TO HEAL AND HARM:
AN ECONOMIC VIEW
OF DRUG SAFETY

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CONTENTS

1 INTRODUCTION

The aims of this book are to:
- provide an historical background to modern pharmaceutical regulation;
- summarise available data on the harm caused by medicines;
- comment on treatment and prevention strategies;
- provide an economic framework for assessing optimal levels of pharmaceutical safety.

A multinational research based industry has grown up during the 20th century to supply pharmaceuticals, the purchase of which accounts for 13% of National Health Service (NHS) expenditure in the United Kingdom (UK). Pharmaceutical treatment can undoubtedly be a very effective, and in many circumstances cost-effective, way to treat disease. However, benefits can rarely be enjoyed without associated risks, and pharmaceutical treatment is no exception.

Maximising the beneficial effects of medicines and minimising their harmful effects, or adverse drug reactions (ADRs), are prime objectives of the medical profession and the pharmaceutical industry. An appropriate balance between risk and benefit, with due concern for the associated costs, should be sought. Unfortunately, debates about pharmaceutical marketing approval and appropriate levels of medicine use are often a sterile stand off between pro- and anti-industry advocates. It is hoped that this study will identify some common ground.

The issues covered here are set in their historical, clinical and economic context. From the outset, it is maintained that some trade off between risks, costs and benefits is unavoidable. Information on safety, along with efficacy and quality, is the cornerstone of any application to market a medicine. However, while it is desirable to have as much information as possible about a pharmaceutical prior to marketing, acquiring information involves costs which must be considered in relation to its benefits for patient health. In use, the risk of ADRs will sometimes be justified for clinical reasons. ADRs may occur after inappropriate rather than carefully considered risk taking, but even appropriately used medicine will produce ADRs in some patients.

Specific questions to be answered include:
- what is the incidence of ADRs in the hospital and community settings?
- how are ADRs caused?
- what steps can be taken to reduce the incidence of ADRs?
- what are the costs and consequences of ADR information gathering?
- how can optimal levels of ADR information gathering and of pharmaceutical treatment be achieved?

The chapters are linked but may be read alone, or in some cases in sections, depending on the interest and knowledge of the reader. Chapter 2 (History) charts the development of medicines legislation in economically developed countries. It has taken some time for the dangers associated with medicine use to be fully realised and for proper public health safeguards to be put in place. The scale and nature of ADRs has now been intensively (if not accurately) studied. Chapter 3 (The Incidence of ADRs) discusses the burden of disease ADRs create and the methodological issues surrounding such assessment. In Chapter 4 (Aetiology) the causes of ADRs and their relationship with proper and improper use of medicine is considered. This is essential to the discussion of the measures we can take to use and improve our knowledge of pharmaceutical action, which is presented in Chapter 5 (Treatment and prevention).

In Chapter 6 (Economics), a framework is developed that gives ADRs a central role in determining the nature of pharmaceutical testing and the extent of pharmaceutical use. The relative absence of existing economic analysis in this area means that Chapter 6 is more speculative in nature than the preceding chapters. It is intended to stimulate, in some cases provoke, debate. It is hoped that the framework developed will provide a useful basis for future research. Chapter 7 offers some conclusions.

2   ADRS AND THE DEVELOPMENT OF MEDICINES LEGISLATION

2.1   Introduction

This chapter briefly describes how safety concerns have influenced the development of medicines' legislation, principally in the United Kingdom (UK) but also with reference to the United States of America (US). Prior to the 19th century medicine safety attracted little political interest, often taking a back seat to concerns about adulteration and the protection of trade. The widespread availability of narcotic medicines (opium etc.) in the late 19th century, and the production of effective medicines by a large-scale industry in the 20th century, forced a change of attitude which is charted below.

2.2   The growth of legislation

Modern government regulation of pharmaceutical manufacture and distribution is designed to ensure the *quality, safety and efficacy* of medicines. The quality of medicines is a long-standing concern, given the tendency of unscrupulous traders throughout the ages to adulterate medicines, and food, of vegetable origin. Efficacy, as we now understand it, was of secondary importance. For example, apothecaries' hand-rolled pills looked elegant, but they were often so well prepared that they proceeded through the digestive system without breaking up and no effect on health status could be expected. The therapeutic revolution, which began with the development of antibiotics from chemical dye stuffs in the late 19th century, brought with it an increased probability of efficacy (Laurence and Black, 1978). The story of pharmaceutical safety and the development of medicines' legislation demonstrate the growing awareness of the need to manage the risks that potent and effective drugs unavoidably present to the public's health.

That medicines have a potential to heal *and* harm has been known since earliest times, '...there the earth, the giver of grain, bears greatest store of drugs, many that are healing when mixed and many that are baneful...' (Homer fl. c. 700 BC, cited by Penn, 1986). In 1566 the

Faculty of Medicine in Paris banned the medicinal use of antimony because of the risk of poisoning presented by the impure element. This ban, the first of its type, could not be sustained when antimony was credited with the cure of King Louis XIV's typhoid a century later (Davies, 1991; Penn, 1986). Antimony has no place in a modern pharmacopoeia but its use in flame resistant mattresses has recently raised concerns that it may be a cause of cot death in infants (De Wolff, 1995). The side-effects of substances still used as medicines today have also been known for many years; for example, the following are accounts of digitalis toxicity:

> The foxglove when given in very large and quickly repeated doses occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green and yellow; increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope[1], death (Withering, 1785).

> Digoxin side effects, usually associated with excessive dosage, include: anorexia, nausea, vomiting, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression; arrhythmias[2], heart block (Joint Formulary Committee, 2002).

In the UK, the formal regulation of medicines' supply on the grounds of safety began in 1852 when sales of arsenic were restricted because of its apparent involvement in murders and the risk of accidental poisoning (Dale and Appleby, 1989). As further dangers arose, Acts of Parliament followed in a piecemeal fashion. Laws passed in 1868 and 1908 were meant to restrict sales of certain 'poisons', which were used for therapeutic purposes, to pharmaceutical chemists. A loophole excluded patent, i.e. branded, medicines from sales restrictions and prosecutions were at the expense of the Pharmaceutical Society. Even so, there is some evidence that over a period of time accidental opium poisonings were reduced (Parssinen, 1983).

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[1] Syncope – fainting.
[2] Arrhythmias – variation from the normal regular heartbeat.

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Around the turn of the 20th century, there were formal inquiries into the adverse effects associated with the administration of chloroform (McKendrick et al., 1880) and *Salvarsen* (Salvarsen Committee, 1922). *Salvarsen* injections had successfully treated syphilitic troops returning from the First World War, but there was a concurrent outbreak of jaundice, which may have been caused by improper use of intravenous infusion equipment (Penn, 1986). In most cases, however, information on ADRs emerged slowly without co-ordinated investigation. Meanwhile, the development of subcutaneous injection had heightened concerns about opium addiction in late Victorian Britain. Sales of narcotic drugs to troops finally prompted comprehensive controls of manufacture and sale in 1920, effectively creating the first class of prescription only medicines (Parssinen, 1983).

The principle of prescription only medicines was extended to non-narcotic poisons in 1933, in response to concerns expressed well by Leake (1929): 'there is no short cut from the chemical laboratory to clinic, except one that passes too close to the morgue.' During the first half of the 20th century, biological products, such as vaccines and antibiotics, were developed. Their final quality could not be tested chemically and controls on manufacture were introduced. The danger that antibiotics might pose to public health was also recognised at an early stage, but they were not made prescription only medicines until 1947 (Dale and Appleby, 1989).

In 1937, around 100 Americans were poisoned by the diethylene glycol diluent[3] in a liquid antibiotic. This incident led directly to the US Federal Food, Drug and Cosmetic Act 1938, which banned the marketing of medicines without prior approval. The US had some pharmaceutical regulation before this time but, as in the UK, no prior approval of marketing was required (Abraham, 1995). In the UK, the disclosure of the contents of proprietary medicines was only made compulsory by the Pharmacy and Medicines Act 1941. At this time, marketing did not require prior approval, although advertising

[3] Diethylene glycol is the 'antifreeze' which was more recently found in contaminated Austrian wine.

medicines to treat certain diseases (e.g. diabetes) was restricted. The Therapeutic Substances Act 1956 replaced previous Acts of Parliament to bring existing controls of manufacture and supply of (non-narcotic) medicines together for the first time.

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The need for better legislation was recognised, but plans for change were interrupted by the thalidomide tragedy in 1961. As a consequence, in 1964, voluntary reporting of ADRs (the yellow card scheme) was initiated in the UK. The Medicines Act 1968 then replaced all previous legislation to comprehensively govern the manufacture, sale and supply of medicinal products.

2.3 Modern concerns

Post-thalidomide, all economically developed countries have a procedure for pre-marketing approval of medicines and post-marketing surveillance of ADRs. There is a continuing concern in some quarters that pharmaceutical companies make the most of their products' benefits but draw little attention to potential risks (National Consumer Council, 1991; George, 1992). One of the most controversial and well known case studies revolves around the initial marketing of benzodiazepine tranquillisers (see Box 2.1) e.g. *Valium* (diazepam) and *Mogadon* (nitrazepam) (Medawar, 1992). Professional and public confidence in marketed medicines is essential. Although the pharmaceutical industry is highly competitive and has been going through a period of major reorganisation, safety issues remain at the top of the industry's agenda. Every step of pharmaceutical development is closely regulated and a vast amount of data is needed to support an application for marketing authorisation.

