption. However, contrary to these findings, a study by M. Y. Peay and E. R. Peay (1994) noted that adoption of new drugs took place fastest among those highest-risk drugs. This suggests that physicians' tolerance of risk also depends on the illness's severity. In terms of the efficacy of the drug, researchers noted that the early adoption of new medicines that to take place faster in the ones with higher perceived efficacy drugs (M. Y. Peay and E. R. Peay 1988; Jones et

al. 2000; Buban, Link, and Doucette 2001; Jones, Greenfield, and Bradley 2001; Groves, Flanagan, and MacKinnon 2002; Ruof et al. 2002; Jacoby, Smith, and Eccles 2003; Prosser and Walley 2003; Greving et al. 2006; Tobin et al. 2008).

Cost: Despite being a quantitatively measurable variable, there are have been no studies systematically analysing the influence of relative price to the adoption of new medicines. Cost is generally considered to be less important as compared to safety and perceived efficacy. It also usually not a significant barrier to the early adoption of new medicines. Although physicians do try to balance between cost and efficacy of drugs, they are not unwilling to prescribe new drugs which are more effective that costs more. Jacoby, Smith, and Eccles (2003) noted that doctors that most frequently adopt new drugs early tend to be the one that are the least conscious of cost. In general, however, doctors do feel that new drugs which are of high costs should be reserved for cases whereby the cheaper alternatives are either not well tolerated or ineffective (Booth-Clibborn, Packer, and Stevens 2000; Ruof et al. 2002; Prosser and Walley 2003).

Marketing budget of the pharmaceutical company: The early adoption of new drugs is influenced by the pharmaceutical company's marketing budget (Glass and Rosenthal 2004; Booth-Clibborn, Packer, and Stevens 2000), although it should be noted that neither qualitative (Jones, Greenfield and Bradley 1999) and quantitative (Tamblyn et al. 2003) studies have identified a relationship between the intensity of advertising and the early adoption of new drugs. Thus, the early adoption of new drugs is not influenced per se by the market budget. However, Glass and Rosenthal did observe a significant and consistently signed influence of the marketing budget that is assigned specifically to a new drug.

<u>Other factors</u>

The early adoption of new medicines take place in complex environments and are subjected to a variety of influencing factors. The channels of information regarding new medicines as well as factors influencing early uptake have been addressed by a substantial amount of qualitative studies. Hence the list of factors identified thus far is comprehensive, even if the studies reviewed is not exhaustive. Physicians may develop an awareness of new drugs through commercial sources, although the ultimate decision to prescribe may be dependent on professional sources of information such as medical journals (Strickland-Hodge and Jepson 1980). The following section will be focusing on the role that various information sources play as well as the role of social network with a highlight on how interpersonal communication influences early adoption.

The extent to which various sources of information are utilized differs between the general practitioners and specialists (Jones, Greenfield, and Bradley 2001; McGettigan et al. 2001). There seem to be an underutilization of objective information sources among the general practitioners (M. Y. Peay and E. R. Peay 1988, 1994; Jones, Greenfield, and Bradley 2001; McGettigan et al. 2001; Tobin et al. 2008). This include journal articles as well as evidence-based information from independent organisations. Instead, general practitioners tend to have a greater reliance on commercial information provided by sale representatives from pharmaceutical companies. General practitioners have been described by Prosser, Almond and Walley (2003) as being primarily reactive and opportunistic when it comes to receiving information about new drugs. It is thought that general practitioners rarely undertake an active role in information search. Specialists, on the other hand, tend to be more closely in touch with new drug development and have a higher likelihood of developing an awareness of new drugs prior to official approval (M. Y. Peay and E. R. Peay 1994). For the specialists, information

sources that serve the greatest practical importance tend to be colleagues from their own or other specialties as well as clinical meetings. The differences in behaviour between these two groups of prescribers have been thought to be partly due to the marked differences in the working environments (McGettigan et al. 2001). General practitioners tend to work along (or with just a couple of colleagues) and hence sales representatives and consultants may be their main channel for exchange of professional ideas. Specialists, on the other hand, may work in hospital settings and hence regular interactions with peers tend to the enhance diffusion of innovations and ideas.

Professional information and evidence

Drug launches are typically accompanied by huge volumes of commercial and professional information. Doctors to whom the safety of efficacy of new drugs are of utmost importance when considering adoption tend to refer to established scientific evidence which are non-commercial in nature. Among doctors, specialists are generally the subgroup of doctors that rate independent research as being a crucial source of empirical validation when considering adoption of new medicines (Jones et al. 2000; Jones, Greenfield, and Bradley 2001; Prosser and Walley 2006).

The role of peer-reviewed journals as sources of information on the adoption of new medicines have been illustrated by many research studies (Coleman, Menzel, and Katz 1959; M. Y. Peay and E. R. Peay 1990; Jones, Greenfield, and Bradley 2001; McGettigan et al. 2001; Jacoby, Smith, and Eccles 2003). Specialist doctors have been observed to request sales representatives for information from the scientific literature (Jones, Greenfield, and Bradley 2001). Among the journal articles, randomized controlled trials and meta-analysis have been considered to be the best (Prosser and Walley 2006). Rigorous research evidence has been reported to exert significant influence on prescribing decisions in both primary and secondary care (Coleman, Menzel, and Katz 1959; Jones et al. 2000; Jacoby, Smith, and Eccles 2003). Nevertheless, the

value of peer-reviewed journals has still been challenged by some researchers, who suggested that there are still some doctors who would consider these as being too complex and overly time consuming as well as the potential of being out of date (Prosser and Walley 2003).

Drug bulletins are indicated by several studies to be an important channel of information for new drugs (McGettigan et al. 2001; Groves, Flanagan, and MacKinnon 2002), with the general practitioners rating these alongside the medical journals as important (McGettigan et al. 2001).

In addition, highly valued sources of information that may influence the early adoption of new drugs also include specialist meetings, presentations, conferences and symposia (Coleman, Menzel, and Katz 1959; Buban, Link, and Doucette 2001; Jones, Greenfield, and Bradley 2001). Through interactions with professionals at national and international events, early information may serve as a catalysis for early awareness and positive evaluation (M. Y. Peay and E. R. Peay 1994). This is likely because doctors who tend to attend such forums are usually more sensitive towards new developments, although cost of attendance may be substantial (Groves, Flanagan, and MacKinnon 2002).

Early adoption of new drugs tends to happen among doctors with a heightened professional orientation. This is typically seen in doctors with some degree of association with academic centres, either holding an academic appointment or are involved in teaching and publishing (Weiss et al. 1990).

New drug uptake is also typically influenced by treatment guidelines and protocols as well as hospital formularies. Specialists would theoretically consider their senior colleagues as being the most important source of information, with the national formulary as the second most important. However, Wathen and Dean (2004) found that in practice, the best treatment guidelines exerted

little impact on the uptake of new medicines in UK. Nevertheless, new drug prescriptions have been increased by technological guidelines when accompanied by other information sources and personal experience. It is important to note that new drug uptake may be facilitated or constrained by treatment guidelines, hospital formularies as well as protocols. In similar fashion to government policies, guidelines may promote news drugs that are therapeutically innovative and cost-effective while discouraging expensive new drugs with little clinical value.

Guidelines, hospital formularies, and protocols might also exert influence on new drug uptake. In theory, specialists consider the national formulary as the second most important source of information on new drugs, senior colleagues being the first (McGettigan et al. 2001). In practice, Wathen and Dean (2004) found that best practice guidelines have little impact on new drug uptake in the UK. Nevertheless, technological guidelines accompanied by other sources of information or personal experience trigger an increase in prescribing new drugs. Of course, new drug uptake might be constrained as well as facilitated by guidelines, hospital formularies, and protocols (Prosser and Walley 2006). Similarly, to government policy (Griffin 1995), guidelines might promote therapeutically innovative, cost-effective new drugs, whilst prohibiting expensive new drugs (Jones et al. 2000). However, specialists can overcome formulary restrictions by recommending new drugs to general practitioners.

Evidence-based recommendations may be provided by prescribing decision support systems which may assist doctors in identifying patients that may benefit from the new drug. These systems may enhance early adoption of new drugs which are therapeutically advanced and cost-efficient. Greving et al. (2006) found that general practitioners who uses these systems tend to have less inclination of prescribing new drugs that are not cost efficient.

Lastly, personal experience also has a significant impact on the prescribing behaviour of doctors (Buban, Link, and Doucette 2001; Jones, Greenfield, and Bradley 2001; Prosser, Almond, and Walley 2003). The willingness to use a trial of the new drug may be triggered by the doctor's personal curiosity, patients or simply when existing therapeutic options are exhausted. Essentially a reflective process, trialing enable doctors to test therapeutic outcomes and interpret evidence in the light of experience (Prosser and Walley 2006). If trial with the new drug is associated with positive experience, a change in prescribing behaviour is more likely. Similarly, any negative experience with the new drug would likely lead to a rejection.

