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*Patient
Compliance and
the Need for
Technologies*

by Faiz Kermani



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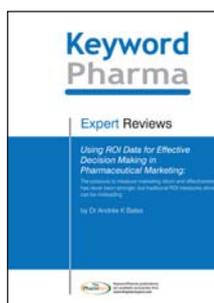
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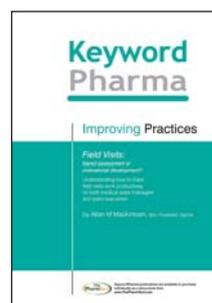
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Patient Compliance and the Need for Technologies

Faiz Kermani

Executive summary

Patient compliance is a widely used but often ill-defined term. It is also a significant challenge for the global healthcare market and all of its major stakeholders, with serious economic and societal implications. In the USA alone it is estimated that patient non-compliance costs the economy around US\$100 billion annually, including US\$8 billion in lost pharmacy revenues. Beyond this, patient non-compliance is proving to be a persistent thorn in the side of a growing global focus on improving health outcomes.

The ramifications for the pharmaceutical industry are huge. Many companies are seeking to develop alternative dosing and formulation strategies to tackle the problem. Studies have shown that once-daily and twice-daily treatments are most commonly associated with good compliance, while injectable medicines are considered the most respected among many patients.

But pharma companies appear very slow to adopt and embrace new interactive technologies to tackle compliance, despite growing evidence that they can help improve performance. Standard communications technologies such as email and SMS (Short Message Service) can now be deployed to deliver timely reminders to patients in routine care settings to take their medicines. But industry uptake is sluggish, perhaps because the escalating costs of traditional drug development are such that the sector appears cautious to invest further in another aspect of the R&D process, uncertain of the value it may provide.

Greater work, therefore, needs to be done to highlight the true value of new technologies in compliance programmes within pharma. But before that battle can be won, a thorough understanding of patient non-compliance and the factors that are central to it is essential. This Expert Review, *Patient Compliance and the Need for Technologies*, explains the background to patient compliance issues and sets the scene for an exploration of how technology can be harnessed to improve this significant but widely under-acknowledged challenge.

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Introduction



Tremendous advances have been achieved through the development of modern medicines, but their effective use is key to how successful they will be as therapies for patients. Therefore, healthcare improvements depend to a large degree on the willingness or ability of patients to take their medicines as instructed. These factors are often referred to broadly as 'patient compliance', with 'non-compliance' indicating the failure of patients to take medicines in their prescribed manner.

The issue of non-compliance is not a new one and has been investigated for many decades worldwide. However, since non-compliance reduces the quality of healthcare and can lead to dangerous consequences for patients, there is currently a renewed emphasis on the problem. In fact, patient non-compliance is taken so seriously in the USA that the *New York Times* has dubbed it the nation's "other drug problem". The economic consequences of non-compliance are profound. For governments and healthcare providers, non-compliance is a waste of valuable healthcare resources that exacerbates the heavy economic impact of major diseases. There are also significant financial implications for the pharmaceutical industry when patients do not adhere to their prescriptions, as recommended by their doctor, mainly due to lost revenue opportunities.

Growing efforts have been made by all parties in the healthcare sector to find optimal therapeutic approaches for patients. A range of technologies and product strategies have been developed to address the problems concerning patient compliance, but these can only succeed if other approaches are also included, such as involving patients as partners in decisions about their medicines. Equally important is a thorough understanding of patients themselves and their attitudes to the medicines they take. Social, economic and cultural issues all play a part in determining patient compliance. Furthermore, such factors can vary widely amongst populations across the world and so care must be taken in making assumptions on how a particular medicine will be accepted in different countries.

Faiz Kermani
May 2007

About the author

Dr Faiz Kermani has 15 years' experience in both academia and the pharmaceutical industry. He has worked in pharmaceutical R&D, pricing and reimbursement, marketing and medical education. Dr Kermani holds a PhD in Immunopharmacology from St. Thomas' Hospital, London, and a First Class Honours degree in Pharmacology with Toxicology from King's College, London. He has written extensively on international healthcare issues, and is on the editorial board of a number of publications, including *Contract Services Europe* (Advanstar Communications, UK), *Contract Pharma* (Rodman Publishing, USA) and *Medical Science Liaison (MSL) Quarterly* (MSL Institute LLC, USA). In March 2006, he was a delegate on the UK Government's Trade and Investment Biotech Scoping Mission to China and contributed to the subsequent report. Dr Kermani is co-editor of the multi-author book *Patient Compliance: Sweetening the Pill* (Gower Publishing, 2006), much of which forms the baseline for this expert review.

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Patient Compliance and the Need for Technologies

Understanding patient compliance

Although patient compliance would appear to be a well-understood term, this is far from the case. Historically, the act of taking or not taking medicines 'as directed' has had numerous words and phrases applied to it. Some of these are used exclusively in the clinical domain, some in the educational/social science area and others in the pharmacoepidemiology/drug utilisation research domain.¹ Care should be exercised as use of these terms is not always consistent. Some of the terminology currently used in the area of patient compliance is given in Table 1.

Term	Definition
Compliance	The degree to which a patient is compliant with the instructions that are given by a healthcare professional and written on the medication label (e.g. prescribed dose and time schedule)
Adherence	Same as compliance but requires the patient's agreement
Persistence	The length of time a patient remains on a drug
Refill compliance	The most common measure of compliance/adherence of populations taking medications under real-world conditions
Concordance	The mutuality of the process of care – the patient 'concord's' with the view of his/her physician
Grace period	A specified time during which a patient, apparently, has no drug available, but may not be considered as non-adherent or non-persistent

Table 1. Terminology used in the area of patient compliance.^{1,2}

For many observers, compliance represents the degree to which a patient is compliant with the instructions that are given by a healthcare professional and written on the medication label (e.g. prescribed dose and time schedule).¹ There may also be cultural differences in how this is interpreted. In France, the terminology for compliance is associated with 'observance', and derives its meaning and connotations from its historical interpretation in the context of religion during the Middle Ages.³ In the French sense, compliance can be taken to mean that the patient should follow the prescription

or advice provided by the physician 'religiously'. In the modern-day setting, compliance translates as the extent to which medications are taken at the dosage and frequency agreed between the prescriber and patient.

Another term that is often used interchangeably with compliance is 'adherence'. Generally, these terms have been taken to mean the same thing, but there is a school of thought that suggests a subtle difference.¹ In particular, a 2003 World Health Organization (WHO) report states that adherence requires the patient's agreement, which would suggest that compliance does not.² Some observers consider the term adherence to be rather authoritarian and so it has its critics.¹

A further complication in this field is the term 'persistence', which is used to describe the length of time a patient remains on a drug.¹ It is considered as a useful indicator of how, in the real world, medications meet the needs of patients. Persistence has to be reviewed in the light of the length of any 'grace periods' (specified times during which a patient, apparently, has no drug available, but may not be considered as non-adherent or non-persistent) that are allowed in a judgement of adherence that might otherwise suggest that persistence had ceased.