Additionally, great emphasis is now placed on the desire of all concerned with the use of medicines to achieve continuous improvements in the safety of medicines in use. Serious ADRs are often only identified post-marketing (Venning, 1983a). Voluntary reporting is supplemented in the UK by independent prescription event monitoring (PEM). Guidelines for company sponsored safety assessment of marketed medicines have been agreed (Joint Working

Box 2.1: **Initial marketing of the benzodiazepines**

The first benzodiazepine, introduced in the US in 1959 and the UK a year later, well before modern regulatory regimes were introduced, was chlordiazepoxide *(Librium)*. The drug was enthusiastically received on the basis of animal experiments and, when prescribed in humans, was thought to be an important advance on barbiturates (sleeping pills) and barbiturate-like tranquillisers. However, early reports suggested a potential problem with dependence and withdrawal reactions and, in 1964, the World Health Organisation (WHO) identified chlordiazepoxide as one of a number of non-barbiturates which could produce dependence of the barbiturate type. In the US, a recommendation was made in 1967 to list *Librium* and *Valium* under the Drug Abuse Control Amendments. Nevertheless, published reports of withdrawal reactions were rare and benzodiazepines continued to be widely prescribed throughout the 1970s. The greater use in the late 1970s of shorter-acting benzodiazepines such as lorazepam *(Ativan)* began to reveal the possible extent of withdrawal reactions with these drugs and a flood of anecdotal reports in the early 1980s suggested that dependence was far more common than previously thought. By the mid-1980s, most data sheets mentioned the risk of dependence and, according to estimates produced around this time, between 200,000 and 500,000 people were thought to be dependent on benzodiazepines.

Party, 1993). All pharmaceutical companies have staff dedicated to pharmacovigilance. However, clarifying appropriate indications may not be an easy task, and it can take some time for a pharmaceutical considered dangerous to be withdrawn from sale.

The role of the European Medicines Evaluation Agency (EMEA) in pharmacovigilance may lead to more co-ordinated and timely medicine withdrawals within the European Union (EU) (Jones and Jefferys, 1994). However, we must expect that the best assessment of a medicine's risk/benefit profile will only emerge slowly over time,

as greater numbers of patients (either inside or outside clinical trials) are exposed to the agent.

Examples of the range of responses there have been to safety concerns about some pharmaceuticals are:
• Cisapride, first marketed in 1988 and licensed for gastro-oesophageal reflux disease, functional dyspepsia and delayed gastric emptying in adults, had its UK product licences suspended in July 2000. Marketing of the drug ceased in the US, Germany and Canada.
• In 1991, the tranquilliser triazolam *(Halcion)* was withdrawn from the UK market more than 10 years after similar action was taken in the Netherlands (Dukes, 1986), but it has never been withdrawn in the US, remains on sale in most European markets, and has received a limited re-approval in the Netherlands (Abraham, 2002).
• Benzodiazepine tranquillisers were first marketed in the late 1950s, but strict prescribing guidelines were only draw up in the late 1980s.
• Xamoterol *(Corwin)* was thought to be a very promising treatment for all grades of heart failure when first marketed in 1988. In clinical use a better picture of its mode of action, contra-indications and side-effects became apparent and from 1990 it has been restricted to the treatment of mild heart failure on a consultant's recommendation.
• Oral contraceptives have a well known mortality risk associated with blood clot formation, which has been highlighted by recent controversies. However, even for smokers taking pills which contain relatively high quantities of the hormone oestrogen the risks associated with chemical contraception are less than or equal to the risks associated with pregnancy (Guillebaud, 1991).

We have also learnt lessons about the potential contribution of pharmaceutical formulation to ADRs. In the UK, for example, recently introduced CFC-free asthma inhalers are subject to intensive ADR monitoring as if they were completely new medicines.

3   THE INCIDENCE OF ADRS

2.4 Summary

Medicines legislation in the UK and elsewhere has developed slowly as political concerns about drug dependence and safety have been awakened. Growing concern for public safety was reflected in the establishment of poisons lists, which restricted the sale and supply of medicines. The need for manufacturing quality control, particularly for biological products, was recognised when the pharmaceutical industry was in its infancy. For non-narcotic drugs, the introduction of more rigorous legislation began in 1938 with the US Federal Food, Drug and Cosmetic Act. The thalidomide tragedy firmly focused attention on the vital importance of safety assessment and monitoring, leading to comprehensive legislation throughout the developed world. Since the 1960s the principles of medicine safety have become firmly established. In the following chapter, the morbidity and mortality associated with modern medicine use is reviewed.

3.1 Introduction

The quantification of the harm that may be caused by pharmaceuticals is now considered of the utmost importance. A medicine's safety and efficacy have usually been investigated for eight to 12 years before marketing authorisation is granted. Yet at the time of first marketing, knowledge of a medicine's properties remains incomplete, as no more than a few thousand humans will have been exposed to it for any length of time. Thus, despite extensive trials, a medicine's final place in clinical practice will almost certainly not be known, and the incidence of less common ADRs will be unknown (Freeman, 1991).

This chapter reviews published evidence on the morbidity and mortality associated with marketed pharmaceuticals. Section 3.2 deals with some important methodological issues. Section 3.3 assesses the ADR incidence shown by studies of spontaneous reporting systems. Section 3.4 assesses the incidence of ADR-related admissions, in-patient ADRs and ADR-related death found in studies of hospital patients. Section 3.5 assesses ADR incidence in the community.

Table 3.1: **Definitions of adverse drug reactions**

An ADR is…	Any response to a drug which is noxious and unintended…	and which occurs at doses in man for prophylaxis, diagnosis or therapy…	excluding failure to accomplish the intended purpose.
Cluff et al. (1964)	✓	✗	✗
WHO	✓	✓	✗
Karch and Lasagna (1975)	✓	✓	✓
An ADE is… Bates et al. (1995a)	An injury resulting from medical intervention related to a drug.		

3.2   Methodology

Over 25 years ago, Karch and Lasagna (1975) described the data on ADRs as: 'incomplete, unrepresentative, uncontrolled and lacking in operational criteria for identification'. Much has changed, but even today there is no universally agreed definition of ADRs, no standard algorithm for establishing a causal link between reaction and medicine, and no common classification system for confirmed ADRs. Further, most of the symptoms which can be associated with the adverse consequences of pharmaceutical therapy can also be suffered by people who have never been exposed to medicines.

3.2.1   Definition

The most common definitions of an ADR are summarised in Table 3.1. The broadest definition (Cluff et al., 1964) can be taken to include intentional overdose and (prescription) drug abuse. Attempts have been made to restrict the definition of ADRs in a way which makes it more relevant to clinical decision making (under the assumption that patients ought to do what they are told!). Thus, the World Health Organisation (WHO) definition does not include intentional poisoning, accidental poisoning, or drug abuse. However, the WHO definition does not explicitly exclude therapeutic failure, which may not be considered 'noxious'. Karch and Lasagna's (1975) widely accepted, and most restrictive, definition does not include therapeutic failure. Unless stated otherwise, it is Karch and Lasagna's definition that is used in the discussion of special studies in Sections 3.4 and 3.5, because this has been recognised as the 'gold standard' by most researchers. Some studies (Classen et al., 1997; Lazarou et al., 1998; Beijer and de Blaey, 2002) cite the WHO definition but explicitly exclude therapeutic failure. Lazarou et al. (1998) take the WHO definition to exclude therapeutic failure.

It has been pointed out by some authors that most *preventable* medicine related injuries occur as a result of errors in use (cf. Chapter 5). The usual definitions of ADRs relate to appropriate use, but Bates et al. (1995a) prefer to focus on adverse drug *events* (ADEs), which

they define as 'an injury resulting from medical intervention related to a drug'. This, they argue, is more comprehensive and clinically significant than Karch and Lasagna's definition, and much more useful when assessing strategies for prevention. ADRs and ADEs are closely related, but ADEs are defined by outcome (an injury), and their identification is focused on patients not medicines. ADEs can be subjected to causality assessment and classification in much the same way as ADRs.

3.2.2   Assigning causality – did a medicine do this?

Karch and Lasagna (1975) suggested that causality could be assigned using the operational definitions: definite, probable, possible, conditional and doubtful. A number of algorithms have now been developed to aid categorisation, but in earlier literature it cannot be assumed that causality has been formally assessed. Whether particular studies under- or over-estimate the true incidence of ADRs, if such a thing exists, depends on the degree of proof researchers deemed appropriate in their studies. The most robust proof of causality is to 1) stop administration of the potentially offending medicine (dechallenge); 2) watch the symptoms subside; 3) administer the medicine again (rechallenge); and 4) watch the symptoms reappear. Clearly, this is not common practice and medicines are rarely, perhaps rightly, given the benefit of the doubt. Rechallenge may also be of little benefit, and is potentially dangerous when an ADR is allergic in origin (Recchia and Shear, 1994; and see Chapters 4 and 5).

Nevertheless, in ideal circumstances, confirmation of an ADR requires that a causal link between pharmaceutical and reaction is established. The probability of such a causal link can be assessed using clinical judgement. Potential confounding factors are: patient variability, disease states, concurrent therapy and the existence of 'ADR-like symptoms' (Knodel, 1992). In the absence of a standard method of establishing causality, there is likely to be substantial disagreement both within and between assessors. This problem led Naranjo et al. (1981) to develop and test an 'ADR probability scale' (Table 3.2). Each question on the scale is marked 'yes' or 'no', and the ADR is

Table 3.2: **ADR probability scale**

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score

	Yes	No	Do not know	Score
1 Are there previous *conclusive* reports on this reaction?	+1	0	0	
2 Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3 Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4 Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5 Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6 Did the reaction reappear when a placebo was given?	-1	+1	0	
7 Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8 Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9 Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10 Was the adverse event confirmed by any objective evidence?	+1	0	0	
			(Total score)	

assigned to a probability category according to the total score: ≤ 0 doubtful, 1-4 possible, 5-8 probable, ≥ 9 definite.

Agreement within and between assessors increases when the probability scale is used to establish causality. The probability scale could also discriminate between ADRs of different probabilities, the questionnaire was simple and the results were both reproducible and valid. The biggest cause of disagreement between assessors was found to be judgement about alternative causes (Table 3.2, Question 5); in complicated cases there was thought to be no substitute for clinical experience. Naranjo et al. (1981) suggested that their scale could be applied to data in published articles and from post-marketing surveillance. Where the patient received several pharmaceuticals then each was to be assessed independently, and the pharmaceutical with the highest score considered the most likely cause.