Commercial Information

Although specialists tend to place a greater emphasis on professional information, they may still rely on commercial information for drugs that are not commonly used in their specialty. General practitioners, on the other hand, tend to have a stronger preference for commercial information. This may partially be due to the time constraints and broad range of conditions which they manage in their practice, hence they are usually not able to thoroughly review all the relevant professional information. Nevertheless, the first source of information regarding the drug for both the general practitioners and specialists is usually the sales representatives, with the commercial information provided by the pharmaceutical companies. Pharmaceutical companies sought to maximize profits through incorporating new drugs early in their lifecycle, creating awareness among the top professionals as well as maintaining the new drug's first-choice status within their respective therapeutic class (Groves, Flanagan, and MacKinnon 2002).

Not only does pharmaceutical marketing increase awareness, it is evident that they influence decision making as well whereby the prominent impact of commercial information on the early

adoption of new drugs have been demonstrated by Avorn, Chen, and Hartley (1982), M. Y. Peay and E. R. Peay (1988), and Prosser, Almond, and Walley (2003).

In particular, sales representatives interaction with the prescriber have been found to have a significant impact on early adoption (M. Y. Peay and E. R. Peay 1988, 1994; McGettigan et al. 2001; Jones, Greenfield, and Bradley 2001; Jacoby, Smith, and Eccles 2003; Prosser, Almond, and Walley 2003; Tobin et al. 2008), with the early prescribers generally showing an intensive usage of the sales representative information (Jones, Greenfield, and Bradley 2001; Prosser, Almond, and Walley 2003; Tobin et al. 2008).

Pharmaceutical marketing information are considered useful by three quarters of US doctors (Kaiser Family Foundation 2002). Even though doctors may intend to minimize the importance of sales representatives so as to avoid any distortion as well as selective information which are overly positive, sales representatives are generally thought to be an expedient means for doctors in acquiring and processing up to date drug information (Prosser, Almond, and Walley 2003; Chauhan and Mason 2008).

Awareness about new drugs can also be facilitated by pharmaceutical companies in numerous other ways, Example of these include the use of direct mails, conferences or journal advertisements in peer-reviewed medical journals, controlled circulation journals or pharmaceutical prescribing reference guides (Strickland-Hodge and Jepson 1982; M. Y. Peay and E. R. Peay 1994)—or through sponsoring of continuing education and funding of clinical trials.

Early adoption of new drugs may also be influenced by direct-to-consumer advertising through the mass media as it stimulates patient requests. When potential benefits of new drugs are

promoted, any unmet demand to treat certain conditions may be stimulated. There may also be a heightened expectation for better relief than the existing products. Empirical evidence has found that there was a positive association between early adoption of new drugs with patients seeking treatment for which they have sought outside information (Buban, Link, and Doucette 2001). Hence, the role of patients should not be underestimated, particularly with the general practitioners reporting that they often receive patient requests for new medicines, and that they often grant them due to a variety of reasons such as time constraints, the desire to avoid conflict as well as recognizing patients' role in shared decision making (Prosser, Almond, and Walley 2003). A contrasting finding was reported by Chauhan and Mason (2008) whereby they found little evidence that prescribing decisions are influenced by patients. However, they did forecast that new drug uptake would increasingly be impacted by patient, in view of the rising prominence of self-care and patient-choice agendas. However, the effectiveness of direct-to-consumer advertising in trigger doctors to actually prescribe is still being debated within the literature (Glass and Rosenthal 2004).

Lastly, new drug update is likely to be influenced by sampling programs, since doctors that received new drug samples have a greater likelihood of adopting as compared to others (M. Y. Peay and E. R. Peay 1988).

In conclusion, pharmaceutical companies have a direct impact on prescribing through a variety of means of providing knowledge and increasing product awareness. With the growing emphasis on the importance and need for evidence-based medicine, a question that would arise is whether or not professional information can counterbalance commercial information. Greving et al. (2006) noted that general practitioners who have a greater reliance on commercial information have a higher likelihood and preference for prescribing new drugs as opposed to the other ones

from the same therapeutic class. Hence they concluded that promotional information continues to play a significant role in determining the early adoption of a new therapeutic class.

Communication among professionals

In order for innovative new drugs to achieve rapid and widespread acceptance and adoption, numerous researchers have found interpersonal communication between leading opinion leaders with their peers to be one of the critical factors (Coleman, Menzel, and Katz 1959; Williamson 1975b; M. Y. Peay and E. R. Peay 1994; Jones, Greenfield, and Bradley 2001; McGettigan et al. 2001). A strong stimulus is provided through personal contacts as key opinion leaders often serve as a reliable and easy-to-digest source of assessment for new drugs. Although other information sources may provide a nurturing groundwork of necessary knowledge, personal advice from colleagues who are informed and respected (Weiss et al. 1990) provide the essential legitimizing power that is often required for behavioural changes in prescribing habits.

The network of informal relations among doctors have been proposed by Coleman et al. (1959) to be a highly effective medium for transferring information and an important factor influencing diffusion of pharmaceutical innovations. Compared to doctors who are more isolated, the ones which are socially integrated tend to introduce new drugs much faster. The findings were noted to be valid for all three social structures, with the only caveat being that the channels of influence which operate among doctors had an impact on the adoption of new drugs most powerfully during the first few months of launch.

The influence of specialists on their specialist colleagues have been addressed by a substantial amount of literature (Weiss et al. 1990; M. Y. Peay and E. R. Peay 1994; Buban, Link, and Doucette 2001; Jones, Greenfield, and Bradley 2001; McGettigan et al. 2001). With regards to

the utility of new drugs, consultants have a heavy reliance on their colleagues'' advice, with their senior colleagues being most frequently rated as important for new drug uptake. M. Y. Peay and E. R. Peay 1994 noted that the number of contacts with other doctors predicts most consistently for early awareness and prescription. This is thought to apply in both theory and practice. However, it should be noted that although doctors that serve as a source of information for their colleagues may learn about new drugs earlier, they may not necessarily prescribe them earlier as well. M. Y. Peay and E. R. Peay 1994 argued that doctors that are defined as information seekers should not only be aware of the new drug earlier, but should also be prescribing it earlier as well.

Beyond just the number of contact, the composition matters as well. Apart from interaction with specialist colleagues within the main practice setting, new drug uptake is also significantly associated with interactions with specialist colleagues outside of their practice (Weiss et al. 1990; Buban, Link, and Doucette 2001). This is because the likelihood of learning about therapeutic advances is increased with the informal communication channels that are outside of the main practice.

Diffusion of pharmaceutical innovations is also significantly influenced by the local opinion leaders (Greer 1988; Soumerai et al. 1998) since their evaluation of the new drug often form the basis for consensus among their groups, which is often a prerequisite for diffusion.

The influence of specialists on new drug uptake among the general practitioners (either through advice or example) have been emphasized by numerous literature (Strickland-Hodge and Jepson 1988; Feely et al. 1999; Jones, Greenfield, and Bradley 2001; Jones et al. 2001; McGettigan et al. 2001; Prosser, Almond, and Walley 2003; Tobin et al. 2008). General practice prescribing has also been found to be significantly hospital-initiated or hospital-led (Jones et al. 2000; Jacoby, Smith, and Eccles 2003). Diffusion of new drugs through general practice appears to

take place via a two-step process. Hospital consultants are typically the innovators while general practitioners are the followers whereby there is a significant reduction in the perceived amount of uncertainty associated with prescribing the new drug (Prosser and Walley 2003). Contrary to these findings however, Florentinus et al. (2009) did not located any evidence supporting this model and instead suggested that general practitioners are responsible for considerable early prescribing of new drugs.

New drug uptake is also promoted by the consistency in evidence, as this reduces the uncertainty with usage (Prosser and Walley 2006). Prescribing behaviour is also likely to be shaped by any perceived local consensus and conformism with consultants (or other respected professionals) or other group norms (Jacoby, Smith, and Eccles 2003). This is supported by Chauhan and Mason 2008, who found that diffusion of pharmaceutical innovations is slowed when there is a lack of consensus regarding the best use.

Lastly, doctors who are on the panel or committees of decision making bodies, such as the drug and therapeutic committees that evaluation drugs for listing into the formularies for example, appears to exert a special influence on the diffusion. This is likely because of their proximity to research and understand of evidence base (Chauhan and Mason 2008).

What attitudes do professional and lay people have to promotion?

It is important to examine what people think about promotions and the effects that they think it has on them as it would allow relevant interventions to be made accordingly. However, it should be noted that the actual effects of promotions cannot be elucidated entirely through research on this topic. This is because people may be affected by promotions in ways that they are unaware of or are unwilling to tell others about. The following review examines the studies on what people think about promotions. Many of the research done on attitude towards promotion relies heavily on the use of survey methods. This usually provides an estimate of the number of people who agree or disagree with certain statements, primarily regarding the effects, effectiveness and appropriateness of various forms of promotions. Some of the more complex studies also explore the variables associated with different attitudes towards promotion. These studies try to find out the kinds of people who have different opinions towards promotion, and hence are more useful. A major gap in the literature is that there is little qualitative research done on people's attitude towards promotion. In depth interviews would be useful to have a better understanding of people's values and perspectives whereby people are able to express themselves in their own way about what they think and feel about promotions and how it affects them. An example of such approach would be ethnographic research whereby the researcher spends time immersing with the doctor and tries to understand how promotions fits into their working lives.