Although other terminology is also used, the terms compliance, adherence and persistence are sufficient to illustrate the care needed when operating in this field. For example, if, over a 100-day period, an individual takes 56 tablets spread out evenly, the compliance is 56%. Another individual takes 56 tablets on successive days and then stops; his/her persistence is 56 days. Yet another individual takes 56 tablets over 70 days and then none for 30 days. Over the first 70 days he/she is 80% compliant, but his/her persistence is only 70 days; however, over 100 days, he/she is 56% adherent.¹

There is, as yet, no standardisation of the terminology in the area of patient compliance

The variation in terms used can be partly explained by the different sources of drug use information, the precise type of data available or sometimes the tone of the message to be conveyed, particularly if work on behavioural science is being reviewed.² There is, as yet, no standardisation of the terminology in this area and so it is important to understand the various terms used

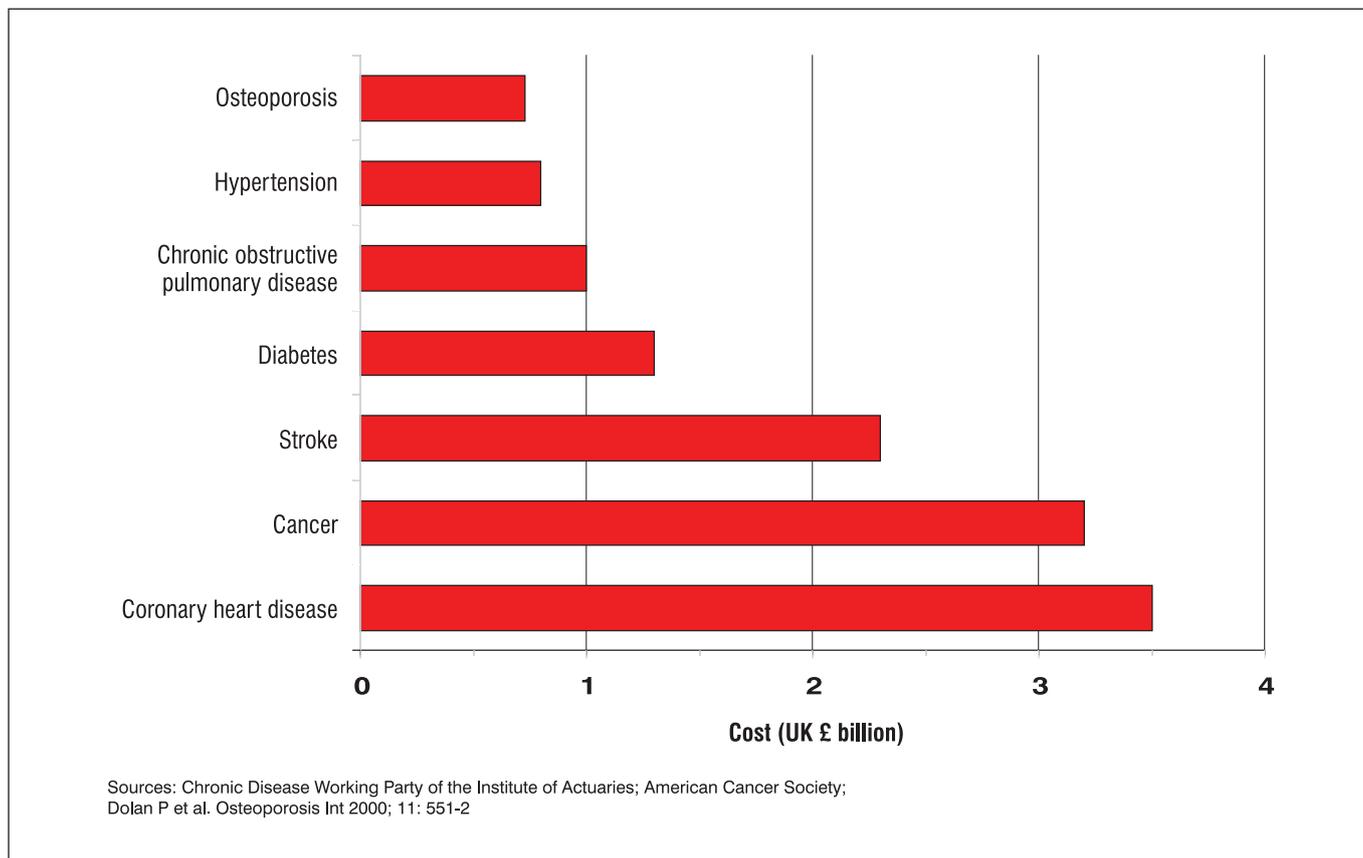


Fig. 1. Estimated annual economic burden for treating major diseases in the UK.

so that results from different compliance studies can be compared in a meaningful manner.^{1,4}

Economic consequences of non-compliance

Many diseases place a huge economic burden on society (Figure 1) and patient non-compliance has the potential to exacerbate this burden. Dubbed the USA's "other drug problem" by the *New York Times*,⁵ it has been estimated to cost the US economy around US\$100 billion per year and, of this total, lost pharmacy revenues account for US\$8 billion.⁶ With the allocation of healthcare resources becoming such an important issue for governments, healthcare providers are keen to tackle the problem of non-compliance.

Patient non-compliance has the potential to exacerbate the economic burden of healthcare

For the pharmaceutical industry non-compliance is also a problem, costing companies up to US\$70 billion each year,⁶ mainly from lost revenue opportunities. As people do not take their (often expensive) medicines as instructed and give up early on a medicine that could have had an impact on their disease, this has an impact

on the potential sales of that product.⁷ Companies have started to implement compliance programmes for patients and have also invested in developing appropriate formulations of drugs that might encourage better patient compliance.

At a more detailed level, the clinical and economic consequences of non-compliance depend on a number of factors. These include:

- the type and pattern of non-compliance
- the extent of drug forgiveness
- the degree of drug effectiveness
- whether the drug alleviates symptoms or affects the progression of the disease
- the severity and chronicity of disease
- whether or not rebound or withdrawal effects may develop.⁸⁻¹⁰

For drugs that are potentially life-saving, non-compliance may have profound negative effects. For instance, non-compliance with immunosuppressants in transplant patients may result in tissue rejection, which is associated with impaired quality of life and which may necessitate expensive remedial surgery.¹¹ By contrast, for expensive but often ineffective treatments (e.g. beta-interferon in unresponsive patients with multiple sclerosis), non-compliance in terms of failure to redeem prescriptions may prove to be cost saving and to have no significant impact on disease progression or symptoms.¹²

It remains difficult to predict the true economic impact of non-compliance with drug therapy, particularly as evidence relating to discontinuers is often not reported. In addition, a wide-ranging review of pharmaco-economic evaluations which considered compliance found many studies to have limitations in their methodology.¹³

For drugs that are potentially life-saving, non-compliance may have profound negative effects

Besides the clear absence of consideration of compliance in the evaluation of pharmaceuticals (only 22 studies were identified from a database of 3000 health economic evaluations), inadequacies were also noted in:

- the reporting of non-compliance
- assumptions relating to the health outcomes and costs associated with poor compliance
- how health economists model the impact of poor compliance.

Nevertheless, there are a number of health economic studies that illustrate the need to investigate non-compliance.