Naranjo's algorithm has been widely used, and was among those reviewed by the US Food and Drug Administration (FDA) who at one time, although no longer (Stephens, 1991), adopted a simple algorithm for their own use (Jones, 1982). The FDA's algorithm rested on an assessment of four critical factors: temporal relationship, 'dechallenge', 'rechallenge' and relationship to disease (Figure 3.1).

In France, there is still an official method of causality assessment based on two groups of criteria: chronological and semiological. The three chronological criteria are: the time interval separating pharmaceutical administration and onset of the reaction; the course of the reaction when the medicine is stopped; and the results of readministration. The semiological criteria are: the clinical picture and validated risk factors; the search for other causes; and (in certain cases) laboratory tests. The combination of the two sets of criteria enables a matrix to be drawn up which ranks causality as unlikely, doubtful, possible, likely or very likely (Bénichou, 1994a). Bénichou and Danan (1994) described an alternative to this method and its application to acute liver injuries, but this is not yet widely used (see also Fletcher, 1993).

Bayesian methods, which take into account prior probability, are also used, particularly by pharmaceutical companies, to assign causality in

Figure 3.1: **Jones's algorithm**

START HERE:*

Does event have a reasonable *temporal association* with use of the drug? — NO → Causal relationship considered *remote*

YES ↓

Was there a *dechallenge* from the drug? — NO → Causal relationship considered *possible*

YES ↓

Did the observed event abate upon *dechallenge*? — NO → Causal relationship considered *possible*

YES ↓

Was there a *rechallenge*? — NO → Could the event be due to an existing clinical condition? — NO → Causal relationship considered *probable*

YES ↓ (from Was there a rechallenge)

YES ↓ (from Could the event)

Did the reaction or event reappear upon *rechallenge*? — NO → Causal relationship considered *possible*

YES ↓

Causal relationship considered highly probable

* Each drug is carried through independently: if >1 drug was dechallenged or rechallenged simultaneously causality for all is ≤ possible.

Questions
1 Did the reaction follow a reasonable temporal sequence?
2 Did the patient improve after stopping the drug?
3 Did the reaction reappear on repeated exposure (rechallenge)?
4 Could the reaction be reasonably explained by the known characteristics of the patient's clinical state?

Source: Jones, 1982.

difficult or important cases (Stephens, 1991). Practical methods exist for these quite sophisticated, and under-used, statistical techniques to be applied to clinical practice (see Fletcher, 1993).

Given the ease with which at least some algorithms can be applied, despite certain limitations, there is little excuse for not using a structured approach in clinical studies in addition to assessment based on clinical judgment. The Naranjo method is reported to compare favourably with Kramer's (Kramer et al., 1979), which although theoretically superior involves 56 questions (Michel and Knodel, 1986). However, the assignment of causality is a truly contentious issue, and a number of methods are commonly used for formal causality assessment. The trend is not to rely on single pieces of information, or even formal algorithms, to assign causality. Instead, attempts are made to build up a comprehensive clinical picture (so called 'global introspection').

3.2.3   Classification – different types of ADR

Confirmed ADRs may be further classified according to incidence, pharmacology and severity. The most common and widely accepted ADR classification is into type A (augmented) and type B (bizarre), as proposed by Rawlins and Thompson (1977). Type A reactions can be predicted from known pharmacology, they are common, dose related and generally of a less serious nature with low mortality. Type B reactions are rare, not dose related and may be more serious than type A reactions with relatively high mortality. This distinction and the pharmacology of ADRs are elaborated on in Chapter 4.

Severity assessment is relatively straightforward, but there is no universal applied scale or terminology. Thus, ADRs may be described as 'minor, moderate and severe', or 'mild and significant'. In studies where minor ADRs are ignored, the scale 'significant, serious, life-threatening and fatal' may be preferred. There is little consistency in the literature, and severity classification always relies on clinical opinion.

3.2.4   ADR-like symptoms

Robust causality assessment should mitigate the fact that most ADR-like symptoms occur naturally in the absence of exposure to pharmaceuticals. However, unless there is a dramatic increase in the observed incidence of a symptom (e.g. cough), formal studies (cohort or case-control) are required in order to clarify the medicine-disease relationship (Lawson, 1991).

This is particularly true of minor ADRs which are indistinguishable from everyday ailments (Lawson, 1991; Reidenberg and Lowenthal, 1968). Reidenberg and Lowenthal (1968) surveyed 670 students and hospital staff by questionnaire: 414 indicated that they had no illnesses and had taken no medication in the previous three days. However, only 19 stated that they had experienced none of the 25 listed ADR-like symptoms in the previous 24 hours. The median number of symptoms experienced was two; 30 otherwise healthy people had experienced six or more. The most common symptoms were: fatigue, sleepiness, irritability, inability to concentrate and nasal congestion.

Similarly, Green (1963) investigated ADR-like symptoms in well and sick individuals before and after the administration of a placebo (inert tablets or liquid). A variety of symptoms were apparent prior to 'treatment'. Placebos worsened the severity of symptoms in some individuals and 'caused' new symptoms in others. Well individuals reported more symptoms than sick ones and, among the sick, pre-existing symptoms were sometimes relieved by the placebo. The incidence of symptoms varied with sex, age and medical condition. Gastro-intestinal (GI) effects, dizziness and blurred vision were among those symptoms reported.

Therefore, as adequate controls are usually lacking, studies to measure the incidence of ADRs within a treatment population are likely to *overestimate* the incidence of symptoms that are in fact attributable to medicine exposure. ADR incidence is also a poor proxy for morbidity, because many reactions attributable to medicine use are relatively

harmless. Importantly, the influence ADRs have on the course of disease and clinical management is poorly understood (see Chapter 5).

Within randomized placebo-controlled trials, ADRs can be attributed to the drug under investigation with more confidence, since confounding factors should be randomly distributed between treatment and control groups. However, the exposure of a few thousand patients to a drug prior to launch will identify only the more common reactions. An option would be to undertake larger trials, perhaps after launch, with patient groups more typical of those presenting in clinical practice. Against the additional benefits of conducting further research, as will be discussed in Chapter 6, must be set the extra costs and the feasibility of collecting the data.

Observational studies may offer advantages in terms of their coverage but, as Edwards and Aronson (2000) discuss, there are a variety of study designs which vary in cost and ability to detect new effects. In practice, detection efforts have centred around what they term 'voluntary organized reporting', also termed spontaneous reporting schemes.

3.3   Spontaneous reporting schemes

Spontaneous reporting schemes are the backbone of pharmacovigilance, but they cannot provide proper estimates of the morbidity associated with ADRs. Prescribing data and ADR reporting are rarely linked, the number of patients exposed to the pharmaceutical is usually unknown (or uncertain), and control populations are not studied (Begaud et al., 1994). However, spontaneous reports are usually timely, and the data generated by them potentially comes from the entire treated population.

All EU countries have systems for the spontaneous reporting of adverse drug reactions. These were originally developed in response to the thalidomide disaster. The EMEA now has the role of co-ordinating EU wide pharmacovigilance (Jones and Jeffreys, 1994).

The origin and structure of the UK's reporting scheme are well summarised by Balfour (1991). Doctors, dentists, coroners, hospital

pharmacists (since April 1997), community pharmacists (since November 1999) and the pharmaceutical industry report problems to the Committee on the Safety of Medicines (CSM). Nurses, midwives and health visitors were included in the scheme in October 2002 and patient reporting to NHS Direct was introduced on a pilot basis in April 2003.

Reports from professionals are made on 'yellow cards' published at the back of prescription pads and in common works of reference, e.g. the British National Formulary, or electronically via the Medicines and Healthcare Products Regulatory Agency (MHRA) website. Most yellow cards are returned to the CSM's main office in London, but there are also five regional adverse reaction monitoring centres. Reports are requested for serious reactions and any suspected reactions to new pharmaceuticals (generally those that have been marketed less than two years). To indicate the special ADR reporting requirements, new medicines are marked with a black triangle on advertisements and prescribing information.

In total since 1964, over 400,000 reports of suspected ADRs have been submitted (CSM, 2003a). In 2002, 16,176 reports were received through the Yellow Card Scheme (CSM, 2003b). According to survey evidence, 63% of doctors (77% of GPs, 55% of hospital doctors) have reported at least one suspected ADR. A perceived unavailability of forms (21% of doctors said forms were not available when needed) and lack of time have hindered more reporting (Belton et al., 1995).

Rawlins (1995) identified four ways in which the Yellow Card Scheme has proved invaluable: 1) it provides early warnings of pharmaceutical hazards, for example warnings of problems with high dose pancreatins used to treat patients with cystic fibrosis; 2) it provides information about ADR risk factors, such as the relationship between the contraceptive pill and thromboembolism; 3) it makes comparisons of medicines within particular therapeutic groups possible, for example, by elucidating the relative toxicity of non-steroidal anti-inflammatory drugs (NSAIDs); and 4) it extends monitoring over the lifetime of the product, as indications change or delayed effects become apparent.

A study conducted by Lumley et al. (1986) was specifically designed to measure the level of ADR under-reporting in UK general practice. Out of the 638 ADRs identified by a group of general practitioners (GPs) (cf. Section 3.5), 10 were serious and 27 were due to pharmaceuticals requiring special reporting. Only five (13.7%) of these 37 'eligible' ADRs were actually reported to the CSM. However, in total, the GPs in the study returned 35 yellow cards to the CSM, an overall reporting rate of 6%. There was therefore a considerable mismatch between the 37 ADRs that should have been reported and the 35 that were reported, indicating large Type 1 errors (false positives – ADRs reported that need not have been) and large Type 2 errors (false negatives – ADRs not reported that should have been). The main reasons GPs gave for not reporting ADRs were: expected or well known (58%), too trivial (11%) and uncertain causality (14%).