Attitudes do not necessarily match behaviour

Several studies have demonstrated that just by finding out what people think about promotions may not be the best way of predicting their behaviour. Peay and Peay's paper in 1984 suggests that a doctor's view in the worthiness of an information source may not be reflected in how often

they use it. This can be extrapolated from the findings whereby sales representatives and other commercial sources are not evaluated highly despite frequently cited to be the first information source about medicines and also one of the most frequently mentioned sources of information required to aid prescribing decision.

Gambrill and Bridges-Webb reported from their study that 56% of the Australian doctors reported using sales representatives as a regular source of information, but only 17% ranked them as the most useful.[2]McCue et al.[3] surveyed physicians (general practitioners, internist and surgeons) in North Carolina about their attitudes towards and use of various sources of information about new medicines. With a low response rate, the authors found that only 27.7% of the respondents found sales representatives to be an accurate and accessible source of information about new drugs despite being the most frequently utilised source of information.

Studies of the prevalence of different attitudes to promotion (excluding direct-to-consumer advertising)

These studies simply report the percentages of people reporting certain attitudes or beliefs about promotion. Although some of these studies start exploring the differences within their samples, it is usually not their main objective. Most of these studies examine the attitudes of medical students, doctors in training, their trainer, or patients rather than practicing doctors or the public in general. Studies are typically conducted at one or two institutions (usually in the U.S. or Canada), with questionnaires being sent to various institutes' training directors. These studies focus on training doctors and their trainers, examining and discussing about what constitutes an appropriate relationship between promotion and training.

Surveys of the prevalence of different attitudes include: Hodges4 who looked at psychiatry residents, interns and clerks in seven Canadian hospitals; Sergeant et al. who looked at family medicine residents in Ontario; Aldir et al.'s survey of practicing and resident doctors in Northeastern Ohio, USA, about their views of promotion; Barnes and Holcenberg's survey of medical and pharmacy students at the University of Washington in 1970; Blake and Early's survey of Missouri patients about their attitudes to gifts given by pharmaceutical companies to doctors; Madhaven et al., who surveyed West Virginia doctors about their attitude to gifts from the industry; and Keim's survey of directors of emergency medicine programmes, and residents in these programmes, about their attitude to interactions with the pharmaceutical industry. Others include: Mainous et al., who surveyed 649 adults in Kentucky about their attitudes to doctors accepting gifts from the pharmaceutical industry; Reeder et al., who surveyed all chiefs of US emergency medicine residency programmes; Strang et al. who surveyed Canadian doctors; Lichstein et al. who surveyed directors of internal medicine residency programmes; and Dunn et al. who surveyed Ontario physicians.

All of these studies do not indicate any clear patterns in physicians' attitudes towards promotion. Further research would be needed in order to know if the variation in findings depend upon the population surveyed, the way questions were asked, who asked the questions as well as the context.

Do trainers and trainees think that sales representatives should be banned during medical training?

Most of the psychiatry trainees (71%) surveyed by Hodges did not feel that sales representatives should be banned from product presentations during their training programme. Similarly, most

directors from the internal medicine residency programmes (67%) feels that the benefits of sales representatives outweighed the negative effects. 42% of them were concerned that company sponsorship of departmental activities would be jeopardised if sale representative interactions with physicians are curtailed. A study by McKinney et al. however, found that 525 of the faculty and 66% of the residents were of the opinion of banning sales representative presentations at their institutions. Only three studies were found to address this question. While some trainers and trainees think that sales representatives should be banned from their institutions, many others do not feel the same. Qualitative research would be required to uncover the reasons.

Do doctors think they have enough training to deal with sales representatives?

70% of the psychiatry trainees felt that they did not have adequate training with regards to interacting with sales representatives. Of the internal medicine faculty and residents surveyed by McKinney et al., only 10% felt that they were adequately trained to handle professional interactions with sales representatives. However, in a study by Aldir et al., 90% of the practising doctors and 87% of the residents felt that they were adequately trained to critically appraised the information provided by pharmaceutical companies. Of the three studies which addressed this question, majority of the physicians from two studies had indicated that they were not adequately trained to handle interactions with sales representatives. However, the majority of physicians in one of the study indicated instead that they were adequately trained and competent to critically appraise information from pharmaceutical companies. The discrepancy may be attributed to differences in framing of the questions e.g. locating deficiency in the training as opposed to in the individual.

Do doctors think that sales representatives have a valuable role in medical education?

29% of the psychiatry trainees agreed that the sales representatives have an important teaching role. 80% of the U.S. emergency medicine chief residents felt that interactions with sales representatives were beneficial to their residency programme. Only six chief resident were strongly against interaction between their residents and the sales representatives. Bucci and Frey did a study on 17 family practice residency programmes and found that 48.3% of the programme directors had indicated that sales representatives were a valuable resource for drug information for residents and 55.1% felt that they were also valuable for the practising physician. Dunn's study on Ontario physicians reported having 10% of physicians (10.9% of primary care physicians and 12.2% of hospital-based specialists) rating pharmaceutical handouts as being an important or very important continuing medical education resource . Hayes et al. did a survey on general practitioners in UK about their attitudes and involvement towards industry involvement in continuing medical education. They found that most of the general practitioners (90%) have had pharmaceutical companies organized meetings with educational content at their practice. The promotional aspect was identified to be the particular characteristic which was most disliked by the physicians. It should be noted that the studies reported here all asked relatively different questions. There are mixed opinions among the physicians towards sales representatives, though the differences may have resulted from the way questions were framed. Hence more research is needed to clarify this.

What do health professionals think about the quality of the information provided by sales representatives and advertisements about drugs?

In the study by Hodges, 32% of the psychiatry trainees agree that information provided by sales representatives about new medicines are useful and accurate. 58% of the family medicine residents from study by sergeant et al. felt that literatures shared by sales representatives are

useful. However, 92% of the Canadian doctors who were surveyed by Strang et al. felt that the primary objectives of sales representatives were to promote their products, with 80% of them feeling that there is usually an overemphasis on the medicines' effectiveness. In addition, 47% of the doctors from Eaton and Parish's study did not feel like they were to obtain an unbiased assessment of newly introduced medicines. Most of them commented that the drug information was too commercial and hence biased. In New Zealand, a study by Thomson et al. reported having 58 of the 67 doctors interviewed met sales representatives regularly. When probed about why they do so, 56 of them stated reasons associated with learning about new or existing products. The director of the Pharmaceutical Manufacturers' Association of New Zealand described a survey of doctors in a letter to the editor of the New Zealand Medical Journal[21]. Without disclosing details about the methodology, he claimed that most of the doctors in New Zealand feels that sales representatives are good sources of information about drugs and are cognizant of the physicians' information needs, although they tend to be overly biased towards their own products.

Contrastingly, a study by Hayes et al. conducted in UK found only 16% of the GPs surveyed had found sales representatives to be a valuable educational resource. Shearer et al. surveyed university and community practice doctors and identified direct mail, journal advertising and detailers to be the three least reliable source of information. Doctors in community hospital tend to rank the sales representatives more highly than the doctors in university hospitals. Staff members from a family medicine residency training programme in Canada (Whelam et al.) did not rate sales representatives as a very useful source of information in response to medical information enquires. In fact, sales representatives were rated poorly on all aspects: frequency

and ease of use, availability, understandability, helpfulness, extensiveness as well as the amount of confidence they had in them.

A study conducted by Cockerill and Williams among Ontario pharmacists found that only 25% of the respondents (25%) had felt that sales representatives were an importance source of information. Only 17% of them thought advertisements and promotional literature were. In complex clinical cases, Boerkamp et al. noted that sales representatives were never mentioned as being a source of information. Lion et al. studied the response of psychiatrist towards various advertisements for psychotropics that were shown to them. However, majority of them did not find the advertisements to be attractive or informative.

68% of the physicians working in a Turkish city surveyed by Güldal and Semin had the impression that information from sales representatives are unreliable, with 94% of them reporting the need for a more reliable source of information about medicine apart from the pharmaceutical companies. Varying degrees of anger and frustration was reported by physicians in New Zealous by Benseman due to the perceived amount of wastage in the materials that are sent by pharmaceutical companies. Almost of the physicians perceived pharmaceutical materials to be biased and hence should not be taken at face value. These physicians indicated a preference for pharmaceutical companies to sponsor journal publications as they find these to be more relevant and beneficial to clinical practice.

A small convenience survey by Mackowiak et al.sample of US community pharmacists and pharmacy students about advertisements for over-the-counter medicines in pharmacy journals. In the USA, these advertisements are regulated by the Federal Trade Commission and hence they must be truthful and not misleading, although it is still considered to be of a lower standard

compared to that enforced for prescription medicines. Around half the pharmacists and students surveyed had felt that the advertisements they were shown were misleading and not truthful, although they also reported high levels of reliance on them. Most respondents (90% of pharmacists and 81% of students) commented that regulations for over-the-counter products should be subjected to the same amount of rigor as prescription products.

The International Federation of Pharmaceutical Manufacturers Associations and the US Pharmaceutical Manufacturers' Association commissioned a study on healthcare providers in Africa and found that 95% of those who received company-provided information reported finding it helpful. However, the design of this study is not well described.