Study one: the impact of non-compliance for hypercholesterolaemia, diabetes, hypertension and congestive heart failure

A recent retrospective cohort study evaluated the impact of medication non-compliance on healthcare utilisation and costs for hypercholesterolaemia, diabetes, hypertension and congestive heart failure in 137,277 patients in the USA.¹⁴ Non-compliance was defined as the number of days' supply of maintenance medications, obtained from administration claims data, for each condition. For hypercholesterolaemia and diabetes, high levels of compliance were associated with lower disease-related medical costs. Higher medication costs were more than offset by medical cost reductions, producing an overall reduction in healthcare costs. For hypertension, medical costs tended to be lowest at 80–100% compliance, but differences were generally not statistically significant. Differences for congestive heart failure were not significant.

Increases in the risk of hospitalisation, defined as the probability of one or more hospitalisations during a 12-month period, were evident in all four conditions, as compliance levels declined.¹⁴ For diabetes, patients in the 80–100% compliance group had a 13% risk of diabetes-related hospitalisation, compared with 20% in the 60–79% group and 24% in the 40–59% compliance group.¹³ Similarly, for hypertensive patients, high levels of

compliance (80–100%) were associated with a reduced risk of hypertension-related hospitalisation (19% compared with lower levels of compliance (40–59%, 24% risk). When considering all-cause hospitalisation, a more pronounced difference was apparent, possibly an indication that non-compliance with one medication is associated with non-compliance with other medications for a comorbid condition(s).¹³

Study two: non-compliance in heart failure using plasma concentrations

In a novel study, intended and projected (based on compliance patterns) mean plasma concentrations of metoprolol in patients with heart failure were compared.¹⁵ It was shown, by use of pharmacokinetic modelling, that deviations from intended concentrations were associated with increased numbers of emergency department visits and hospital admissions. Thus, for metoprolol, maintenance of adequate plasma drug concentrations, achieved by patients compliant with the dosing instructions, results in improved outcomes and reduced healthcare utilisation.¹³

Study three: medication compliance in diabetes

Another interesting study involved using insurance claims as a measure of medication compliance in 57,687 diabetic patients, where it was noted that increased compliance was associated with decreased medical care costs.¹⁶ However, increased compliance was not associated with decreased overall healthcare costs because medication costs offset medical care cost savings.¹³

The potential impact of non-compliance on health benefits and on healthcare resource utilisation is considerable

The inclusion of non-compliance with medications is often omitted from health economic evaluations.¹³ As a significant proportion of evaluations are based on efficacy trials, attention should be given to issues of generalisability. In particular, as poor compliance is one of the most important elements responsible for the differences that may exist between the effectiveness and efficacy of interventions, greater consideration should be given to compliance when generalising from the results of a controlled clinical trial.¹³ An optimal cost-effective treatment strategy chosen on the basis of efficacy data may not be as attractive once 'real-world' compliance figures are taken into account.

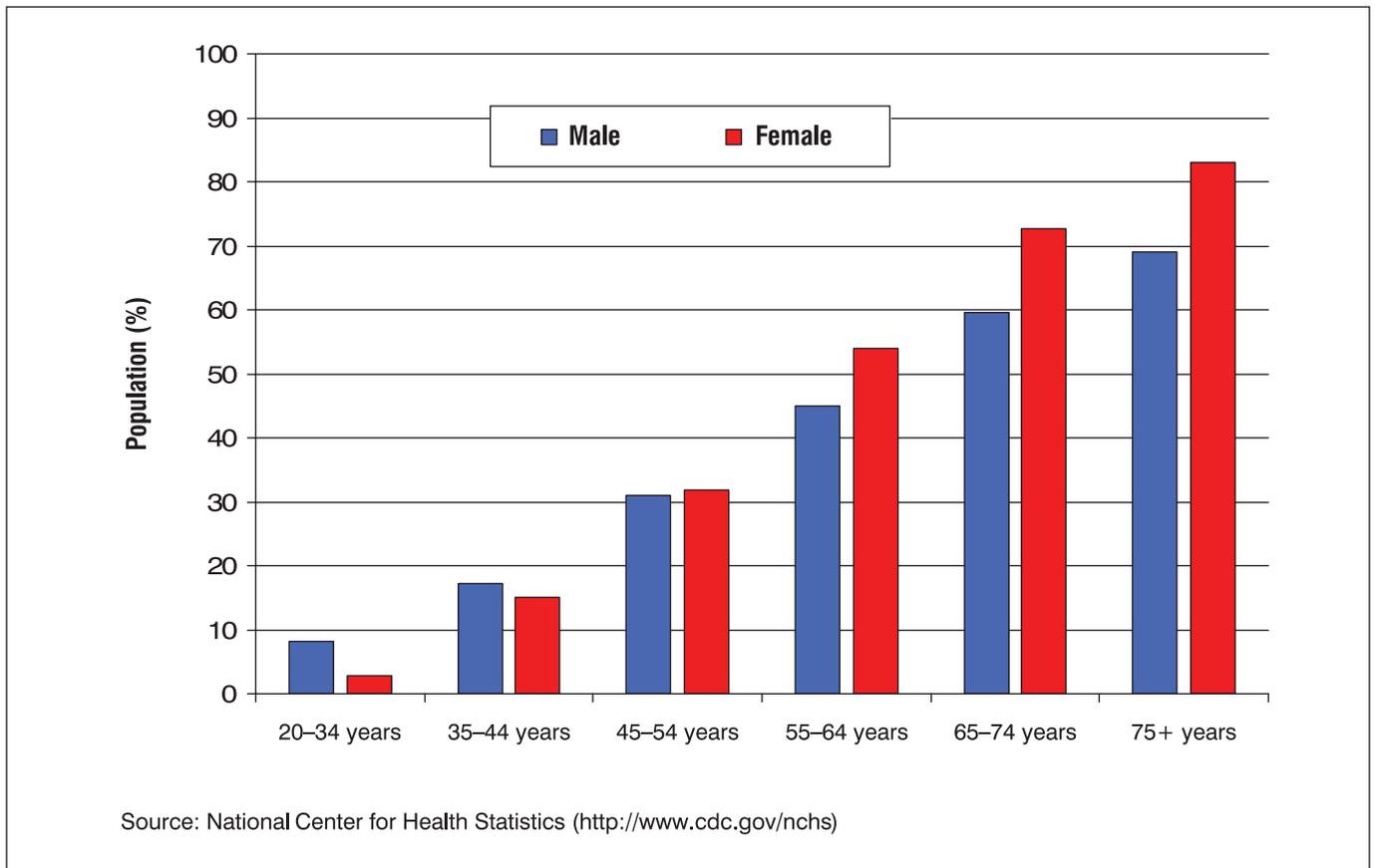


Fig. 2. Per cent of US population with hypertension.

Clearly, the potential impact of non-compliance on health benefits and on healthcare resource utilisation is considerable.¹³ Measures to contain costs and improve outcomes need to be evaluated. These may include programmes to improve compliance, which should be assessed in terms of their cost-effectiveness according to standard methodology. It may be that for treatments effective against serious conditions, where non-compliance significantly affects operational effectiveness, targeted programmes to improve compliance may be appropriate and promote cost-effective use of healthcare resources.