Prescription event monitoring (PEM) is an alternative to spontaneous reporting which combats under-reporting, but is not as expensive as full-blown clinical trials. Researchers in the UK, studying a limited number of medicines at any one time, obtain all the prescriptions which have been submitted for pricing (i.e. dispensed). A 'green form' is then returned to the prescribing GP asking for details of any ADRs in the named patient. A recent PEM study showed a similar level of under-reporting for newly marketed drugs (those with an inverted black triangle on the product literature) as that observed in the studies already discussed. Martin et al. (1998) found that, for 3,045 events reported on the green forms as suspected adverse reactions across 10 drugs, GPs had reported only 275 (9%) to the CSM. The main advantage of PEM is that the numerator and denominator in the ADR rate calculation are both known. However, for a new medicine it can take time to build up a suitable cohort of patients (Inman, 1987).

Taking the UK as an example, assuming that spontaneous ADR reporting (in hospital and community) represents approximately 5% of the true incidence (Lumley et al., 1986; Montastruc et al., 1993), there may currently be around 320,000 ADRs per year, on the basis of approximately 16,000 yellow cards being submitted. To put this figure into some sort of context: in 2001/02, approximately 730 million

prescription items were dispensed in the community alone (OHE, 2003). Thus, if two-thirds of all ADRs occurred in the community, then about one in 3,400 (0.03%) prescription items led to an ADR. As 12.4 items per head of the population were dispensed in 2001/02 (OHE, 2003), on average no more than one in 275 (0.4%) people would have suffered an ADR.

However, this information by itself is of little value. In particular it ignores the fact that a large proportion of the population are not 'medically active' (i.e. ill and/or seeking medical treatment) and that some people use medical services much more than others. In order to understand the risks associated with medical treatment, special studies of ADRs must be undertaken.

3.4 ADRs in hospitals

Einarson (1993) conducted a systematic review of the published literature regarding drug-related hospital admission. He identified ADR-related admission rates (using the Cluff et al., 1964, definition of ADRs, which is the broadest) from 49 hospitals published in 37 studies between 1966 and 1989. His main results are summarised in Table 3.3.

Lazarou et al. (1998) estimated, on the basis of a meta-analysis of studies in US hospitals, that the incidence of patients being admitted to hospital due to a serious ADR (these being ADRs resulting in hospital admission, permanent disability or death) was 4.7%. These authors refer to the WHO definition, excluding therapeutic failures,

Table 3.3: **Studies of ADR-related hospital admissions**

	Range	Median	Mean
Sample size	41-11,891	714	1,412
Prevalence of ADR related admissions	0.2%-21.7%	4.9%	5.5%

Source: Einarson (1993).

intentional and accidental poisoning and drug abuse as well as adverse events due to errors in drug administration and non-compliance. The number of patients affected was estimated to be 1,547,000 in 1994. This study has been criticized in an article published on Medscape by Kvasz et al. (2000), although the authors did not present their own estimates of the incidence of ADRs. Beijer and de Blaey (2002), in a meta-analysis based on 68 studies primarily from the US (25 papers), Europe (19) and Australia (15), estimated that the hospitalisation of 4.9% of hospital patients across all the studies reviewed was ADR-related. They also based their study on the WHO definition, excluding therapeutic failures, intentional and accidental poisoning and drug abuse.

Wiffen et al. (2002) carried out a systematic review of the worldwide literature, covering 69 unique studies, with the top three areas in terms of numbers of studies being North America (21), Europe excluding the UK and Ireland (21) and the UK and Ireland (7). These authors excluded events caused by administration errors, non-compliance, overdose, drug abuse or therapeutic failure and information on deliberate or accidental self-harm. Weighted mean rates of ADRs, on the WHO definition, were 4.6%, 14.1% and 7.5% for the three areas. Overall, 3.7% of patients experienced an ADR while in hospital and 3.1% of patients admitted to hospital were admitted because of an ADR. The authors acknowledge the criticisms of Kvasz et al. (2000) but argue that these criticisms ignore the magnitude of ADRs reported across clinical areas and across countries. They estimate the impact of ADRs as a cause of hospital admissions and of ADRs experienced by hospitalized patients in England to be equivalent to around 15-20 400-bed hospitals.

Classen et al. (1997) estimated the rate of 'adverse drug events' (defined according to the WHO definition but excluding therapeutic failures) experienced by patients in hospital to be 2.43 per 100 admissions among patients hospitalized in one tertiary care institution over a four year period. Extrapolated to the US, over

770,000 patients would experience an ADR on this basis. This figure is considerably lower than that suggested by Lazarou et al. (1998) who estimated, on a similar definition, that a *serious* ADR occurred in 2.1% of patients in hospital, or a total of 702,000 patients in 1994, and that the incidence of ADRs of all severities among these patients was 10.9%. 76% of ADRs of all severities experienced while in hospital were estimated to be Type A reactions and 24% Type B reactions (Lazarou et al., 1998).

In Einarson's (1993) review, the death rate resulting from ADRs, on the broad Cluff et al. (1964) definition of an ADR, was estimated at 5% of patients admitted because of pharmaceuticals and 0.3% of all admissions. Classen et al. (1997) found a crude mortality rate of 3.5% among the patients experiencing an ADR in their sample who were matched with a group of controls. Mortality among the control patients was 1.05%. In the study by Lazarou et al. (1998), using the WHO definition excluding therapeutic failure, intentional and accidental poisoning, drug abuse and adverse events due to errors in drug administration or non-compliance, the incidence of fatal ADRs in the US associated with hospital admissions due to an ADR was 0.13%. Combining this with an incidence of fatal ADRs associated with ADRs experienced in hospital of 0.19% gave a combined rate of 0.32%. There were an estimated 43,000 deaths due to the former type of ADR and 63,000 due to the latter type in 1994. Fatal ADRs altogether, on this definition, would have been between the fourth and sixth leading cause of death in the US depending on whether the mean incidence or the lower bound of the 95% confidence interval was used. However, the validity of the death rates obtained by Lazarou et al. (1998) has been challenged by Kvasz et al. (2000) and Ross (2001) since only those studies that reported a death were included in the estimated pooled incidence rates of fatal events. Although neither commentary suggested an alternative estimate, they both argue that the exclusion of those studies in which no deaths were reported "is likely to dramatically overestimate the death rate".

3.5 ADRs in the community setting

The biggest survey of ADRs (using the WHO definition) in UK general practice was conducted by Lumley et al. (1986). One hundred doctors in 24 training practices in the former South West Thames health region collected data from 36,470 consultations over the course of four weeks. There were 638 reported ADRs (1.7% of consultations). The main areas identified are set out in Table 3.4. In around half these cases the ADR had actually caused the consultations (0.8%). However, only 10 ADRs (1.6% of ADRs reported, arising in 0.027% of consultations) were judged to be serious.

In a further survey of a more qualitative nature, Walker and Lumley (1986) surveyed a quota sample (matched to the GP population) of 402 GPs. The GPs who completed the questionnaire correctly (348) estimated that they held 650 consultations a month and saw two ADRs (0.3% of consultations). This is a much lower incidence rate than that in Lumley et al. (1986). Reports of severe or life-threatening ADRs were rare (2% of all ADRs – a figure consistent with the Lumley et al., 1986 survey), while moderate ADRs (requiring a change in therapy) made up 40% of reports and trivial ADRs 58%.

Table 3.4: **ADRs in the community**

Clinical manifestation	Number (%)
GI disturbances	198 (13)
CNS* effects	128 (20)
Rash	70 (11)

Drug class causing ADR	Number (%)
Cardiovascular drugs and diuretics	147 (23)
NSAIDs and analgesics	128 (20)
Anti-infectives	115 (18)

Source: Lumley et al., 1986.
Note: * CNS – central nervous system

3.6 Conclusion

Studies to measure the incidence of ADRs within a treatment population are likely to *overestimate* the incidence of symptoms that are in fact attributable to medicine exposure because adequate controls are usually lacking. ADR incidence is also a poor proxy for morbidity, because many reactions attributable to medicine use are relatively harmless. The definition of ADR used in a study can also have a big impact on the findings; in particular, whether or not therapeutic failure is included.

With these qualifications, the likely annual incidence of ADRs in different population groups is summarised in Table 3.5. When investigators rely on others to notify them of ADRs, yields have been low, but independent researchers identify much greater numbers of reactions (Lawson, 1991). Successful reporting systems are simple, accessible and incorporate incentives for involvement. ADRs are an important cause of hospital admission.

It seems reasonable to conclude that, although more than 10% of medical in-patients may suffer from an ADR, fewer than half of these patients suffer any real injury and in only 1-2% of in-patients is this injury of a serious nature. ADR-related deaths do occur, but they are rare (0-0.3%) and are usually connected with pharmaceuticals whose toxicity is well known, which are used for treating patients whose medical condition is of a serious nature. In the community, most

Table 3.5: **Likely annual incidence of ADRs in different patient groups**		
Patient group	**ADRs per person**	**ADRs per drug exposure**
General public	0.4% (1 in 275)	0.03% (1 in 3,400)
People consulting a GP	1.7% (1 in 60)	
Patients admitted to hospital	5% (1 in 20)	
ADRs experienced while hospital in-patient	3.5% (1 in 29) to 11% (1 in 9)	

people suffer ADR-like symptoms occasionally and the lack of proper controls means that the exact incidence of ADRs in the community is difficult to determine. Serious ADRs, such as those which lead to further consultation, appear to be rare but not without clinical significance.

Compared with the extent of pharmaceutical use in both hospital and community the number of ADRs which it can be shown to have occurred is small, but the consequences may be significant. Trivial ADRs cause little or no permanent harm, but can tangibly alter the doctor-patient relationship. More serious ADRs can result in permanent disability and/or hospital admission. The cause of 1 in 20 hospital admissions cannot be ignored, but we know little about the courses many diseases would take in the absence of pharmaceutical therapy.

In the following chapter the aetiology of ADRs (i.e. what causes them) will be discussed, with particular focus on whether ADRs are due to intrinsic pharmaceutical properties or their inappropriate use. If the causes of ADRs can be determined, then it should be possible to reduce the level of ADRs. In economic terms, the challenge for policy makers is to find mechanisms that will lead clinical decision makers to choose a socially optimal level of reactions. It is not possible to eliminate ADRs altogether and still obtain the benefits of pharmaceutical use.