In conclusion, physicians' opinions regarding the usefulness of information from pharmaceutical companies vary but the general belief is that such information is biased.

What do other groups of people think of promotional information?

Journalists who wrote about medicines claimed to be critical of material from the drug industry in a study by van Trigt et al. Companies were not considered important sources for drug information in general, but the manufacturer was seen as a major source of information when a new drug was registered or became available.

What are doctors' views of pharmaceutical company support of conferences and speakers?

From the survey by Hodges on psychiatry trainees, most (77%) agreed that sales representatives supported important conferences and speakers. Family medicine residents surveyed by Sergeant et al. mostly agreed that the content of continuing medical education activities should be set by

doctors who are organizing them as opposed to the company who is sponsoring. More research is required to obtain a more detailed idea.

Do trainee doctors plan to see sales representatives in their future practice?

In a survey of family medicine residents in a Canadian centre by Sergeant et al., 76% stated that they would be seeing sales representatives in their practice. 42% of the Canadian psychiatry trainees surveyed by Hodges commented that without the gifts from sales representatives, they would not maintain the same degree of contact.

What are professionals' and patients' attitudes to the appropriateness of gifts?

A study by Sergeant et al. on family medicine residents found that 55% of them are open to attending pharmaceutical company sponsored meals with sales representatives. However, 36% of them felt that gifts from sales representatives to doctors led to greater medicine costs to patients. A group of doctors surveyed by Aldir et al. deemed smaller gifts to be more appropriate than valuable ones. From a survey on Canadian doctors, Strang et al. reported that 85% of them agreed that sales representatives should be able to offer free samples, though 74% of them were against all-expenses-paid trips to pharmaceutical company organised meetings. Over half of the residents surveyed by Keim et al. received various gifts such as textbooks from pharmaceutical companies as they required the financial assistance with their education. From his survey, 78% of the programme directors and 92% of students felt that textbooks were appropriate gifts and were not against sales representatives offering this. Keim et al. suggested that in general, those who were more sensitive to bioethical issues were more reluctant to accept non-educational gifts. A survey by Sigworth et al. noted that 25% of the resident doctors in Virginia were unwilling for their patients to be aware that they had received gifts and awards from pharmaceutical

companies. They would also hide this from their patients. Palmisano and Edelstein did a study involving 100 medical students and 100 family planning nurses with regards to the propriety of various people accepting gifts. 85.4% of the 50 medical students felt that it was inappropriate for government officials to accept US$50 gifts from individuals wanting to secure a contract. The other. 46% of the remaining 50 medical students were of the opinion that it was inappropriate for resident doctors to accept US$50 gifts from pharmaceutical companies. The nurses were segregated into three groups and asked different versions of the question. 97% felt that it was inappropriate for government officials to accept gift and that 64% felt that it was inappropriate for resident doctors to receive gifts. Surprisingly, only 30% were against the idea of nurse practitioners accepting gifts. Guldal and Semin did a survey with Turkish doctors and noted that 33% of them felt that gifts were unethical, 36% felt that gifts were unethical in some respects, while 21% were of the opinion that gifts were ethical. 64% of the patients surveyed by Blake and Early[8] felt that the costs of medicine would be increased by pharmaceutical gifts to the physician. They were approving towards the acceptance of certain gifts such as medicine samples, medical textbooks, pens, conference expenses as opposed to other non-educational gifts such as dinners, baby formula and golf tournaments. Notably, it was the men, older people as well as those with tertiary education who tend to disapprove of gifts. Likelihood of disapproving gifts (except free medicine samples) if they feel that these influenced prescribing and increased cost. A study limitation was that most patients were aware of such gifting practices from the pharmaceutical companies and hence did not have much time when considering their opinion of them while completing the questionnaire.

A study by Mainous et al. found that many more people (82%) know about doctors receiving office-based gifts as opposed to personal gifts (32%). The study utilised a population-based

sample as opposed to practice-based sample. A substantial group of people felt that gifts negatively impacted health care costs (42% for personal and 26% for office gifts) and quality of healthcare (23% for personal and 13% for office gifts). Amongst the respondents, these beliefs were more common in the ones with higher levels of education.

Lastly, a study by Gibbons et al. proposed a list of the same 10 gifts to doctors and patients. They noted that the gifts were rated by patients to be less appropriate and more likely to influence prescribing than how the doctors rated. Patients with higher levels of education (i.e. those who had completed high school) were more likely to think that the cost of gifts was passed on to patients. Before the survey, only about half of the patients (54%) had knew that physicians accepted such gifts. Out of those who were unaware previously, 24% commented that their perception about the medical profession is significantly changed after learning about such practices.

In conclusion, seven studies have been found to address the question of professionals' attitudes to gifts. Available studies demonstrated that although there exist a range of views about gifts, it is generally felt that gifts that were smaller or more relevant to helping patients were regarded to be as more acceptable. There is evidence that professionals believe that their acceptance of gifts goes below community standards and their own standards for other people in positions of responsibility. Three studies investigated lay peoples' attitudes towards physicians receiving gifts and they noted that only a minority of them disapproved of such practices as only a minority were aware that physicians received personal gifts from pharmaceutical companies. There was also a greater likelihood for people with higher levels of education were more likely to disapprove of such behaviours.

Do health professionals feel that discussions with sales representatives affect prescribing?

From Hodge's study, 35% of the psychiatry trainees felt that their prescribing behaviour were not influenced by discussions with sales representatives, although there was a lesser prevalence of this attitude among the more senior trainees. Sergeant et al. did a similar study on the Canadian family medicine residents with 34% of the physicians agreeing and 43% disagreeing that their prescribing habits were influenced by sales representatives. In the emergency medicine discipline, Keim et al.[10] reported having 75% of programme directors and 49% of the residents felt that promotional efforts from pharmaceutical companies affected the residents' prescribing practices. 70% of the Canadian doctors surveyed by Strang et al.[13] concurred that physician prescribing habits are affected by sales representatives. Lichstein et al. surveyed internal medicine residency programme directors and found that 31% of them were concerned and 13% were very concerned about the impact of sales representatives on the attitudes and prescribing behaviours of their residents. In the U.S., most of the family medicine residency programme directors felt that information and resources provided by sales representatives offered affected their residents and practising doctors' prescribing habits.

In India, Bansinath et al. stated that only 5-6% of Indian cardiologists felt that sales representatives played a role in their decision making between branded or generic medicines. In a Turkish city, 63% of doctors in a Turkish city surveyed by Güldal and Semin felt that information from sales representatives did not influence their prescribing. Those who found information from sales representatives reliable tended to report that this information had more influence on them. In a survey on American general practitioners by Pitt and Nel, sales representatives were rated as the third most influential factor in their prescribing decision, with advertisements and gifts ranked fifth and sixth respectively. The study had a low response rate,

with journal articles also being excluded from the list of possible influences. Hume and Shaughnessy surveyed clinical pharmacists from family medicine residency programmes and found that both journal articles and sales representatives were rates as the third most important source of drug information influencing the prescribing decision of family medicine residents. 91% of the resident doctors in Virginia surveyed by Sigworth et al. reported that sales representatives affect their prescribing decision. The authors suggested that the high rate could be due to recent publicity and discussion on these issues even though the residents did not have any formal educational sessions on drug promotion.

Many physicians in general deny that their prescribing decisions are influenced by drug representatives. Available data also seem to suggest that physicians tend to point out that other doctors are easily influenced than they themselves.

Do people feel that accepting gifts influences prescribing?

In a survey study conducted by Hodges, 56% of the psychiatry trainees surveyed were of the opinion that accepting gifts from the pharmaceutical industry did not influence their prescribing decision. Aldir et al. reported that very few doctors would think that a gift of a textbook would influence their prescribing habits (less than 6%). Similarly, the general consensus was that meals that were provided by the industry had little influence on them, although they did feel that free samples affected their prescribing. However, a study conducted by Barnes and Holcenberg reported that 60% of medical students and 75% of pharmacy students felt that prescribing decisions were influenced by promotional practices. Patients surveyed by Blake and Early also felt that gifts from the pharmaceutical industry to doctors were likely to influence prescribing (6% said it never did, 18% said rarely, 43% sometimes, and 16% frequently). Disapproval

against accepting of gifts (except free samples) were also more likely if the patients felt that they influenced prescribing and increased cost. However, a limitation of the study was that many of the patients were unaware that such gifts were given, and hence had little time to consider their opinion of them when completing the questionnaire. Eighteen per cent of the Turkish doctors in Güldal and Semin's study felt that gifts strongly affected prescribing, 12% felt they had a medium effect, 44% low, and 27% felt that they had no effect on prescribing.