Compliance and chronic disease

When non-compliance has been studied in long-term disorders, all therapeutic classes and all diseases are affected. For example, this has been noted with medicines for the treatment of metabolic diseases such as hypercholesterolaemia or type 2 diabetes mellitus, and in long-term conditions such as hypertension or asthma.³ Patients suffering from serious infection also do not follow their prescriptions as required. Indeed, 57% of patients suffering from HIV infection have been found to be non-compliant with their medication;¹⁷ non-compliance was noticed only when patients were hospitalised as a result of serious side effects.³

Hypertension is one area that illustrates the need for better patient compliance. Hypertension is one of the most common conditions seen in general practice and represents a major public health burden (Figure 2).¹⁸ Despite the availability of effective treatments, and the fact that randomised clinical trials have demonstrated that the treatment of mild-to-moderate hypertension can reduce the risks of stroke and myocardial infarction by 30–43% and approximately 15%, respectively, the control of high blood pressure in the community is far from optimal.^{19–22}

A major reason for inadequate control of hypertension is poor compliance with the treatment regimen

Worldwide, hypertension is adequately controlled in less than one-quarter of patients afflicted with this condition.²³ This lack of blood pressure control could be due to a wide array of possibilities, including under-diagnosis and under-treatment of the condition, non-compliance with lifestyle modifications and non-compliance with medications. However, the main reason for inadequate control of hypertension is poor compliance with the treatment regimen, both pharmacological and behavioural (e.g. weight reduction, sodium intake restriction and exercise).²⁴

Poor compliance with antihypertensive drug therapy in asymptomatic patients has long been recognised as a major problem,¹⁹⁻²⁷ with estimates of 'good compliers' among patients receiving treatment for hypertension being as low as 20% in real-life situations. Up to half of patients being treated for hypertension drop out of care entirely within a year of diagnosis.^{19,26} Consequently, approximately 75% of patients with a diagnosis of hypertension do not achieve optimum blood pressure control.^{19,25,26} Good compliance has been associated with improved blood pressure control and reduced complications of hypertension.^{18,19}

Recommended actions
Provide clear, direct messages about the importance of a behaviour or therapy
Include patients in decisions about prevention, and treatment goals and related strategies
Incorporate behavioural strategies into counselling
Use evidence-based practice
Assess patient compliance at each visit
Develop reminder systems to ensure identification and follow-up of patient status (e.g. telephone follow-up)

Table 2. American Heart Association recommendations to enhance compliance.²⁸

A key issue is that the patient must take the decision to control their cardiovascular disease risk factors into his/her own hands, having first understood the rationale and importance of commitment to the therapy.¹⁸ The healthcare provider should provide clear, direct messages about the importance of a behaviour or therapy, in the form of verbal and written instructions, including the rationale for the treatment. Good communication skills are essential when involving the patient in decisions about treatment, utilising active listening, anticipating barriers to compliance and discussing solutions. The American Heart Association expert panel on compliance recommended a multilevel approach, involving patients, healthcare providers and healthcare organisations, and requiring educational and behavioural strategies (Table 2).²⁸

The patient must take the decision to control their cardiovascular disease risk factors into his/her own hands

Patient attitudes and the dynamics of compliance

Research shows that the most important factor determining whether, when and how patients take medicine is *their* beliefs about the medication.²⁹ Various

reports have shown that the way a patient thinks about a product depends on their age as well as on their health status.³ For example, among adults (aged 20–40 years) there can be a surprising mistrust of the medicine prescribed. Because the medicinal product is a chemical product, some consider it as potentially dangerous in comparison to a herbal product, which they consider to be safe. These respondents express fears concerning side effects and have concerns regarding the risk of becoming too dependent on a product.

In contrast, patients over 60 years old have a different opinion concerning medical products, and this is no doubt due to the fact that the majority are accustomed to taking medicines.³ Some among this category of patients often consider the product prescribed to have potential dangers, but they continue to take their medicine as it is seen as a means to maintaining a high quality of life, enabling them to carry out normal everyday tasks. In a sense, they accept the possibility of side effects from the medicine as they believe that it is an unavoidable risk associated with the use of the medicine, and they evaluate this risk in the general context of how they wish to live their lives and not be dependent on others.

Another reason for the different opinions of this category of patients regarding medicines is that they are old enough to have witnessed tremendous changes in healthcare and appreciate the benefits that modern medicines can bring to their daily life.³ For example, early in the 20th century, very few people could afford to go to a physician and a drug would have only been prescribed in extreme circumstances. During this time, deaths from conditions such as asthma, bronchitis and tetanus were commonplace in many countries.

A lack of compliance is essentially due to a combination of different factors. It should be considered as a dynamic phenomenon, which changes over time.³ The same patient will not be compliant in the same way over time even if there is no change in extrinsic factors. Patients take their medicines when the disease they suffer from presents apparent symptoms, which make them feel conscious of the disease. What tends to occur is that patients remain compliant with the medication prescribed when the symptoms prevent them from having a normal life. This is certainly the case when diseases are associated with pain.

In contrast, patients suffering from metabolic diseases such as hypercholesterolaemia or type 2 diabetes are not very compliant with their medicines.³ In most cases, the only sign of the disorder they suffer from is abnormal haematology or biochemistry, and this tends to have little direct meaning for the patient. In asthma, the majority of patients take medicines when they suffer from an asthma attack, as this is when they become conscious of the disorder having an immediate impact on their daily life.

As well as patients needing to be conscious of the disorders they suffer from, they must also accept their condition in order to be compliant. A lack of acceptance is a very common phenomenon in conditions such as

HIV infection,³⁰ epilepsy or mental diseases such as depression or schizophrenia. The fact that such diseases are still considered to be taboo by society in general certainly does not help the situation.

Patients therefore need to develop a more realistic understanding of the risks and benefits of their medicines, and this will only happen when health professionals enter into more open dialogue with patients about treatment choices. Efforts to improve compliance have in the past focused on providing education and clearer instructions about medicines, both in writing and face to face. Future success will involve looking at the problem of compliance from the patient's perspective. It is increasingly recognised that the key to making better use of medicines is involving patients as partners in decisions about their medicines.²⁹

The nature of the medicine

The nature of the drug itself and its effects can have a strong bearing on the degree of patient compliance. As well as the way patients think about medicines, the formulation prescribed should be suitable in terms of their lifestyle, age or health condition.³ Patients expect a drug to treat a disease or symptoms, not to provide discomfort or further symptoms. The concept of a risk/benefit ratio is unfamiliar to the majority of the population and, even in cases where patients are aware of the potential risk and seem to accept it, their demeanour will change when they experience a side effect.

The most respected formulation of a medicine, according to many patients, is the injectable medicine

The dosage formulation also plays an active role in the way patients comply with their prescriptions. Patients do not consider different formulations of a medicinal drug to have equal importance.³ Indeed, many patients of all age groups tend to classify a medicine according to the formulation, not the active ingredient. On this scale of value, the most respected formulation of a medicine, according to many patients, is the injectable medicine. According to this perceived view, an injectable formulation is a medicine that 'deserves' to be taken according to the strict requirements of the prescriber.³ Moreover, as the patient is often in a hospital setting, a nurse will administer the injection, and this conveys even greater importance upon the product.