4   AETIOLOGY – THE CAUSES OF ADRS

4.1 Introduction

Regulations are in place to limit the adverse effects medicines may cause, in particular all marketed medicines must have demonstrable quality, safety and efficacy. Yet, as we have seen in the previous chapter, pharmaceuticals in widespread approved use can have significant detrimental effects on some patients' health status. This chapter explores the causes of medicine-related morbidity and mortality at two levels. In Section 4.2, the classification of confirmed ADRs is discussed (cf. Section 3.2.3), the mechanisms of pharmaceutical action are explained in simple terms and the interrelationship between therapeutic and toxic drug effects is highlighted. Section 4.3 discusses possible human causes of ADRs and their relationship to the mechanisms of pharmaceutical action. The information presented here is fundamental to the discussion of ADR treatment and prevention which follows in Chapter 5.

4.2 Therapy and toxicity

The therapeutic and toxic effects of medicines are mediated by the same physical and biological processes. Maximising the health gain from drug treatment requires an understanding of pharmacology and an accurate assessment of the causality of suspected ADRs.[1]

4.2.1   Classification of confirmed ADRs

A common and useful classification of ADRs is into type A 'augmented' and type B 'bizarre' (cf. Section 3.2.3). Variation is one of the defining characteristics of biological systems; pharmaceutical administration to a number of individuals will rarely elicit a uniform response. Patients experience pharmaceutical toxicity at one extreme of the dose-response relationship and therapeutic failure at the other.

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[1] The interested reader is referred to Rawlins and Thompson (1991) and Grahame-Smith and Aronson (1992) for a comprehensive introduction to the relevant clinical pharmacology; these works are the major reference material for Section 4.2.

Type A ADRs result from this variation in the dose-response relationship. They are common, and may be due to: excessive primary therapeutic effects e.g. morning after 'hangover' with sleeping tablets; primary therapeutic effects in a part of the body where they are not required e.g. fungal overgrowth in the gut after taking antibiotics to treat an infection elsewhere; or secondary (but predictable) effects e.g. drowsiness associated with some antihistamines, which are used to treat allergies.

In certain circumstances secondary effects may be used for therapeutic purposes. A major group of antidepressants was discovered following the observation of mood elevation in patients undergoing pharmaceutical treatment for tuberculosis. The drowsiness caused by antihistamines may be a useful side-effect, and these agents are found in many children's over-the-counter medicines. The potential effect of Viagra (sildenafil) in erectile dysfunction was initially discovered in trials among patients with angina, for which the molecule had been developed. Minoxidil was developed as an antihypertensive but has also been marketed for the treatment of male-pattern baldness after hirsutism was identified as a side-effect.

Type B reactions have been described as aberrant, inexplicable and heterogeneous (Rawlins and Thompson, 1991); fortunately they are also rare. Unlike type A reactions, they may be both quantitatively and qualitatively different from a medicine's normal therapeutic effects. Allergic reactions are usually considered to be type B, unless the pharmaceutical implicated is a known antigen e.g. vaccines or non-human insulin. Prior to marketing only the most common, type A, reactions will be known. Table 4.1 shows the number of patients that must be studied to have a good chance (95% probability) of detecting one, two or three cases of an adverse reaction given a variety of expected incidences (Lewis, 1981).

Table 4.1 refers to reactions with no background incidence: the numbers of patients who must be investigated to detect reactions that mimic everyday ailments (cf. Section 3.2.4) are correspondingly higher (Grahame-Smith and Aronson, 1992). Given the average

Table 4.1: **Number of patients to be observed to detect adverse reactions**

Expected incidence of adverse reaction	Number of patients to be observed to detect 1, 2 or 3 reactions with 95% probability		
	1	2	3
1 in 100	300	480	650
1 in 200	600	960	1,300
1 in 1,000	3,000	4,800	6,500
1 in 2,000	6,000	9,600	13,000
1 in 10,000	30,000	48,000	65,000

number of people that are exposed to a medicine prior to marketing, reactions occurring at an incidence of one in 200 will almost certainly be detected, whilst those occurring at an incidence of less than one in 1,000 will almost certainly not be detected.

Long-term and delayed ADRs do not fit neatly into type A/B classification, but may be particularly significant once a medicine reaches the market place (Grahame-Smith and Aronson, 1992). Long term effects include: adaptive changes (e.g. tolerance to analgesics) and rebound phenomena (benzodiazepine withdrawal, rebound congestion with nasal decongestants). Delayed effects are among those most feared: cancer, impaired fertility and birth defects. Edwards and Aronson (2000) report a broader classification of ADRs to accommodate these types of adverse reactions. Type C or 'chronic' reactions are dose-related and time-related, Type D or 'delayed' reactions are time related and Type E or 'end of use' reactions are associated with withdrawal, with Type F or 'failure' reactions characterised by unexpected failure of therapy. Studies conducted over a relatively short time span are unlikely to identify and assign causality to rare or delayed effects. The identification of delayed effects is one of the particular concerns of spontaneous reporting (see also Chapters 3 and 5), and it relies on astute clinical observation.

4.2.2   *Mechanisms of pharmaceutical action*

The mechanisms of pharmaceutical action are extremely complex, but they can be broken down into three fundamental stages:
- how the medicine gets into the body (pharmaceutics).
- what the body does to the medicine (pharmacokinetics).
- what the medicine does to the body (pharmacodynamics).

In this section each of these stages is described in turn, together with examples of associated type A and B ADRs. Those aspects of physiology and pharmacology that lead to *quantitative* changes in drug action will normally increase the likelihood of type A reactions. On the other hand, *qualitative* changes, which are often related to immunological (allergic) or pathophysiological (influenced by disease) mechanisms, increase the likelihood of type B reactions.

a) Pharmaceutics

Pharmaceutics is the science of dosage form design. Pharmaceuticals must be formulated into suitable dosage forms before they are prescribed (usually by a doctor), dispensed (usually by a pharmacist) and administered (by the patient, nurse or carer). Errors at any of these stages can lead to ADRs. Type A 'pharmaceutical ADRs' result from variation in the rate and extent of drug absorption, whereas type B pharmaceutical ADRs are associated with variation in what is absorbed e.g. degradation products rather than active drug.

The actual quantity of drug in a tablet must fall within specified limits, but particle size, tablet coating and the excipients used in manufacture can all alter bioavailability (the percentage of the dose reaching the general circulation). Certain pharmaceuticals (e.g. digoxin) have a narrow therapeutic index, i.e. a small ratio of toxic to therapeutic dose, which means bioavailability must be carefully monitored. Different brands of modified (slow) release preparations often release the active constituent at different rates, leading to potential problems if the prescriber or dispenser switches brand. *Osmosin*, a slow release indomethacin (NSAID) preparation, was withdrawn from the market because the jet of drug released though a

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specially designed hole in the capsule effectively drilled though the gastric mucosa.

Pharmaceuticals may be administered wrongly. Deaths have occurred, for example, following the intravenous injection of intramuscular formulations. Patients may not be aware of the best way to use special formulations, for example, an incorrectly used asthma inhaler will deposit drug at the back of the mouth, rather than in the airways. Improper use of steroid inhalers will make a patient susceptible to both oral thrush and therapeutic failure. Patients' compliance with instructions varies considerably and may lead to dangerous under- or over-dosing.

b) Pharmacokinetics

Variations in pharmacokinetics are the major cause of type A ADRs. The action of the body on administered drugs can be broken down into four key stages: absorption, distribution, metabolism and excretion (Table 4.2).

Table 4.2: **What does the body do to drugs?**

Stage	Important sites	Major influences
Absorption	Small intestine Rest of GI tract	Physical characteristics of drug GI motility Interaction with food and drugs 'First-pass' metabolism*
Distribution	Plasma	Cardiac output Blood flow through particular organs Plasma protein binding
Metabolism	Liver	Enzyme activity, influenced by: smoking and drugs
Excretion	Kidney	Filtration rate Active secretion Passive reabsorption

* Drug breakdown in the liver *prior* to first reaching the general circulation

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Instructions to take certain tablets before or after food are usually designed to promote absorption or minimise the risk of ADRs. Penicillin tablets are broken down by stomach acid, so that taking them on an empty stomach minimises drug breakdown, which would result in therapeutic failure. Iron preparations are absorbed better on an empty stomach, but may cause stomach upset which is minimised by taking them after food.

During distribution, many drugs bind to plasma protein, while only free (unbound) drug is available to produce a pharmacodynamic effect (see below). The drug warfarin (an anticoagulant) is highly protein bound; therefore, small changes in binding can lead to large changes in free plasma concentration and unexpected decreases in blood clotting time (a potentially serious excessive effect). Some drugs cause ADRs by binding to tissue, for example, the antibiotic tetracycline is unsuitable for treating children because it forms a complex with bone, leading to diminished growth and discoloured teeth. Binding to DNA is an indicator of a drug's potential to cause cancers.

Drugs that are not readily water soluble undergo metabolism prior to excretion. The liver is the home of many enzymes, biological catalysts that speed up certain chemical reactions, which carry out metabolism. Inhibition or induction of these enzymes can cause ADRs. As cigarette smoking is an enzyme inducer, patients who both take theophylline, to dilate their airways, and smoke may experience toxic drug effects if they stop smoking and drug levels subsequently increase. Some ulcer treatments (H_2 antagonists) are also enzyme inducers, but the clinical significance of some theoretical interactions may be small.

Unbound drug is filtered out of the plasma, via glomeruli into the renal tubules, and ultimately is excreted in urine. The elderly and those with renal disease typically have low filtration rates. Thiazide diuretics, commonly prescribed for hypertension, compete with uric acid (one of the body's 'waste products') for active secretion into the tubules, a process which may lead to the accumulation of uric acid in the tissues, precipitating gout (Figure 4.1).