Madhaven et al. found that physicians tend to think that other doctors' prescribing were more likely to be influenced by gifts as compared to their own. They noted that doctors with greater number of patients tend to feel that most doctors are not influenced by gift and that it is not inappropriate to be accepting gifts. At the University of Kentucky, a survey by Banks and Mainous evaluated a list of gifts from sales representatives and none of these was seen to influence prescribing by more than half the respondents. However, 66% of the faculty felt that personal relationships with the sales representative would influence prescribing. As compared to MD staff, PhD staff were more likely to think that prescribing decision is influenced by gifts. 67% and 77% of internal medicine faculty and residents by McKinney et al. felt that doctors would be compromised by accepting gifts, though others (23% of faculty members and 15% of residents) strongly believed that doctors could not be compromised despite the value of gifts received). In a survey of Ontario pharmacists, Cockerill and Williams[24] noted that 50% of the pharmacists felt that accepting benefits from pharmaceutical industry brought about a conflict of interest, although those who were licensed after 1980 had a lesser tendency to think so.

Most of the studies reviewed found that majority of the doctors would deny being influenced by gifts. Interestingly, many of the doctors are more willing to suggest that other doctors are influenced gifts as compared to themselves. Patient's attitude towards physicians accepting gift

is generally negative (apart from free drug samples) as they feel that it influences prescribing decisions.

Attitudes to direct-to-consumer advertising of prescription drugs

Since direct-to-consumer advertising of prescription medicines (DTCA) was introduced in the USA in the 1980s, spending on this have been increasing phenomenally, estimated to be around US$1.6 billion spent on DTCA in 1999. In a questionnaire study (Petroshius et al.) administered to doctors (general practitioners, family practitioners, internists and dermatologists) by sales representatives found that the older doctors and internists were less supportive of drug advertising, particularly for prescription medicine. Negative response to DTCA was noted in those aged above 50 years old, with a mean response of 2.84 on a scale of one to five, with one being strongly agree and five being strongly disagree. The authors noted that doctors' attitudes towards DTCA were indicative of their attention towards such advertisements as well as they responded to patients' enquiries and requests for advertised drugs. Doctors who do not accept visits from sales representatives were excluded from the study. In a survey of Texax doctors by Cutrer and Pleil, it was found that there were largely negative attitudes towards DTCA of prescription medicines, though the study response rate was noted to be very low (17%). Doctors surveyed had felt that DTCA would lead to increased demand for the medicines as well as increased queries by patients for the medicine. Active members of the American Academy of Family Physicians were surveyed by Lipsky and Taylor to examine their attitude towards DTCA and it was noted that physicians reported an average of 6.9 patients in the past six months requesting a specific prescription medicine, although it was not explicitly stated in the study that the physicians were asked specifically about patient requests arising from DTCA. 80% of those surveyed opposed to printing DTCA and 84% opposed to broadcasting DTCA.

Although there is some agreement about the possible positive outcomes of DTCA (56% agreed that it encourages patients to seek medical attention and treatment for conditions which may otherwise go untreated and 73% felt that it inform and alert patients to new products), there is also consensus with regards to the potential negative outcomes (89% disagreed that doctor-patient relationship are enhanced by DTCA, 71% felt that DTCA causes unnecessary pressure on doctors to prescribe drugs that they usually may not use, and 72% felt DTCA discouraged the use of generics). Hence, physicians in general are opposed to DTCA.

Studies of differences in attitudes to promotion (excluding DTCA)

A study by Peay and Peay noted two reasonably clear patterns among doctors. Physicians who report using journals as an important information source rated journals more highly as compared to commercial sources. Similarly, physicians who report using commercial sources more rated these more highly than journals. However, a group of around 15% of doctors had a consistent and exclusive reliance on commercial sources of drug information. Older physicians tend to cite sales representatives as providing information required for prescribing medicines whereas physicians who cited journals were the younger ones.

A study by Linn and Davis found that physicians who preferred medical journals to be a source of advice tend to possess a more conservative attitude in other areas as compared to those who preferred sales representatives. Thomson et al. surveyed New Zealand doctors and noted that physicians who reported seeing more sales representatives tend to have lesser peer advice available. 60% of the Ontario pharmacists who were surveyed by Williams did not place any restrictions on sales representatives visits, those it was noted that those who attained their license after 1980 had a higher likelihood to have restrictions. Surveying doctors form four teaching

hospitals in Pennsylvania, Andaleeb and Tallman found that those who treated a higher volume of patients had a more positive attitude towards sales representatives and tended to see sales representatives as providing informational and educational support. However, it should be noted that this study had a low response rate. Stinson and Mueller did a survey on 309 Alabama doctors and health professionals, noting that doctors with more professional experience tend to report using sales representatives and unsolicited medical literature more frequently than others. General and family practitioners also report using them more as compared to specialists.

A study by Evans and Beltramini noted that respondent GPs had a higher likelihood of soliciting information about prescription drugs from sales representative compared to specialists. Older doctors were more likely to rely on sales representatives for information compared to younger doctors. However, the overall doctors which they surveyed had a preference for non-industry sources of information for prescription medicine. It should be noted thought that the study had a low response rate and response bias was not assessed. County doctors in Oppenheim et al.'s study tended to rely more on sales representatives as a source of information on prices, compared to other doctors; county physicians and faculty members had limited knowledge of medicine prices and tended to overestimate them. Miller and Blum also found that doctors had limited knowledge of the price of advertised prescription medicines. This study of doctors attending a continuing medical education event had a low response rate.

Hospital pharmacy directors and pharmaceutical company sales directors were surveyed by Santell et al. about sales representatives' role in hospitals. Response rate was noted to be low, especially for sales directors. Most sales directors surveyed felt that the needs of hospital pharmacists were met by sales representatives 80% of the time, though most hospital pharmacy

directors felt these were met less than 61% of the time. In addition, they also disagreed about what services were important as well as how often they were provided.

In an international study of GPs' sources of medicine information, Hull and Marshall[61] reported that sales representatives were viewed to be very important in Sweden, Finland and Yugoslavia (now Serbia and Montenegro) as compared to countries like UK and Belgium. However, results of the study should be interpreted cautiously as the study had very low numbers and also no details were given about the selection process. Nevertheless, the study brings to attention the potentially large national differences in attitudes to promotion, which should be considered when interventions are being designed.

Physicians can be segregated into different groups according to the most used sources of drug information. Existing evidence from the literature point indicates that those who are reliant on information from the pharmaceutical industry tend to be those who are older, less conservative, see more patients, have lesser access to peer support. They also tend to be general practitioners as compared to specialists, and also have more positive attitudes to the use of drugs. Although the finding that older doctors and general practitioners have a great reliance on commercial information is supported by multiple sources, confirmatory evidence is lacking from other observations about differences between physicians using non-industry versus industry sources.

Physicians' attitude towards promotions vary and do not necessarily match their behaviour. There is also differing opinions on the value of sales representatives and if they should be banned during medical training as well as whether or not physicians have adequate training to interact with them. Although majority of doctors feels that information from pharmaceutical companies are biased, many think that the information are still useful nonetheless. Healthcare professionals

in general find it is acceptable to receive small gifts from pharmaceutical companies. Most believe that they are not influenced by sales representative or gifts but that many of their colleagues are. Very few patients are aware that doctors receive promotional gifts, and generally disapprove of such behaviour. Physicians who are reliant on promotion tend to be older, less conservative and see more patients. These physicians are usually general practitioners who have lesser access to peers and have a more positive attitude towards medicine. Opinions towards DTCA are also mixed whereby it is favoured by most pharmaceutical companies, the advertising industry as well as the media whereas physicians and others (e.g. government, NGOs and health professional organizations) oppose it in general. Consumers and patients are divided on this issue, with some of them (such as the less educated) welcoming more information from any sources available while others distrust and are concerned about the biases of commercial sources.

The impact of pharmaceutical promotion on prescribing behaviour

This is both the most difficult area to research and the most important. Doctors may not be aware of how much promotion they are exposed to. Therefore, as much as possible, research on the effect of promotion on behaviour should avoid relying on self-report data to show causal relationships. Self-report data are appropriate for finding out what people think is happening, or how they want to present themselves to others, but in this area, that may be far from the reality. This review looks at the evidence for several different possible effects of promotion on behaviour. These are the impact of promotion on individual prescribing behaviour, on overall drug sales, and on requests for formulary additions; the effect of DTCA on consumers' decisions, the effect of promotion on the content of continuing medical education courses, and the impact of industry funding on research outcomes.

In an ideal scenario, studies would utilise actual prescribing data before and after documented exposure to promotion while keeping other factors which influences prescribing constant. However, it is extremely challenging to create this in real life. Hence researchers often have to rely on self-assessments of exposure to or reliance on promotions and self-reported prescribing.

In this section, various approaches utilised to study how promotions affect physician prescribing is examined. One approach uses self-reported reasons that account for changes in prescribing and investigate whether or not promotions is mentioned to be one of these reasons. It is inherent in such approaches that the exposure to and relative influence of promotions is self-assessed by the physicians. Consequently, such approaches often do little more than allow the physician to present researchers with their self-image of being people who are, or are not, influenced by promotion.