Oral dosage formulations are also ranked highly by most patients. They are also popular with healthcare professionals as they are easy to handle, manufacture, dispense and administer. It has been noted, however, that even among the oral formulations available, there can be variations in their acceptance depending on the market in question. For example, sales of tablets

tend to be considerably higher in Japan than sales of capsules.³¹ The preference of Japanese patients for tablets, which they consider easy to swallow, partly explains this observation. However, the other reasons for the trend towards tablets result from the physical properties of typical new drug candidates and the preference of Japanese pharmaceutical scientists to explore this formulation strategy.³¹ Another interesting aspect is that granules and powders are popular with Japanese consumers. The tradition of Chinese herbal medicines, which are administered as powders, has heavily influenced the Japanese patient in this respect.³¹ Hence, the route of administration is not specific enough to predict optimal compliance and companies must determine which formulation is most acceptable to the patient.

Non-compliance is also due to factors inherent in the patient. Among these various factors, the social group the patient belongs to heavily influences the way he/she will interact with the physician and medicine prescribed. Patients with a good level of education and adequate financial means will be more compliant than poor patients in the manner that they buy medicines that are not reimbursed by healthcare systems.³ However, at the same time, this category of patients has a better medical knowledge picked up from the television, the internet or magazines. Better information makes the patient more demanding (Figure 3). One interesting observation is that the greater the degree of education patients possess, the less trustful of physicians they appear to be.³ Their qualifications may make them believe that they possess the skills to better analyse their physician's decisions, and they are more likely to have the confidence to challenge the physician's judgement.

Using technologies to improve compliance

Interactive technologies can provide a valuable component of compliance and disease management programmes, and can be used independently or in combination with human operator interactions.³² In particular, the electronic collating of patient-reported outcomes using either 'gold standard' or bespoke instruments and diaries provides a valuable opportunity for patients to become more engaged with their treatment and to obtain appropriate and motivational feedback on their progress. Where possible and appropriate, this feedback can provide useful insights to enhance the physician-patient meeting, either by direct reporting of outcomes to the physician or by providing reports that the patient can bring to their appointment.

Patients find these approaches helpful when they are used to provide positive and useful benefits toward their health-related and personal goals.³² In 2003, the *Wall Street Journal* reported that 80% of patients forget most of their doctor's instructions immediately after an office visit.³³ In addition, half of what they think they remember

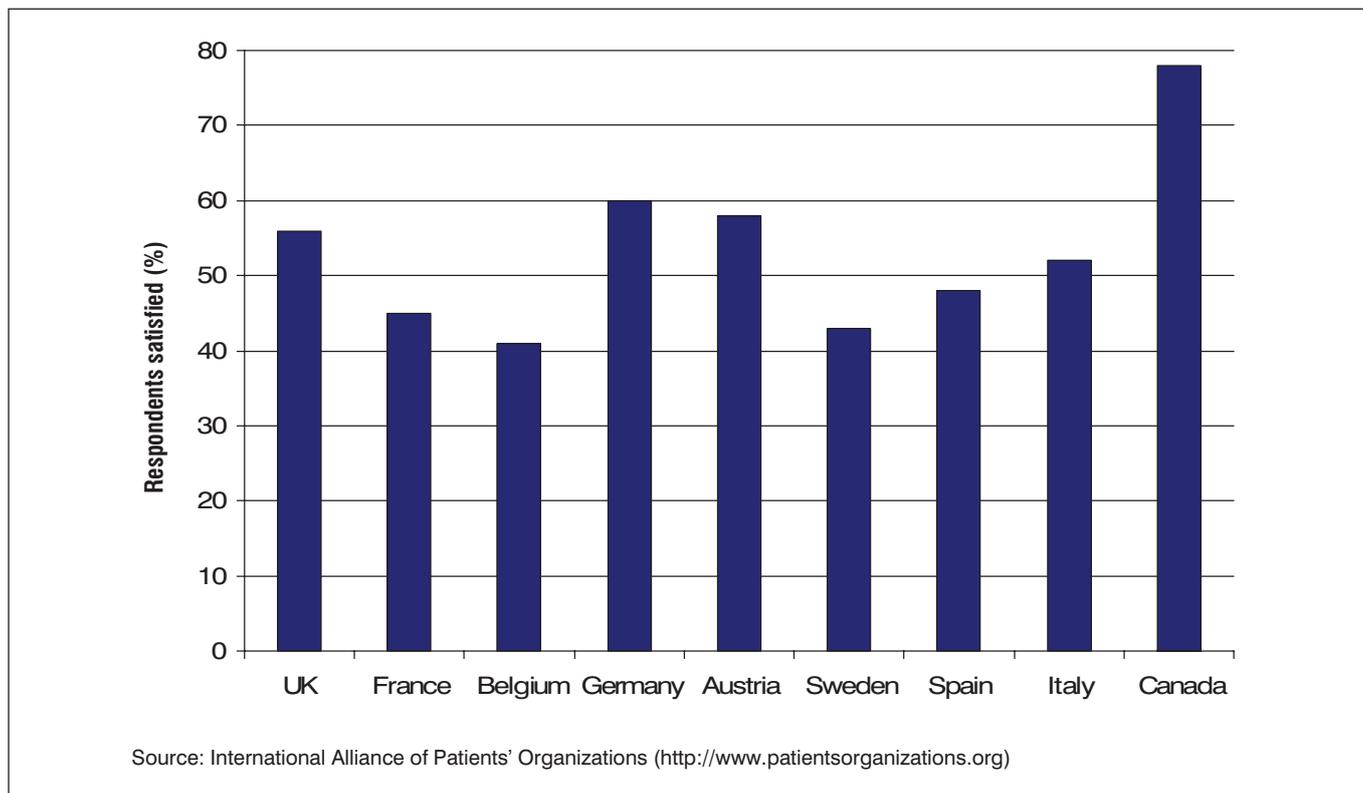


Fig. 3. Patient satisfaction with ability to access information on new medicines or treatments.

is actually incorrect. Therefore, use of interactive communications technologies for follow-up after an office visit has the potential to increase patient's recall and understanding regarding treatment.³² Additionally, the use of such communications prior to an office visit may facilitate more effective communication between the doctor and patient.

Interactive technologies can provide a valuable component of compliance and disease management programmes

Communications technologies such as email, SMS (Short Message Service) and outbound recorded telephone messages have been successfully employed to deliver reminders to patients in routine care settings. In a disease management or compliance programme these messages might, for example, serve to remind the patient to take their medication as scheduled, or to obtain a repeat prescription at the appropriate time.³² Making these messages interactive enables not just the delivery of a message; in addition, simple feedback can be collected to enable the programme to be tailored to the individual needs or behaviour of the patient.

An analogous interactive reminder message using SMS may consist of three messages (two outbound to the patient and one reply sent by the patient to the central computer).³² This could take the form of the

patient responding through keying in a number to a set question sent with a reminder (e.g. 'Do you have a new prescription?' or 'Do you intend to stop taking the drug?').

Email reminders

Email reminders, as an option for patients, can operate in two ways.³² First, in a similar way to SMS, patients can respond to an email message, which in turn triggers an automated 'thank you' email. Alternatively, an email can contain links to a secure website at which feedback can be entered. The choice of solution will depend on the quantity of information to be collected, but generally it is anticipated that only small amounts of focused feedback will be collected during a reminder message.