Figure 4.1: **Characteristics of the elderly**

Small lean body mass
Poor kidney function
Impaired liver function
Reduced organ reserve capacity

Source: D'Arcy 1986.

c) Pharmacodynamics

Somewhere between absorption and elimination, drugs exert their pharmacodynamic effect e.g. lowering blood pressure, increasing neurotransmitter release (to treat depression), or lowering blood sugar (to control diabetes). These processes are quantitatively influenced by body weight, age, sex, and drug administration, which may lead to type A ADRs. For example, blood pressure and body temperature fluctuate more widely in the elderly than in the young as homeostatic mechanisms begin to fail. Endogenous substances and drug molecules interact with receptors to produce their effects, and the number of receptors may change with age and disease state.

Qualitative changes in drug action may be caused by genetic, immunological, neoplastic and teratogenic mechanisms which result in type B ADRs.

Allergic and immunological responses are the main causes of type B ADRs (Table 4.3). There are many (but individually relatively unimportant) genetic disorders that also influence drug toxicity. Metabolism may produce novel antigenic compounds and drug allergy is often unpredictable. Type A ADRs are primarily due to a drug's secondary effects – actions different from the drug's therapeutic actions but still rationalisable from the known pharmacology of the drug – as opposed to augmentation of the drug's therapeutic action (primary pharmacology).

Table 4.3: **The classification of ADRs resulting in hospital admission**

Type A		Type B	
Description	**% of all reactions**	**Description**	**% of all reactions**
Secondary effects	71.5	Allergic	11.3
Excessive effects	16.8	Idiosyncratic	0.4
All Type A	88.3	All Type B	11.7

Note: Based on 13 studies, published between 1966 and 1989.
Source: Einarson, 1993.

4.3 The major causes of ADRs

The mechanisms of ADR production outlined in the preceding sections may appear, for the non-specialist, to be of little value or limited interest. However, knowing the mechanism of ADR production allows us to assess where ignorance or negligence in clinical practice will result in harm to patients. All ADRs are the end result of a chain of physical, biological and chemical processes. It seems clear that the biggest problem is what the body does to drugs, which implies that doses should be individualised to suit particular patients. It is also important to consider the extent and severity of diseases that influence the way the body handles drugs. Finally, care must be taken during medicine storage, preparation and administration.

The fundamental cause of an ADR, which we may modify, is the first step in its chain of production – often human error. For example, some drugs, patients and diseases are less tolerant of standard medicine doses. This section outlines where problems occur in practice, and provides a focus for treatment and prevention strategies. Reducing the number of ADRs most probably relies on better application of knowledge about drugs and changing human behaviour.

The biological mechanisms through which the therapeutic and toxic effects of drugs are mediated have already been outlined. In

understanding these processes, the distinction between type A and B ADRs has proved itself useful. However, it is slightly disingenuous to say that type A ADRs can be predicted from known pharmacology (cf. Section 3.2.3) whereas type B ADRs cannot. It would be more accurate to say that type A ADRs can be *explained* by known pharmacology; prediction is a different matter entirely.

There are certain intrinsic factors (related to patients' physiology, disease processes or fundamental drug characteristics) which may increase the likelihood of ADRs at normal drug doses, in the absence of any error and that no one could in any sense predict as far as the individual patient is concerned. There are other extrinsic factors (related to pharmaceutical manufacture, prescribing and administration) which may result in ADRs for entirely predictable reasons, for example, incorrect dosage. Major causes of ADRs are discussed below. The toxic nature of drugs, patient age and gender are intrinsic factors. Patient compliance and medical error are extrinsic factors. This distinction is important when considering prevention.

4.3.1 Toxic drugs

There are two reasons why a small number of drugs are usually held responsible for the majority of ADRs (see Chapter 3). Firstly, some pharmaceuticals are inherently toxic (i.e. they have a narrow therapeutic index). Secondly, a small number of disease states (e.g. infections, cardiovascular disease) are responsible for a great amount of morbidity: hence, many people are exposed to similar treatments and some will inevitably experience toxic effects. Caranasos et al. (1974) found that in their study just eight medicines caused one-third of all ADRs and 101 medicines the remaining two-thirds. In a report from the Boston study, Millar (1974) states that five medicines were responsible for 37% of ADR related admissions and 113 medicines for the remainder.

In the treatment of serious illness when there are few other options, pharmaceuticals with a generally unacceptable toxicity profile may be used. Taking into account widespread use, however, the majority of drugs are 'remarkably non-toxic' (Jick, 1974) when used appropriately.

Table 4.4: **Why does digoxin cause ADRs?**	
Use	Heart failure, especially in the elderly
Primary effect	Increases the force of heart contractions
Secondary effect	Excites other tissues, e.g. the gut, leading to nausea and vomiting (Neal, 1987:40)
Absorption	Sensitive to formulation and GI disease (Grahame-Smith and Aronson, 1992:14)
Elimination	Reduced as renal function deteriorates

Digoxin will serve as an example of a widely prescribed drug that is one of the commonest causes of ADRs and should be prescribed with care for a variety of reasons (Table 4.4). Significant predictors of ADRs to digoxin are digoxin dosage, *advanced* age (more than 80 years of age) and renal function (Pahor et al., 1993).

4.3.2 Age

The association between age and ADR incidence has been investigated intensively. However, despite an association between increased age and the incidence of ADRs (Korrapati et al., 1992), it is doubtful whether age can be considered an independent risk factor for ADRs. The number of medicines taken is probably more important, either because of exposure to a wider variety of potentially hazardous agents (increasing the cumulative risk of type B reactions for example) or the possibility of drug interactions (which may lead to type A reactions).

Grymonpre et al. (1988) set out to determine the cause of drug-related adverse patient events (DRAPEs) in older (over 50 years of age) medical patients. The risk of a DRAPE was related to the number of diseases prior to admission and the number of drugs used (see Table 4.5). Age was not correlated with the risk of a DRAPE, but females were significantly more likely to suffer an ADR (see Section 4.3.3 below).

A study of out-patients (see also patient non-compliance below) concluded that (Klein et al., 1984):

Table 4.5: **The causes of DRAPEs in the elderly**

Description	Percentage
ADRs (Karch and Lasagna definition)	49
Intentional non-compliance	27
Treatment failure	19
Alcohol	14
Medication error (accidental or unintentional non-compliance)	10

Source: Grymonpre et al. (1988).

- either the elderly are not more susceptible to ADRs (past reports that they were had been based on in-patient studies);
- or they do experience effects but are not aware of them;
- or younger patients are more likely to blame medicines regardless of the real cause.

As the population ages, it is possible that more truly age-related ADRs may be discovered. For a general review of age and ADRs see Beard (1992).

At the other end of the age spectrum, children are usually found to have lower ADR-related admission rates (range 1.8 – 3.2%) than the adult population, although child cancer patients had the highest rate (21.7%) of ADR related-admissions overall (Einarson, 1993). Lower rates of ADRs in children may also have little to do with age *per se* and may be explained by the nature of disease and treatment. Typically children may have milder disease, fewer medicines and more care; children also tend to have better compliance as they are not responsible for their own medication.

4.3.3   *Gender*

Perhaps surprisingly, Kando et al. (1995) concluded that female gender is a risk factor for ADRs. It was speculated that this could be explained mainly by pharmacokinetic factors, although pharmacodynamics and differences in hormone levels may also have

been responsible. FDA guidelines now state that women should be included as subjects in early clinical trials, which establish dosage regimens for later studies. Published evidence for the significance of female gender as a predictor of ADR-related admissions is equivocal (Einarson, 1993).

4.3.4   *Patient non-compliance*

In the community the possibility of compliance problems leading to ADRs is real. In studies of ADR-related hospital admission, where the issue of compliance was investigated, 22.7% of admissions were induced by non-compliance (Einarson, 1993). Under-compliance appeared to be a greater problem than over-compliance, but the issue can be complex and it is difficult to determine the direction of any cause-effect relationship.

Kruse et al. (1993) investigated the relationship between compliance and ADRs in patients taking an oral infertility treatment. The occurrence of side-effects was not associated with low compliance. However, compliance did decrease as the number of ADRs rose and with the occurrence of nausea and vomiting. Compliance dropped even further in patients who rated side-effects as moderate or severe compared to those with mild ADRs.

In an interesting approach to ADR investigation, 299 randomly selected out-patients were asked how often they linked adverse events to their medication and what action they took (Klein et al., 1984). Non-compliance among the subjects was common at 37.6%, of which 24.4% was due to forgetfulness and 22.5% incorrect dosing. However, patients' response to suffering an ADR rarely included intentional non-compliance (i.e. making a decision to change their own treatment regimen), and less than 5% of variation in medication compliance could be explained by reports of ADRs. An additional finding was that subjects who experienced an ADR were only moderately likely to discuss the issue with their medical care provider. The implication is that if we are serious about ADR prevention we must be prepared to seek out problems rather than relying on spontaneous reporting.

4.3.5   Medication error and ADEs

Medication error is error in the process of treatment choice or delivering the medication. Figure 4.2 illustrates the relationship between ADEs (injury resulting from medical intervention related to a drug), ADRs and medication error, which is implied by the *strict application* of the definitions given in Table 3.1. In practice, the distinctions between different types of drug-related incident may become blurred. It is, therefore, difficult (and perhaps dangerous) to consider them in too much isolation from each other. Consequently, it is appropriate to consider medical error and negligence as a cause of drug related harm, even if these incidents may not be considered ADRs *per se*. Recently, the problems of adverse events and medical error have been highlighted by the publication of 'To err is human: building a safer health system' by the US Institute of Medicine (Kohn et al., 2000) and, in the UK, 'An organisation with a memory' (Department of Health, 2000) and 'A spoonful of sugar: medicines management in NHS hospitals' (Audit Commission, 2001). The National Patient Safety Agency has been established within the UK NHS in order to reduce the risk of harm through error.

Doctors were judged to be primarily responsible for 72% of the incidents (actual and potential ADEs) investigated by Bates et al. (1993). Responsibility for the remaining incidents was equally divided between nursing, pharmacy and clerical personnel. Potential ADEs were all related to medication errors. Actual ADEs were assessed according to: preventability; type A/B nature; and whether or not they qualified as ADRs (WHO definition).