Stronger evidence which elucidates some form of association between promotion and physician prescribing decision can be obtained from studies which examine the associations between variations in prescribing decisions and variations in reliance on promotion. Physicians are typically asked general questions in these studies, such as how reliable or useful promotional information is as well as whether or not such information is important in their prescribing decision. Comparison is then made between those who have a positive assessment of promotion and those are more sceptical. Real prescribing data may be used, or can also be self-assessed or elicited in response to hypothetical situations. A general consensus from these studies strongly suggest that doctors that rely on promotional information tend to heavier and less rational prescribers. They also tend to adopt new medicines earlier than those who are less reliant on promotion. However, a limitation of such studies is that it cannot demonstrate causal relationship between promotion and prescribing. Confounding of the results by other factors such as the

method of payment as well as practice setting. In addition, these studies are also unable to establish a temporal relationship between promotions and inappropriate prescribing – are physicians who tend to rely more on promotion may already be poorer prescribers to begin with, or does a reliance on promotion lead to poorer prescribing habits? Therefore, research in this area does not prove that prescribing decisions would improve if doctors had a lesser reliance on promotion.

The third group of studies examines the different levels of exposure to promotion (between doctors or over time), and prescribing. Specific drugs and the promotions related to them are explored in these studies, thereby providing the best kind of evidence that associate promotion with the changes in physician prescribing behaviour. Some of these studies include the ones done by Peay and Peay, Orlowski and Wateska and Gönül et al, provided rather convincing findings which are worth replicating in other situations and with other drugs so as to further validate the argument that being exposed to promotion results in changes in prescribing habits. Similar studies of this kind have also been conducted which are somewhat suggestive, but the value are limited by methodological shortcomings such as the possibility of a recall bias, uncertainty about generalizability, and reliance on self- reporting of prescription. Some do not provide sufficient methodological details, such as the method of selecting doctors to be surveyed, to allow a rigorous evaluation.

This section ends with a discussion of the effect of samples on prescribing. This is discussed separately because it presents different methodological challenges, so different approaches have been used.

Self-reported reasons for prescribing changes

A study done in Scotland by Taylor and Bond used real prescribing data, whereby they asked 201 doctors to fill out duplicate prescriptions that included details about perceived influences on prescribing. Of the prescriptions, most were either repeat prescriptions or drugs that the prescribers had prescribed in the past. New drugs formed a median of 3.5% of the prescription items per doctor. Sales representatives were mentioned as influences for 20% of new drugs added to doctors' prescribing repertoires during the research period. Sales representatives were more likely to be listed as an influence on the prescribing of drugs used short-term. It is difficult to know how generalizable these findings might be. They may depend on the type of drugs that are being heavily marketed at the time, and other influences on prescribing at the time (Taylor and Bond note the concurrent introduction of a 'limited list').

Dasta et al. also obtained objective prescribing evidence through their study which received partial support from Abbott Laboratories. Conducted in one inpatient and several outpatient medical care facilities, they examined physicians' sources of information about Clarithromycin. Physicians in the hospitals who ordered for clarithromycin were contacted via phone while a questionnaire was sent to physicians in outpatient facilities when a prescription written by them was sent to the pharmacy. At the first interview, 65% of the doctors in the hospital reported that they have not had any contact with sales representatives nor used any samples. 18% of the outpatient prescribers reported hearing about clarithromycin first from a commercial source.

Peay and Peay examined the role of different information sources in the specialists' decision making when adopting new drugs. The specialists were asked about their general drug adoption practices as well as one of one of eight target drugs. Their findings suggest that commercial information sources are relatively unimportant to specialists whereby only 4.7% named

commercial information sources as being the most influential in their decision making when prescribing the target drug.

These studies are better at identifying the influence of promotion than those that ask for a general self-assessment of the influence of promotion, because they isolate particular prescribing decisions. But they cannot be taken at face value because they rely on doctors' own assessments of what has influenced their decisions.

Two studies, by Curry & Putnam and Lurie et al., relied entirely on self- assessments of reasons for prescribing changes. The former found that only 0.3% of their respondents (practicing doctors in Maritime Canada) reported changing their practice in the last year because of discussions with sales representatives. The latter surveyed faculty at seven university teaching hospitals in the USA and house staff in two of the teaching programmes, about their interactions with pharmaceutical representatives. Twenty-five per cent of the faculty and 32% of the residents reported that they had changed their practice at least once in the last year as a result of a discussion with a sales representative.

Hence, to conclude, doctors rarely acknowledge that promotion has influenced them to make specific prescribing changes. Specialists tend to report that promotion has less effect on them.

Prescribing by those who rely on commercial information

A study by Hemminki observed no link between physicians' prescribing characteristics and self-reported reliance on promotion. Specifically, Hemminki noted that the observed frequency of prescribing psychotropic drugs did not differ between doctors who chose journals, textbooks or commercial sources as their primary source of information.

However, most other studies found links. A study by Mapes noted that doctors who reported relying on pharmaceutical industry literature had a greater likelihood of prescribing three or more drugs which frequently caused side effects. Using prescribing data collected by the Department of Health in the UK, it was found that doctors who did not endorse industry as a source of post-graduate knowledge tend to prescribe medicines that were newer, safer and more effective. Family physicians who reported having a lesser reliance on sales representatives (Bower and Burkett) tend to prescribe more generic medicines. Similar behaviour was also observed in residency trained doctors as well as regular readers of the New England Journal of Medicine. The self-assessed ability to recognise generic medicine names were also noted to be highest amongst doctors that had the least reliance on journal advertising and were regular readers of the Medical Letter. In Kentucky USA, a study by Caudill et al. found that primary care doctors and those who rated information from sales representatives highly (as credible, available, and applicable) and reported using it more tend to select more expensive prescribing options. However, the study had a low response rate. Becker et al. and Stolley et al. utilised self-reported data on the attitudes to and re. They noted that doctors who were reliant on journal articles who demonstrated disdain towards journal advertisements, sales representatives as well as retail pharmacists as sources of information received higher from the experts and also prescribed less chloramphenicol.

The study reported in Becker et al. and Stolley et al. used self-report data on attitudes to and reliance on promotion; expert ratings of responses to questions about prescribing for certain conditions, and knowledge about certain drugs; and analysis of actual prescribing of chloramphenicol (an antibiotic that should not be widely used). They found that doctors who relied on journal articles and tended to be disdainful of journal advertisements, sales

representatives and retail pharmacists as sources of information received higher ratings from the experts and prescribed less chloramphenicol. Better prescribers were more positive about generics, and gave other indications of a less positive attitude towards the industry and promotion than other doctors. A single question, about whether sales representatives were good sources of prescribing information about new medicines, produced the highest correlation with prescribing appropriateness. Berings et al. found that Belgian doctors in their study who felt that commercial sources of information were more important, prescribed more benzodiazepines than those who rated these sources as less important. Their prescribing was observed through the use of special prescription forms provided by the researchers.

In the Netherlands, Haayer presented eight case studies of hypothetical patients to GPs and asked them if they would prescribe medication for this patient, and if so, what they would prescribe. An expert panel assessed the rationality of their prescriptions. The GPs were later interviewed and asked about their use of different sources of information about medicines. Less than half (48%) of the prescribing decisions made were rated as ‘entirely rational’.

Differences between doctors accounted for more variance than differences between cases: that is, doctors seem to be more or less rational prescribers, over a range of different conditions. Haayer found that reliance on information provided by the pharmaceutical industry was negatively associated with prescribing rationality. That is, doctors who relied on promotional information wrote less rational prescriptions for the case studies than those who reported relying less on promotion.

Cormack and Howells did a survey on UK GPs before and after attending a course on benzodiazepine prescribing. Their prescribing habit was analysed using Prescription Pricing Authority data and adjusted by their number of patients and the number over 65 years old. A

very wide range of scores were produced and doctors were classified as high or low benzodiazepines prescribers. Through interviews, it was found that low prescribers viewed information from pharmaceutical companies with greater scepticism than high prescribers.

In Ontario, Williams and Cockerill found who reported writing higher weekly numbers of prescription had greater contact with the industry (i.e. interaction with sales representatives, accepting benefits such as meals or conference fees) and had a greater likelihood than others of rating sales representatives and industry-sponsored seminars as important sources of information. It was suggested that the higher prescribers may be likely to have spent more time in their medical practice per week compared to the lower prescribers. However, Williams et al. noted that the higher prescribers reported prescribing more medicines per patient, which reinforced the idea that these doctors are those who prescribed heavily. One other possible explanation of these findings is the notion that sales representatives selectively targeted doctors known to be heavier prescribers. These findings are shared by Williams, Cockerill and Lowry.

Evidence also suggest that those who have a greater reliance on promotion tend to be older, and are usually earlier adopters of new medicines. Stross investigated the reasons of changing the management of chronic airway obstruction in small community hospitals between 1978 and 1983. Through chart audits, he noted significant changes in the management of the condition during this period. Through the study years, he also interviewed the doctors who managed patients at these hospitals and found that older doctors reported having a greater reliance on sales representatives as a source of information for changing patient management. Stross examined the decisions to adopt three types of medicines - single-agent bronchodilators, beta-sympathomimetic agents and corticosteroid aerosols, with approximately 35% of doctors mentioning sales representatives to be their most important source of information for the last two

medicines when deciding to adopt them. Early adopters of the change had a greater likelihood than late adopters to regard sales representatives as a major source of information. Findings from this study is useful as it reports significant observed changes in prescribing that were identified by the researcher.