Much published work shows the value and success of these techniques in providing reminders, collecting outcomes, and providing education and counselling.³² Patient acceptance of these approaches has tended to be high. One published review found the use of outbound recorded messages in 19 clinical studies (including paediatric and adult studies involving 16–3158 individuals) to have been beneficial in increasing compliance among patients and caregivers, and in improving health outcomes.³⁴

SMS reminders

Another interesting finding comes from a study in South Africa, where an SMS reminder system was constructed to enhance medication compliance among patients

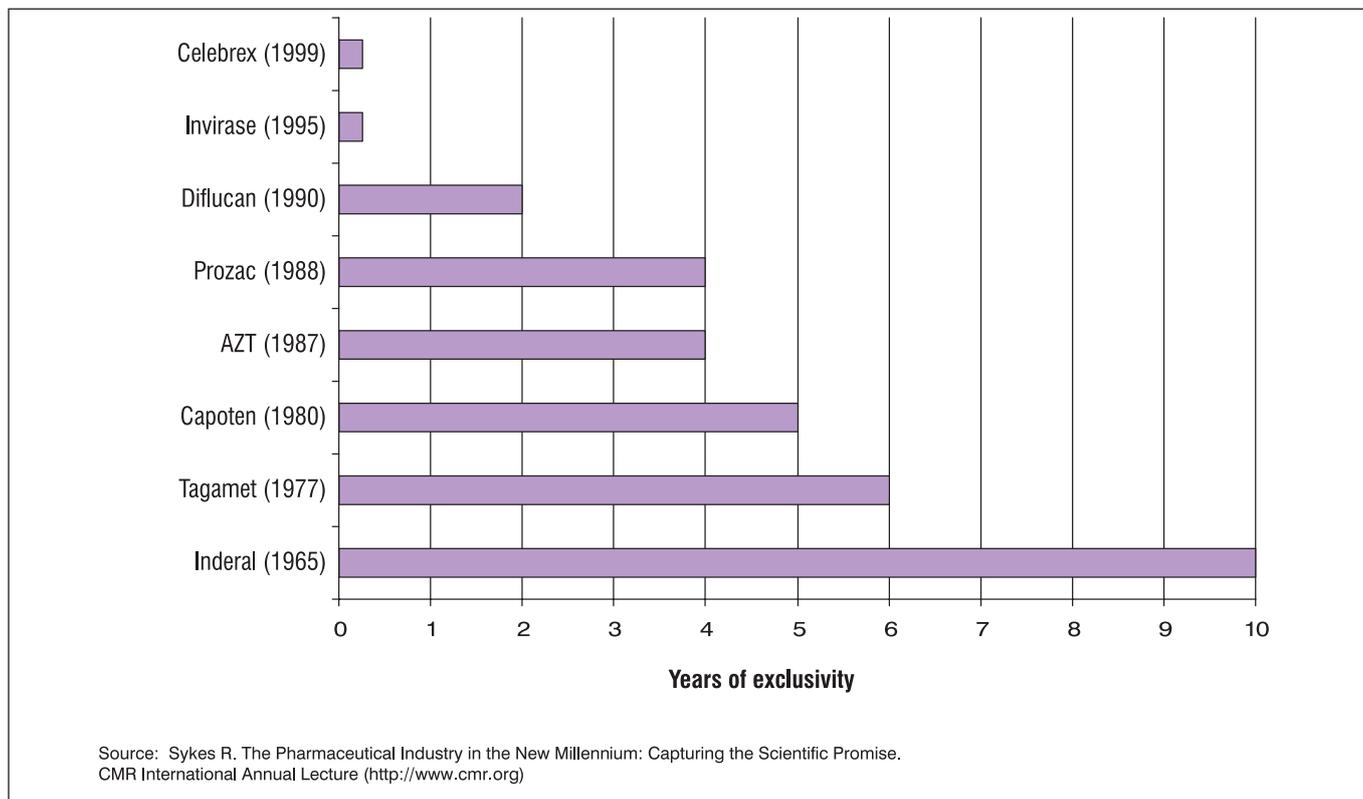


Fig. 4. Periods of market exclusivity between launch of innovative medicine and competitor products.

suffering from tuberculosis in Cape Town. The treatment of tuberculosis requires adherence to a strict regimen, usually four tablets five times a week for 6 months.³⁵ Poor adherence to treatment regimens results in a low cure rate and an increasing incidence of multidrug-resistant strains of the tuberculosis virus. Interestingly, despite the disadvantaged socioeconomic background of many among the local population, over 50% of people in the Cape Peninsula and 71% of tuberculosis patients at the clinic studied had access to a mobile phone.³⁵ SMS messages were issued on a regular basis to over 300 patients reminding them to take their medication. More than 300 patients were involved in the pilot study, in which there were only five treatment failures, a result so successful that the scheme has been identified by the WHO as an example of best practice.^{33,35}

In addition to providing value to the treating physician, compliance and outcomes information is important to managed-care organisations, healthcare insurers and other payers.³² These organisations have a vested interest in ensuring that patients adhere to their treatment, use their prescriptions properly and receive quality care from their doctors. It is not difficult to recognise the value of helping a patient to take a medication that will prevent costly hospital visits.

Compliance programmes collecting health outcomes, quality of life, compliance and patient satisfaction data provide a rich stream of information valuable in additional product marketing and public relations campaigns.³² Although sponsor companies may not obtain individual data, aggregated reports provide a rich picture of the treatment under naturalistic conditions. Such reports

of data collected across a large population of patients may influence future prescribing attitudes. Subsets of data may also be reported on a regional level, providing medical sales representatives with useful relevant information to discuss in doctor meetings and to use as a lever to see doctors who may otherwise be reluctant to devote time to a meeting.³²

Patient compliance and the pharmaceutical industry

The pharmaceutical industry is aware of the importance of non-compliance and has made considerable advances, particularly with respect to dosing and formulations. A good example of the way the industry has attacked the problem of non-compliance is illustrated by the antiretroviral treatment of HIV infection. Clinical data suggest that near-perfect adherence to therapy is required for a maximal response to HIV therapy, but compliance rates in studies have been shown to vary between 33% and 100%, and often decrease over time.³⁶

One study has also shown that whereas once-daily and twice-daily treatments are associated with good compliance, this is not the case for treatments that have to be taken three times a day.⁴ It was concluded that once- or twice-daily treatments are more successful as they fit in better with patients' lifestyles. Similarly, the use of fixed-dose combination antiretrovirals, which contain two or three antiretroviral drugs in a single formulation, can improve compliance. The use of these combination antiretrovirals also helps in preventing suboptimal therapy that can lead to viral resistance.³⁷

One area where many pharmaceutical companies have seemed less assured is in using technology options to improve patient compliance. As has been seen, there is now a wide range of interactive technology options available and these have been shown to improve compliance and have proved popular with patients and healthcare providers. The issue appears less to do with the technology and more to do with understanding how it fits in to the general R&D process and the value it can provide.