Figure 4.2: **The relationship between medication errors, ADRs and ADEs**

70% of ADEs were type A and 30% type B; with one exception, preventable ADEs were all type A. Patients who suffered non-preventable type A events were usually very ill, and being treated by drugs with a narrow therapeutic index. By WHO criteria, 44% of the ADEs (all of which were judged preventable) would not be ADRs: two-thirds because the pharmaceutical was inappropriate given patient characteristics, and one-third because of error in administration (e.g. wrong dose) (Bates et al., 1993).

The aim of a further study was to determine the frequency of medication errors, and how often these were associated with ADEs (Bates et al., 1995b). Medication error was common (5.3 errors/100 orders), and in about 1% of cases resulted in an ADE. Missing dose information (the most common error) is not in itself dangerous (see Figure 4.2); the practical difficulty was contacting the prescriber to find out his/her intentions. The other main causes of drug related injury were ADRs (Bates et al., 1995b).

To assess when medication errors occur and where preventive strategies could be targeted, Bates et al. (1995a) investigated 4031 hospital admissions over a six month period (Table 4.6). Medication errors which occurred at prescribing were more likely to be intercepted (48%). Transcription is not a problem in UK hospitals, because the prescription and medication administration record (MAR) are part of the same form. Wrong medicine dose was the most common error, followed by wrong choice of drug, known allergy, wrong frequency, and drug-drug interaction.

Table 4.6: **At what stage do errors occur?**

Stage	% of errors
Prescribing	56
Administration	34
Transcription	6
Dispensing	4

Source: Bates et al., 1995a.

4.4 Conclusions

Every effective pharmaceutical has a propensity to cause ADRs to a greater or lesser degree. Summaries of product characteristics give advice on the approved indications, suitable doses, cautions in use and contraindications. The greatest source of ADRs is inappropriate prescribing, which may include: use outside licensed indications, failure to adjust doses in the elderly, over medication and poor patient information. Powerful NSAIDs (e.g. indomethacin or naproxen) are occasionally used for simple pain relief risking needless GI bleeds and consequent hospital admission.

Patients are rarely told what common ADRs to expect. However, the minor gastric disturbances that are associated with many drugs would surprise few. On occasion patients do ask for a list of possible effects, in order to weigh risks and benefits in their own mind, or at least to know what to expect. Age, though often considered otherwise, is *not* an independent risk factor for ADRs. Patient compliance and medical error are the major problems relating to administration, and possible focuses for preventive action. Multiple medication, multiple illness, gender and drug toxicity must also be taken into account, particularly when considering appropriate management. Current management of ADRs and possible strategies for their management are the themes taken up in the next chapter.

5   TREATMENT AND PREVENTION

5.1 Introduction

The last chapter discussed the human causes of ADRs, and how they relate to the mechanisms of drug action. Preventive strategies are focused on the former, whilst the successful treatment of ADRs relies on a knowledge of the latter. In this chapter, Section 5.2 briefly discusses ADR treatment and Section 5.3 discusses prevention. In the case of an individual suffering a minor ADR, perseverance or cessation of drug administration are probably equally likely. Patients may take the decision to stop drug administration without taking professional advice. When professional advice on ADRs is sought it is unlikely to extend beyond reassurance, drug withdrawal, treatment of any symptoms and alternative therapy (if appropriate). Section 5.2 describes a model ADR treatment clinic in some detail.

The main emphasis of regulatory and spontaneous reporting systems is on early ADR detection. In Section 5.3, further steps that could be taken to prevent ADRs are discussed; firstly, in relation to what we could do to use our knowledge of pharmaceutical action and human failings; and secondly in relation to the steps necessary to improve that knowledge. Depending on their particular view of the world, health care professionals, politicians and patients concerned with ADRs are likely to prefer different means of prevention. In Chapter 6 an economic framework will be used to clarify the implications of this fact and show how a social optimum may be found.

5.2 Treatment

The broad distinction between type A and B ADRs is important for treatment. The conventional wisdom is that type A ADRs can be avoided or minimised by careful dose titration, limiting the need for active treatment. Type B ADRs, in contrast, require symptomatic treatment, of allergy for example, and drug withdrawal to prevent recurrence (see Section 5.3.1). The severity of ADRs is normally classified (see also Section 3.2.3) according to the treatment needed. Severe ADRs cause permanent damage or require intensive medical

care, e.g. surgery to control GI bleeding. Moderate ADRs require a change of therapy, withdrawal of the responsible drug and perhaps use of an alternative, or an increased length of stay in hospital. Mild ADRs require no treatment or extra care.

In hospitals where adequate information systems exist, prescriptions for common ADR treatments, e.g. steroids and antihistamines, can be used to help determine ADR incidence or trigger further investigation. In the worst cases, e.g. ototoxicity (leading to deafness) caused by aminoglycoside antibiotics or liver damage caused by paracetamol overdose, predictable ADRs can lead to lasting, untreatable and perhaps fatal damage. Although there has been some debate about the merits of adding methionine to paracetamol tablets to prevent liver damage, there has never been a requirement to do so. Jones et al. (1997) have expressed concerns about combined preparations, noting that one product (Pameton) was voluntarily removed from the market due to safety concerns. Although one product (Paradote) remains on the UK market, it is several times as expensive as generic paracetamol.

It is not possible, or useful, to reproduce here a comprehensive guide to the treatment of the ADRs affecting different organ systems or caused by particular medicines. Details of such matters can be found in Davies (1991). However, it should be clear that in the majority of cases it is not possible to separate the therapeutic and toxic effects of medicines: the difference is usually one of degree not nature. Often pharmaceutical treatment will be necessary despite adverse events, and a carefully tailored medicine and dosage regimen will be needed to maximise therapeutic and minimise toxic effects. This is most obvious in the treatment of cancer by chemotherapy.

Pharmaceuticals used to treat cancer are chosen for their ability to halt cell multiplication. Therefore, steps are often taken to minimise the effects on the body's normal cells. The normal cells affected by anti-cancer drugs are those with a fast turnover e.g. in the hair follicles and gastric mucosa. 'Cold caps' have been developed to limit blood (and drug) flow to the scalp, and anti-emetic drugs are routinely given as an adjunct to cancer treatment.

ADR treatment, therefore, consists of a combination of: 1) the management of ADR symptoms; 2) optimising therapeutic effects; and 3) the secondary prevention of further ADRs. Prevention, as discussed in Section 5.3, is taken to be the primary prevention of ADRs, i.e. trying to ensure that they do not occur in the first place. The identification and primary prevention of ADRs are partly public health issues. However, the management of ADRs, particularly in complicated cases, is firmly focused on the individual. The remainder of this section describes an ADR treatment clinic, which may form a model of best practice.

A clinic (in Ontario, Canada) devoted to the assessment and management of ADRs is described by Recchia and Shear (1994). Specialist treatment of ADRs was thought to be necessary for a number of reasons:
- traditional management, by referral to a single specialist or drug withdrawal, was often an exercise in avoiding responsibility;
- ADRs complicated and interrupted treatment;
- ADRs increased patient anxiety and clinician frustration;
- ADRs prolonged hospitalisation.

They believed proper assessment and treatment of ADRs was central to improving patient care. For example, whilst many people claimed to be allergic to penicillin, far fewer actually were. Alternative medicines may be expensive and unnecessary. Spontaneous reporting was believed to be too focused on the identification of idiosyncratic reactions to new pharmaceuticals. Epidemiological evidence of low ADR incidence was considered cold comfort to the individual patient who thought they had suffered a reaction in the past and feared the same medicine might cause one again. Clinical trials were limited to small groups of individuals with similar problems to the exclusion of relevant sub-groups.

In response to some of these problems, the clinic combined clinical and laboratory methods with clinicians having the best knowledge of pharmacology and up-to-date knowledge of ADRs. It conducted 300 patient consultations per year. Referral to the clinic (from GPs, other specialists and dentists) involved five distinct stages:

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- initial assessment;
- history taking and determination of relevant issues;
- detailed analysis by a team of specialists;
- communication of findings to the patient and family physician;
- follow up (particularly important if the patient was 'cleared' of a suspected ADR).

ADR history taking in the clinic was complicated by many factors. Reaction details were unknown in 10% of cases; recall bias was a problem; GI upset and fatigue were often reported (incorrectly) as 'allergy'; dosage, onset, challenge, rechallenge, and drug history were sometimes unclear. Underlying illness was crucial as ADRs could be caused by physical health, the environment or the emotional state of the patient. Diagnosis was often not possible on the basis of symptoms because a limited number of clinical manifestations were associated with a large number of drugs. In all, 48% of patients visiting the clinic complained of skin lesions as their main ADR. Although patients rarely ended up with a conclusive assessment of their allergy status, they did obtain a 'rational conclusion about whether the attribution of the suspected agent to the reaction is plausible, given the details of the history and the pathology of the reaction observed'.

Where there is a demand, this type of clinic would seem to provide a comprehensive model for the management of complicated clinical cases. However, its cost-effectiveness has not been determined, and should be the subject of further investigation.

5.3   Prevention

The type A/B distinction is based on incidence and known pharmacology. ADRs can also be classified on purely mechanistic grounds as those related or unrelated to the principle pharmacodynamic action of the drug (Rang et al., 1995). These distinctions make sense respectively for the practising clinical pharmacologist who deals with ADRs in a patient with particular problems, and the scientist studying mechanisms of action.

However, a distinction between ADRs due to intrinsic (fixed characteristics) and extrinsic (adaptable behaviour) causes identifies more clearly what can be done to reduce ADR incidence. At the population level, extrinsic causes will usually lead to type A ADRs which can usually be reversed by reducing the dose or withdrawing the drug (Pirmohamed et al., 1998). Intrinsic causes lead to type B ADRs which cannot be predicted from a drug's known pharmacology. In individual cases, the distinction is not so clear cut; type A and B reactions may result from intrinsic and extrinsic causes.[1]

Preventing 'extrinsic ADRs' requires better application of the knowledge we have already, and it must include a consideration of human motivation and behaviour. The prevention of 'intrinsic ADRs' requires better knowledge of drug action and interaction, with other drugs and in living systems, which is best gained from fundamental research.