In an area in the UK, Strickland-Hodge and Jepson compared the characteristics of the first and last 100 doctors prescribing cimetidine. Despite having a response rate of only 50%, they observed that earlier prescribers tend to rate commercial sources of information significantly higher than that of the late prescribers. Examples of commercial information sources included sales representatives, advertisements in medical journals, direct mail, MIMs as well as controlled circulation journals. Early prescribers were also found to read more of their direct mail than late prescribers and tend to read fewer journals.

These studies collectively suggest that doctors who regard promotions more highly and report having a greater reliance on it as a source of information tend to prescribe more medicines and adopt newer medicines earlier than other doctors and also prescribe in a less rational manner. However, only circumstantial evidence exist for a causal link between promotion and individual prescribing. These results may partly be due to other doctor characteristics such as attitudes to risk, beliefs about clinical experience and evidence, views of new technologies as well as academic inclination or ability. For example, doctors who place a greater emphasis on their clinical experience over scientific evidence is less likely to respond to evidence presented in journals and hence may not prescribe as rationally i.e. according to the evidence. Doctors who are less academically inclined also may not read journals and have a greater reliance on advertising due to its accessibility, leading to less optimal prescribing habits. The main limitation

of these studies is that they cannot demonstrate that doctors who report reliance on promotional information would prescribe differently or more rationally had they not rely on promotions.

Prescribing and exposure to promotion

A relationship between seeing sales representatives and prescribing new drugs was showed by Peay and Peay in 1988 whereby they interviewed 124 private practice physicians with regards to their perception and use of temazepam (a benzodiazepine hypnotic) as well as their information sources about the drug. Conducted in 1981 (about a year after introduction of temazepam in Australia), they found that contact with a sales representative about temazepam consistently led to a favourable reception of the drug at various points of the adoption process. Physicians who had seen a sales representative reported earlier awareness and prescription of the drug. They also had a greater tendency to rate the drug as a moderate (rather than minor) advancement over other drugs, and were more likely to prescribe it routinely over other alternatives. Amongst the physicians who saw sale representatives, those who see them more than once a week were aware of the drug earlier and prescribed it earlier, with a greater tendency to prescribe it over other alternatives. Apart from contact with sales representative, Peay and Peay did not find any relationship between the physicians' professional involvement or involvement in the medical community and their beliefs about temazepam.

Advantages of this study include that it does not rely on physicians' self-assessment on whether or not promotions affected their prescribing decisions as well as their level of reliance on commercial information. Questions such as "have you seen a sales representative regarding temazepam?" requests for a simple fact that will be significantly easier for physicians to recall as opposed to questions such as the number of journal advertisements seen, etc. The group of GPs who had seen sales representatives about temazepam may have included more of the commercial

information oriented doctors described above, but this is unlikely to account completely for Peay and Peay's results.

Another important study was conducted by Orlowski and Wateska, who analysed the effects of drug company sponsored educational symposia in resort locations (all expenses paid trips) on physicians' prescribing. Utilising the pharmacy inventory, the use of two drugs were tracked within one institution 22 months before and 17 months after each symposium about them. Data on the national usage of these drugs were also collected, with informal interviews conducted with doctors who had attended the symposia. Majority of the physicians mentioned that their prescribing decision would not be influenced by the symposia, although some indicated that it may trigger them to think of the drug more and may also convince them on the benefits of using the drug. The authors noted a highly significant and dramatic increase in the usage of these drugs after the relevant symposia. However, these increases were not reflected in national data, nor do they seem to affect the hospital's use of alternative drugs. From this study, it indicates that promotions does have the potential to increase prescribing regardless of whether or not those exposed to it consider themselves prone to such influences.

The impact of visits by sales representatives and samples on prescribing was examined through a study by Gonul et al. The author used data from Scott-Levin Inc (a pharmaceutical consulting firm) derived from surveys administered to doctors, which included prescribing, minutes of detailing received for different drugs as well as the number of samples received in a typical week in each month from January 1989 to December 1994. A single condition was examined along with the seven drugs that are used to manage the condition. However, a major weakness of the study is that it is not clearly mentioned whether or not these were seven different drugs, or different d the probability of the medicine being prescribed (other things being equal). However,

from the study, it was also shown that no further increment in sales ibrands of the same drug. Through a multinomial logit model, exposure to personal selling towards a particular medicine i.e. sales representative visit and sampling increases observed from excessive detailing or sampling. In addition, promotions also had lesser influence on physicians who manages a high proportion of Medicare or Health Maintenance Organization patients. The authors also suggested that there was no negative social consequences associated with personal selling. However, there is little evidence in the study to support this from the study. It is difficult to evaluate the study's conclusion as it is unclear if the study examined seven brands of the same drug or seven different drugs. The health consequences in selecting different drugs in response to marketing are likely to be different from those of changes in different brands of the same drug.

Walton suggested that prescribing is also associated with the recall of print advertisements. A study in 1980 examined 1000 private practice doctors who were shown print advertisements whereby the drug and company names and logos were blacked out. The physicians were asked if they had seen the advertisement before. They were then read a list of the advertised products and asked if they had prescribed or recommended these in the last month. For 95% of the advertisements, the percentage of doctors who prescribed them were higher in those who were aware of the advertisements as compared to those who were not.

Research by Walton, a pharmacist and advertising executive, suggests that recall of print advertisements is associated with prescribing. In one study published in 1980, results are presented from a study of 1000 doctors in private practice who were shown print advertisements with drug and company names and logos blacked out. They were asked whether they had seen each advertisement before, and were then read a list of the advertised products and asked if they had prescribed or recommended these in the last month. For 95% of the advertisements the

percentage of doctors who prescribed them was greater for those aware of the advertisements than for those not aware of them. However, the effect of specialty was not controlled for. That is, doctors may be both more likely to notice and recall, and to prescribe, drugs relevant to their specialty. A similar study by Walton appears to be a smaller version or subset of this study.

A range of advertising industry-related studies was reviewed by Matalia. These studies claimed to show the effectiveness of print advertising. Advertisements were evaluated by family practitioners and internists in the first study.

Matalia reviews a range of advertising industry-related studies that claim to show the effectiveness of print advertising. In the first, family practitioners and internists evaluated advertisements. 'Prescribing data' were also collected but it is unclear whether these are self-assessments of willingness to prescribe, or actual prescription data. Matalia claims that as non-prescribers became more familiar with the advertisements their willingness to write trial prescriptions increased. It seems from his earlier description that this study assessed correlations between attitudes and familiarity with advertisements, so he seems to be extrapolating from data collected at one point in time from a range of people, to trends over time. The account of the second study is somewhat more convincing, but again the methods and analysis are not described well enough for proper evaluation. The study was an experiment where different groups of doctors (who had prescribed similar numbers and value of prescriptions in the previous six months) were sent identical journals but with varying numbers of advertisements for a mature cardiovascular drug (i.e. one that had been on the market for some time). Those in the group who received the most advertising increasingly prescribed the drug. After 12 months the manufacturers market share was 4% higher in the high intensity and 2.3% higher in the medium intensity group, than in the lower group. The third study was also a kind of experiment.

Companies stopped all promotion for four products from nine months before the study. Four advertisements were designed for the study and placed in half the copies of eight journals. Doctors were interviewed, and those who had received the advertisements were more likely to recall the products than those who had not. However, prescribing was not analysed: the outcome variable was simply recall of the products. To conclude, exposure to promotion influences prescribing more than some doctors realise.

Exploring the impact of samples on prescribing

There is little literature on the effect of samples on prescribing. Backer et al. report an ethnographic study of 18 medical practices. At least four weeks of fieldwork were done in each practice. Samples were used in 19.8% of the 1588 patient encounters observed. This varied widely between practices (range 4% to 39%) and also between doctors within each practice. Reasons given for using samples included, to test for efficacy and tolerability, to offer temporary relief or convenience, and/or to reduce costs to patients. In Morelli and Koenigsberg's study samples which were dispensed as new medication for chronic problems were accompanied by a prescription for the same brand 48% of the time. This finding is hard to interpret, but it may suggest that the availability of a sample influences the choice of brand prescribed. This area needs further investigation. Chew et al. used three hypothetical case studies and asked their respondents (131 general medicine and family physicians) which medicine they would prescribe. They were then given a list of samples available and asked whether they would prescribe their drug of choice, or give a sample of another drug. For a patient with hypertension (and no health insurance) almost all respondents (92%) ideally chose a diuretic or beta-blocker (consistent with practice guidelines). However, when samples were available, 27% (35 doctors) said they would dispense a sample. In almost all of these cases the sample was a different class of drug (e.g. ACE

inhibitor or calcium channel blocker). Almost all of those who would give a sample (97%) said avoiding cost to the patient was an important or very important reason for their choice. A follow-up scenario in which the patient returns, with their hypertension well controlled on the sample drug, and now with health insurance, was presented. Of the 35 doctors who had said they would dispense a sample, 24 would now write a prescription for the sample drug, to avoid switching the patient. If this reflects real behaviour, it suggests that in some circumstances drug samples may strongly influence prescribing. To conclude, samples appear to influence prescribing but more research is required on this issue.