The pharmaceutical industry is aware of the importance of non-compliance and has made considerable advances, particularly with respect to dosing and formulations

Justifying expenditure on pharmaceutical R&D is always a difficult exercise. A worry for companies is that, as the cost of new drug development continues to rise, the revenue they must generate to recoup R&D investment and associated promotional activities for products must increase correspondingly.³⁸ In 2001, the Tufts Center for the Study of Drug Development (CSDD) estimated the cost of successfully getting a drug to market at around US\$802 million and raised this figure to US\$897 million in 2003.³⁹

One area where many pharmaceutical companies have seemed less assured is in using technology options to improve patient compliance

Another feature of drug development is the high failure rate. According to the CSDD, only 21.5% of drugs entering phase I trials gain market approval,³⁹ whereas CMR International has estimated that only about 15% of new drugs entering development subsequently reach the market.⁴⁰ Although the chances of a new drug reaching the market increase at each stage of the R&D process, the failure rate at the latter stages of development remains high. Success rates from phase III to market can range between 50% and 70%.⁴⁰ Therefore, with these initial considerations at the forefront of their minds, it can be difficult for senior managers to invest in additional technology aimed at compliance. However, the pharmaceutical market is all about adding value to products and so compliance programmes must be viewed with this in mind.

With many innovative compliance technologies on offer, senior managers may be unsure as to which option

to choose, but they should realise that this is far from being an untested and risky field. Thus, the value of compliance technology needs to be illustrated to these personnel with examples so that they understand how it supports their product on the market. Rather than being considered an additional technological risk factor in the R&D process, compliance programmes will add value to the end product. In an increasingly crowded and competitive pharmaceutical marketplace (Figure 4), the value of being able to establish a high degree of patient compliance with a product should not be underestimated. In addition, as those behind these technologies work across therapeutic areas they may be able to bring a degree of objectivity to the compliance goals being set. Although some initial investment will be required for the compliance technology, it will serve to add value to the company's offering on the market and allow it to maintain a competitive edge over rival products that do not feature measures to improve compliance.

The value of being able to establish a high degree of patient compliance with a product should not be underestimated

Patients are having a greater influence on healthcare than ever before and any improvements in compliance will be seen to directly benefit them.³⁸ Thus, the incorporation of a compliance programme into the pharmaceutical company's efforts effectively acts as a support measure for the healthcare of patients and may also engender positive publicity (Figure 5). Similarly, these programmes will fit in with the goals of healthcare providers who want to ensure better clinical outcomes and a more effective use of healthcare resources.

The incorporation of a compliance programme into the pharmaceutical company's efforts effectively acts as a support measure for the healthcare of patients

Furthermore, by using compliance programmes, companies will gain a better understanding of which factors are influencing how patients take their medicines. This information will prove of immense value to future drug development projects, whether in guiding efforts at the R&D stage or in positioning the product in the run-up to a global launch. In essence the value of using compliance programmes will extend far beyond the initial project that they are used for.

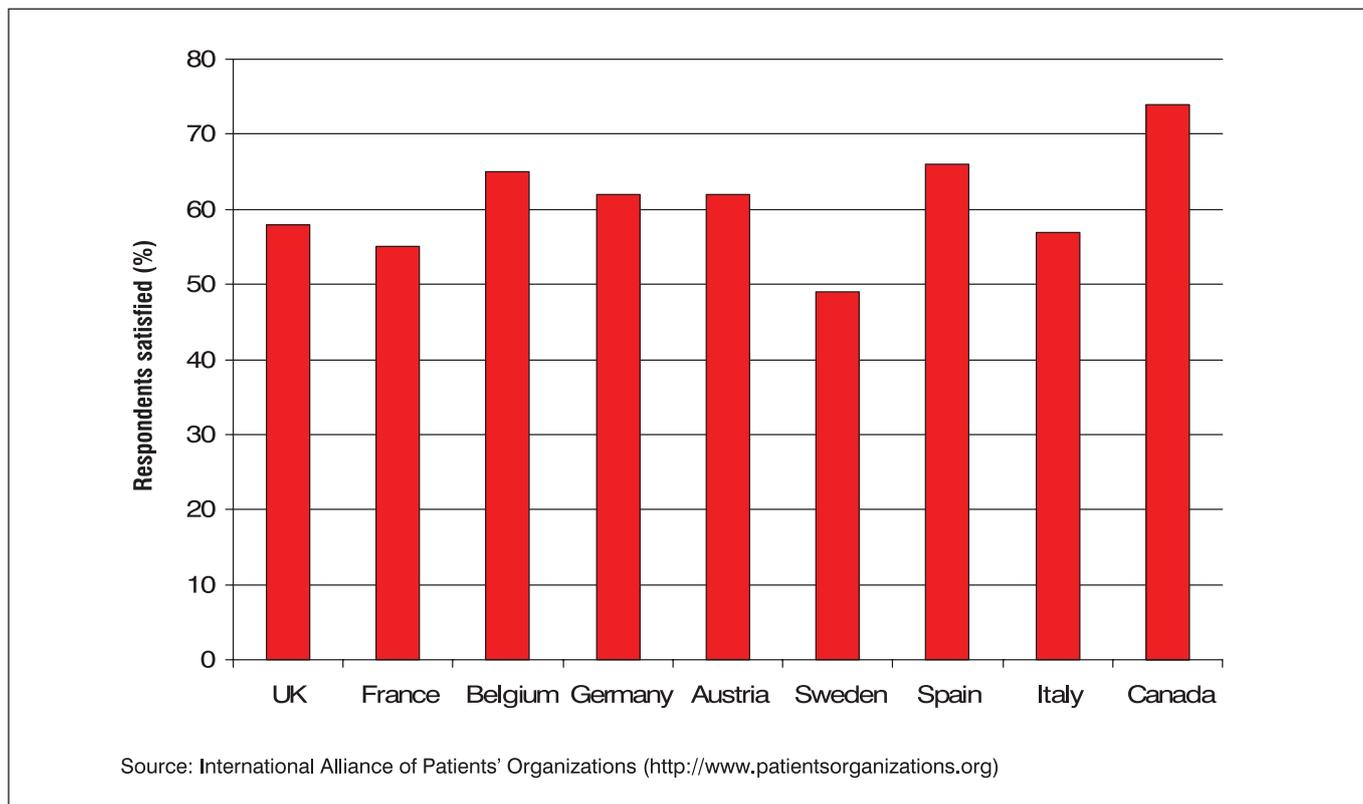


Fig. 5. Patient satisfaction with quality and effectiveness of healthcare received.

Conclusion

We must appreciate that there is no universally applicable means of improving compliance. What works in one particular therapeutic area may be inappropriate for another and what works in one country or region may be of little use elsewhere. What we can conclude is that, by having an open and proactive approach to compliance issues, we may be able to draw upon a range of options from different scenarios and modify them to suit the particular situation that faces us. Addressing compliance must be viewed by all stakeholders as a key part of delivering value in healthcare.

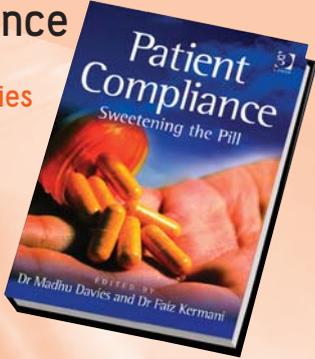
References

1. Parkinson J, Wei L, MacDonald TM. View from the real world. In: Kermani F, Davies M (eds). *Patient Compliance: Sweetening the Pill*. Aldershot: Gower Publishing Limited, 2006: 7-21. ISBN-13: 978 0 566 086588.
2. World Health Organization. *Adherence to Long-term Therapies: Evidence for Action*. World Health Organization, 2003. ISBN: 92 4 154599 2.
3. Narayan-Dubois C. Patient compliance: a French perspective. In: Kermani F, Davies M (eds). *Patient Compliance: Sweetening the Pill*. Aldershot: Gower Publishing Limited, 2006: 57-68. ISBN-13: 978 0 566 086588.
4. Kermani F, Davies M. Patient compliance: setting the scene. In: Kermani F, Davies M (eds). *Patient Compliance: Sweetening the Pill*. Aldershot: Gower Publishing Limited, 2006: 3-6. ISBN-13: 978 0 566 086588.
5. Zuger A. The "other" drug problem: forgetting to take them. *New York Times* 1998; 2 June.
6. Center for Business Intelligence Annual Forum on Patient Compliance. 3-4 October 2002, Philadelphia, PA.
7. Carkeek P. Cultivating compliance. *Pharmaceutical Executive* 1 May 2006. Available at www.pharmexceurope.com/europharmexec/article/articleDetail.jsp?id=321971
8. Hughes DA. Economic impact of poor compliance with pharmaceuticals. *Expert Reviews in Pharmacoeconomics & Outcomes Research* 2002; 2: 89-97.
9. Hughes DA, Bagust A, Haycox A *et al*. Accounting for noncompliance in pharmacoeconomic evaluations. *Pharmacoeconomics* 2001; 19: 1185-97.
10. Cleemput I, Kesteloot K. Economic implications of non-compliance in health care. *Lancet* 2002; 359: 2129-30.
11. Dobbels F, De Geest S, van Cleemput J *et al*. Effect of late medication non-compliance on outcome after heart transplantation: a 5-year follow-up. *J Heart Lung Transplant* 2004; 23: 1245-51.
12. Hughes DA, Bagust A, Haycox A *et al*. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: A review of the literature. *Health Econ* 2001; 10: 601-15.
13. Hughes DA. Health economic aspects of patient non-compliance. In: Kermani F, Davies M (eds). *Patient Compliance: Sweetening the Pill*. Aldershot: Gower Publishing Limited, 2006: 23-40. ISBN-13: 978 0 566 086588.
14. Sokol MC, McGuigan KA, Verbrugge RR *et al*. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005; 43: 521-30.
15. Tu W, Morris AB, Li J *et al*. Association between adherence measurements of metoprolol and health care utilization in

- older patients with heart failure. *Clin Pharmacol Ther* 2005; 77: 189-201.
16. Hepke KL, Martus MT, Share DA. Costs and utilization associated with pharmaceutical adherence in a diabetic population. *Am J Manag Care* 2004; 10(2 Pt 2): 144-51.
 17. Vous avez dit observance? *Actions Traitements* 2004; 1 January. Available at www.actions-traitements.org/article.php3?id_article=445 [in French].
 18. Peterson GM, Jackson SL. Patient compliance in the prevention and treatment of cardiovascular disease. In: Kermani F, Davies M (eds). *Patient Compliance: Sweetening the Pill*. Aldershot: Gower Publishing Limited, 2006: 43-56. ISBN-13: 978 0 566 086588.
 19. World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action*. World Health Organization, 2003. ISBN: 92 4 154599 2.
 20. Schroeder K, Fahey T, Ebrahim S. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. *Cochrane Database Syst Rev* 2004; 2: CD004804.
 21. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. *Arch Intern Med* 2004; 164: 722-32.
 22. McInnes GT. How important is optimal blood pressure control? *Clin Ther* 2004; 26(Suppl A): A3-11.
 23. Neutel JM, Smith DH. Improving patient compliance: a major goal in the management of hypertension. *J Clin Hypertens* 2003; 5: 127-32.
 24. Thrall G, Lip GY, Lane D. Compliance with pharmacological therapy in hypertension: can we do better, and how? *J Hum Hypertens* 2004; 18: 595-7.
 25. Krousel-Wood M, Thomas S, Muntner P *et al.* Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. *Curr Opin Cardiol* 2004; 19: 357-62.
 26. Flack JM, Novikov SV, Ferrario CM. Benefits of adherence to anti-hypertensive drug therapy. *Eur Heart J* 1996; 17(Suppl A): 16-20.
 27. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clin Ther* 1998; 20: 671-81.
 28. Miller NH, Hill M, Kottke T *et al.* The multilevel compliance challenge: recommendations for a call to action: a statement for healthcare professionals. *Circulation* 1997; 95: 1085-90.
 29. Kelham C, Shaw J, Mynors G. No quick fix: shared decision making and tailored patient support as the route to more effective medicine taking. In: Kermani F, Davies M (eds). *Patient Compliance: Sweetening the Pill*. Aldershot: Gower Publishing Limited, 2006: 179-96. ISBN-13: 978 0 566 086588.
 30. Bême D, Guéniot C. La précarité handicape l'observance. Available at www.doctissimo.fr [in French].
 31. Kusai A. Formulating for compliance success. In: Kermani F, Davies M (eds). *Patient Compliance: Sweetening the Pill*. Aldershot: Gower Publishing Limited, 2006: 83-108. ISBN-13: 978 0 566 086588.
 32. Byrom B, Stein S. The use of interactive communications technology in disease management and compliance/persistence programmes. In: Kermani F, Davies M (eds). *Patient Compliance: Sweetening the Pill*. Aldershot: Gower Publishing Limited, 2006: 145-66. ISBN-13: 978 0 566 086588.
 33. Landro L. The informed patient. *Wall Street Journal* 2003; 3 July.
 34. Krishna S, Balas EA, Boren SA *et al.* Patient acceptance of educational voice messages: a review of controlled clinical studies. *Methods Inf Med* 2002; 41: 360-9.
 35. Green D. South Africa: a novel approach to improving adherence to TB treatment. *Essent Drugs Monit* 2003; 33: 8.
 36. Miller L, Liu H, Beck K. Providers' estimates of adherence overestimate reports from medication event monitoring system (MEMS) for patients on protease inhibitors (PIs) [abstract]. In *Program and Abstracts of the 6th Conference on Retroviruses and Opportunistic Infections*. Chicago, IL 1999: 97.
 37. Tang JW, Pillay D. Transmission of HIV-1 drug resistance. *J Clin Virol* 2004; 30: 1-10.
 38. Kermani F. Marketing and PR in clinical trials. Institute of Clinical Research. Available at www.icr-global.org/documents/publications/Marketing%20and%20public%20relations.pdf
 39. Total cost to develop a new prescription drug, including cost of post-approval research, is US\$897 million. The Tufts Center for the Study of Drug Development Press Release 13 May 2003. Available at csdd.tufts.edu/NewsEvents/NewsArchive.asp?archiveyear=2003&subsection=archives
 40. Ashton G, Kermani F. Getting to grips with attrition rates. *CMR News* 2002; 20: 8-9.

Patient Compliance

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