Doctors' own assessments of whether promotion affects their prescribing are of limited value in establishing whether this is the case. The research clearly shows that doctors who report relying more on commercial information, prescribe more heavily, less rationally, and adopt new medicines more quickly. Some researchers have interpreted this finding as showing that 'relying on pharmaceutical company information increases prescribing'. This interpretation is not justified by evidence from these studies. The studies cannot show whether doctors would prescribe differently if their level of reliance on promotion were to change. Some doctors may have characteristics (such as attitudes, skills) that lead to both reliance on promotion, and heavy or irrational prescribing.

The studies that look at different levels of exposure to promotion (between prescribers or over time) and prescribing provide more convincing evidence that promotion changes behaviour. Further research using this kind of approach would be valuable. Simply replicating the Peay and Peay study in another place, using another drug, would strengthen the evidence considerably: similar findings would add substantial weight to the argument that contact with sales representatives does change prescribing behaviour. In addition, other studies that look at

prescribing changes after exposure to promotion would be very useful. Cormack and Howells and Strickland-Hodge and Jepson used prescribing data from the Prescription Pricing Authority in the UK. Such data could be utilised further to observe prescribing changes, for example, before and after visits by sales representatives. Other countries where all or most prescriptions are subsidised by the government, such as Australia and New Zealand, have similar data available.

Samples appear to influence prescribing, but this has received little attention and needs further study. Other literature has highlighted the widespread misuse of samples by health professionals, sales representatives and others, but ironically less is known about their use for patients. Marketing literature tends to assume that evidence of behaviour changes is a good outcome: it shows investment in advertising is worthwhile. The public health and medical based literature tends to assume that higher prescribing levels of what is judged to be a sub-optimal medicine will lead to worse health outcomes. Some of the research suggesting that doctors who rely heavily on promotion prescribe differently does explicitly look at the quality of the prescribing (e.g., Haayer's use of an expert panel, or the extent of chloramphenicol prescribing in the study by Becker et al.). Such measures of appropriateness need to be used more.

Conclusion

In order for patients to receive optimal care, there is a need for doctors to consider patient characteristics as well as the risks and benefits of new medicines. Constraints and limitations of healthcare budget should not be ignored since initiating treatment for one patient would often mean taking away therapy availability for other patients. Prescribing efficiently is complex and early adoption of new medicines takes into account the interaction between prescribers, patients, drugs as well as the interpretation of evidence. The decision to prescribe is influenced by

numerous variables interconnected in many ways which often can also be conflicting. Nevertheless, a thorough literature review on the phenomenon found some of the variables which demonstrated a consistent prediction of early adopters. On the prescriber level, adoption of new medicines tends to occur earlier among male general practitioners as compared to female general practitioners. Higher rates of new medicine usage are also associated prescribers with foreign qualifications or have graduated from recently formed medical schools. New medicine uptake is also influenced by the interest in particular clinical or therapeutic areas. Special-purpose drugs are more likely to be adopted early among the specialists as compared to generalists, while medicines used for a wide spectrum of therapies have a faster diffusion among general practitioners. Along the lines of clinical interact, participation in clinical trials is also a powerful predictor of early adoption. Lastly, the adoption process is also significantly influenced by prescribing habits where wider prescribing portfolio and a greater total number of prescriptions written for all types of drugs are associated with a higher probability for new medicine prescriptions.

On the patient level, factors which consistently predicted new medicine uptake include young age and high socioeconomic status – high level of formal education, high income, belonging to the majority race/ethnicity of the country. In addition, poor health status (as a result of poor response to existing therapies or due to comorbidities) also promotes the uptake of new medicines.

At the practice level, new medicine uptake is consistently associated with the volume of diagnostic and therapeutic activity whereby higher number of healthcare services delivered as well as increased severity of the patients' health status accelerated the adoption of new medicines.

Drug characteristics are generally measured qualitatively through the use of survey questionnaires and in-depth interviews, though an exception is in the amount of budget which companies put into the new drug launch whereby quicker adoptions is seen with higher marketing budgets.

Categorizing early and late prescribers according to other variables have not been possible, mostly due to inconsistent results. On the prescriber level, age of the doctor is a much debated characteristic whereby majority of the studies did not find an association. In studies that did note an association, it was in line with intuition that early adoption tends to be favoured by early age. Neither board certifications nor hospital affiliation demonstrated a consistent association with new medicine uptake.

At the patient level, characteristics of the early receivers of new medicines varied between different medicines, primarily depending on the therapeutic goal and target audience of the medicine. Neither gender nor marital status of patients were consistent predictors of early adoption. Old age however, favoured the adoption of medicines that were designed specifically for geriatrics.

On the practice level, variables which quantified the likelihood of new medicine adoption produced inconsistent results. Some studies suggest new drug uptake to be associated with group practices, though it is likely because of the larger numbers of patients requiring these therapies as opposed to professional stimulation from colleagues, although that still play a role. Location of practice (urban or rural) is also not a consistent predictor of new medicine uptake. This is likely because marketing activity and drug-related information has a good reach across geographic areas and hence a similar demand for the new medicines are stimulated in both urban and rural areas. Practice size, determined by prescribing volume or the number of patients, also does not

demonstrate a consistent association with new medicine uptake. Hence it is likely that individual doctor's innovative and conservative behaviours tend to cancel out one another when summed up at the practice level.

New drug launches are typically accompanied by huge amounts of data and information. In general, specialists tend to place a greater emphasis on established professional information when assessing safety and efficacy, whereas general practitioners have a greater reliance on commercial information. Pharmaceutical companies strive towards commercial information dissemination, providing knowledge and enhancing produce awareness while directing acquisition of further information.

Professional and social integration is an important factor influencing adoption, whereby information that is relayed through direct and personal contacts being especially powerful for new medicine uptake (Coleman, Menzel, and Katz 1959; Greer 1988; M. Y. Peay and E. R. Peay 1994; Weiss et al. 1990; Jones, Greenfield, and Bradley 2001; McGettigan et al. 2001; Tobin et al. 2008). Specialist peers seem to be the most powerful contacts among hospital consultants, whereas new medicine uptake among general practitioners is driven by both sales representatives and hospital consultants. This is possibly the richest medication of communication, exerting significant influence over uptake of new medicine and hence has major implications both pharmaceutical companies as well as healthcare strategists. Pharmaceutical companies should continue to dedicate a significant amount of their marketing budgets towards sales representatives while striving towards providing customized and scientifically valuable information for key opinion leaders. Concurrently, healthcare strategists need to navigate carefully with projects relying on electronic databases as efforts in utilizing objective information to improve prescribing has had ambiguous outcomes (Chauhan and Mason, 2008).

Preferably, healthcare strategists should rely and work with specialists towards a systematic dissemination of new drug information and prescribing guidelines.

Early adoption of new medicines is an extremely complex process. The diffusion of pharmaceutical innovations is the outcome of interactions among doctors' prescribing behaviours and their social networks as well as the pharmaceutical companies' product strategies, all within the healthcare institutional settings established largely by governments. Glass and Rosenthal (2004) controlled for the impact of pharmaceutical marketing on the adoption of new drugs, with their product strategy variable as an aggregate to reflect the marketing budget seize rather than prescriber demographic or practice characteristic, which is something to be examined in future research.

Individual characteristics of doctors and their social interactions are particularly important in influencing their prescribing behaviour. Research in the area of predicting doctors' prescribing behaviour has been challenging, both in the past and future, due to the complex and multifactorial nature of the phenomenon. As such, researchers have not been able to make consistently accurate predictions with regards to the early adoption of new drugs by doctors. Hence subsequent research investigating the early adoption of new drugs should focus not only on the specific characteristics of doctors, patients, pharmaceutical companies and drugs, but more importantly also towards the interactions among characteristics and social networks. Pioneering research in this have been done by lyengar, Van den Bulte and Valente (2011) who examined new drug adoption by combining individual level data, demographic as well as social network data on discussion and patient referral ties among doctors. Sales call data at the individual level was provided by a pharmaceutical company. After controlling for doctor-level marketing efforts, evidence of social contagion in new drug adoption was found by the authors.

Hence they argued that targeting heavy users (a common practice in the pharmaceutical industry) is a good strategy as these doctors not only have a higher customer lifetime value, but also a higher network value by exerting greater social contagion.

Administrative data available from health insurance funds (Pham et al. 2009; Barnett et al. 2011; Landon et al. 2012) may allow social network data to be combined and constructed by researchers with the doctors' sociodemographic and professional characteristics. Patient-sharing networks may also be constructed by researchers through such data, whereby a link between two doctors represents caring for the same patient, due to various reasons such as referral, patient self-selection, administrative rule, or even chance (Barnett et al. 2011). Early adoption of new drug is influenced by this as doctors have to communicate effectively and regularly with other doctors that share responsibility for the same patients in order to coordinate patient care (Pham et al. 2009).

To understand the diffusion of pharmaceutical innovations, the model is not that of pharmaceutical company-doctor-patient, but rather a model of doctor as the node of a network that involves pharmaceutical companies, other doctors (particularly specialists), patients as well as the drug characteristics. Being a form of social action, prescribing decisions require an understanding of the network within which lies the embedment of individual doctors.

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