The distinction between extrinsic and intrinsic ADRs is not fixed. For example, if the mechanism for the production of a bizarre allergic reaction remains unknown the cause may be considered intrinsic (to the medicine or patient). However, there must be some explanation for the reaction even it is beyond our current understanding. When we do understand the mechanism, putting us in the position to identify individual patients prone to allergic reactions or test pharmaceuticals more properly, the cause of any subsequent ADRs would be considered extrinsic (associated with the prescriber or manufacturer).

5.3.1   ADRs caused by extrinsic factors – using knowledge of drug action

Extrinsic factors are changeable e.g. dosage, formulation, route of administration, concurrent therapy, storage conditions. The prevention of 'extrinsic ADRs' (the application of our knowledge) begins with an assessment of the size and nature of the problem (see Chapter 3) and ends with systems of quality assurance and risk

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[1]   Bates et al (1995b) use the same framework to distinguish 'preventable' and 'unpreventable' adverse drug events.

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management. Prevention of this sort must necessarily focus on individual actors (pharmaceutical companies, doctors and other medical staff, patients, managers) and the interactions between them. Much of the literature is focused on medical error and its relationship with adverse drug events (ADEs). It is also apparent that when patients experience problems with therapy they will not necessarily consult with their carers.

Schumock and Thornton (1992) suggest that preventable ADRs include (but are not limited to): known allergic reactions; avoidable dose-related reactions; ADRs secondary to drug interactions; idiosyncratic reactions that have occurred previously; and drug reactions associated with inappropriate compliance, prescribing or administration. They suggested seven questions (Figure 5.1) to assess preventability, which should be fed back into the improvement process. Answering 'yes' to one or more questions suggested that the ADR may have been preventable.

Pearson et al. (1994) studied factors associated with the preventable adverse drug reactions (classified by the Schumock and Thornton criteria) in a community hospital patient population. They hoped to use this information to develop strategies by which pharmacists could prevent ADRs (the Karch and Lasagna definition) in their patient population. Interestingly the hospital of 500 beds actually had

> *Figure 5.1:* **Questions to assess ADR preventability**
>
> 1 Was the medicine involved in the ADR *not* considered appropriate for the patient's clinical condition?
> 2 Was the dose, route and frequency of administration *not* appropriate for the patient's age, weight and disease state?
> 3 Was the therapeutic drug monitoring or other laboratory test *not* performed?
> 4 Was there a history of allergy or previous reactions to the medicine?
> 5 Was a pharmaceutical interaction involved in the reaction?
> 6 Was a toxic serum drug level documented?
> 7 Was poor compliance involved in the reaction?

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departments of risk management and quality assurance. 203 ADRs (1.9% of admissions) were reported and 38 (19%) classified as preventable. Preventable ADRs were found to be more severe than non-preventable ADRs. These ADRs were also associated with longer lengths of hospital stay. The main causes of preventable ADRs were: known pharmaceutical allergies in individual patients; anticoagulant or thrombolytic medicines ('clot-busters'); lack of appropriate monitoring; and failure to adjust dosage in patients with impaired renal function. Suggestions for prevention (specific to the hospital) were: a cephalosporin protocol for patients allergic to penicillins; amended admission forms, which included a section on pharmaceutical allergy; for nurses, a list of drugs that should be avoided for patients with a history of codeine/morphine allergy; the employment of a pharmacy specialist in cardiology to educate staff on appropriate use of cardiovascular agents; and expanded services for drug dose monitoring and adjustment.

Medical error (see Chapter 4) is undoubtedly a major cause of harm related to pharmaceutical use. The prevention of this harm might involve an extension of those quality assurance systems that govern pharmaceutical manufacture. A guiding principle of quality assurance (QA) is that quality must be built into the production process. Quality control is an important part of QA, but quality cannot be tested into an end product. In the clinical setting, perhaps ADR incidence assessment is analogous to quality control. However, knowing the size of the problem is not enough. Hence, many hospitals have established quality assurance and risk management teams. Such initiatives require careful monitoring and investigation, in order to highlight successes, failures and relative performance.

QA, in hospitals or general practice, should aim to reduce rates of error to an optimal level, since the cost of preventing ADRs entirely would be prohibitive (Leape et al., 1991, and see Chapter 6). Negligence, which may account for 25% of ADEs (Brennan et al., 1991), requires corrective and disciplinary actions. However, real progress depends heavily on systems analysis, education, development, dissemination of guidelines and standards setting. All these factors, including their

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relationship with each other, should be considered, rather than just identifying culpable individuals (Leape et al., 1991).

All hospitals operate a system for pharmaceutical ordering for patients which clearly defines prescribing, dispensing and administration. But responsibility for ensuring the patient does not receive a harmful dose is shared. To give a simple example, deaths have been caused by the administration of the wrong strength of intravenous potassium chloride. Of course we expect hospital staff to read labels correctly, but a systems approach would limit the number of strengths available and clearly label (perhaps with colour coding) stronger solutions. Human error will always occur, but can be minimised. An example is the administration of vincristine by spinal injection rather than intravenously, an error which proved fatal in a well publicised UK case in 2001 (Dyer, 2001). A report on this particular incident recommended that systems be introduced requiring intravenous cytotoxic drugs to be given at different times, by different people, and in different locations to spinal drugs. National guidance on the safe administration of intrathecal chemotherapy was subsequently issued to the NHS.

Optimal prevention strategies may cover many types of pharmaceutical. Doctors' ordering practices are an obvious target for intervention (Bates et al., 1993). Bates et al. (1995a) found that no single pharmaceutical accounted for more than 9% of preventable ADEs. Use of sedatives and analgesics was often discretionary, and initial doses were found to be too high. Many errors could be checked for by computerised prescribing systems. What constitutes an optimal strategy for prevention will, however, vary from institution to institution depending on the systems already in place. As clinical pharmacology is reported to be one of the less well taught subjects in postgraduate medicine, education could have a major part to play (Health Committee 1994: p.39). For example, Chan et al. (1992) reported that, in their study, 18 out of 21 ADR induced admissions in those over 60 years old which were associated with sulphonylureas used along with diet to treat non-insulin dependent diabetes mellitus, were caused by long acting drugs inappropriately prescribed in that age group.

In terms of in-patient ADR incidence assessment, active medication chart review is much more successful than waiting for spontaneous reports (Bates et al., 1993, see Chapter 3). Persuading people to report mistakes is problematic if they expect to be disciplined, or if they do not consider the adverse events to be drug related. Unfortunately chart review is expensive.

It has also been found that errors made by doctors were more likely (than those made by nurses and pharmacists) to lead to actual injury (an ADE). This suggested that prevention could be directed at doctor decision making or checks on those decisions. However, the data was also consistent with the hypothesis that nursing and pharmacy staff have already come further than doctors in developing effective safeguards for the process of giving drugs (Bates et al., 1993). Non-medical staff are perhaps more likely to go by the book or, to put it another way, are less likely to be involved in judgements that involve calculated risks based on extensive clinical experience. Medicine remains an art as well as a science (Weatherall, 1995).

Bates et al. (1993) found that 25% of ADEs in their study were unpreventable because they represented calculated risks in very ill patients. ADEs were also more common in intensive care and medical units, in which more drugs were administered and the severity of illness was higher. It should also be remembered that much routine prescribing in hospital is done by relatively inexperienced (and highly stressed) junior doctors. Medication errors are 100 times more common than ADEs (Bates et al., 1995b). Basic medication errors are unlikely to harm patients, but they create work for hospital staff (Bates et al., 1995a), and the cost-effectiveness of their prevention should be investigated.

GPs have an important role to play preventing ADRs, because they are in a position to regularly monitor patients. It has been suggested (Ioannides-Demos, 1994) that they should routinely:
- identify patients at risk from ADRs;
- ensure that the most appropriate drug and dose is prescribed;
- recognise potential ADRs and interactions;
- prescribe the minimum number of pharmaceuticals;

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- regularly review all drug treatment;
- adequately instruct patients in the administration of medications and the action to take if any unintended reaction occurs.

This list of actions is both comprehensive and challenging. However, other members of the primary health care team, particularly the pharmacist, are in a position to help by offering specialist advice to both GP and patient. In a recent UK study, a pharmacist investigated 216 nursing and residential home patients' regular medication. It was found that around 10% of the patients' regular medications were unnecessary (116 out of 1158 items) and 7.4% (86) were subsequently discontinued with no adverse effects. Additionally, dosages of 38 (3.3%) medications were found to be incorrect and 26 (2.2%) were altered on the pharmacist's recommendation (Wright et al., 1994).

In a US study, one-third of new cimetidine users filled both a prescription for cimetidine and a drug known to interact with it within a 30 day period. Increased hospital use was significantly lower for such 'at risk' patients who used a single pharmacy than for those who used several pharmacies (McCombs et al., 1993).

5.3.2   ADRs caused by intrinsic factors – gaining knowledge of drug action

Intrinsic factors are those we cannot change: a patient's age, genetic make-up or the fundamental properties of a pharmaceutical. However, we can do our best to understand these factors and use particular drugs chiefly for the treatment of the most suitable patients. The main debate concerns whether this process is best conducted pre- or post-marketing. Allied to this is concern about the length of the licence approval and amendment process.

a) Pre-marketing

Pre-clinically, drug toxicology (e.g. carcinogenicity and effect on reproduction) is determined in animal models. Clinical research and

development is normally conducted in three phases:
- Phase 1. healthy volunteers are given single and multiple doses to determine potential toxicity (e.g. common type A ADRs) and the human pharmacokinetic profile;
- Phase 2. small numbers of patients receive the drug, which enables information on efficacy and dosage to be collected;
- Phase 3. full scale clinical trials are arranged that build on the information from earlier phases and provide the information on safety and efficacy required for marketing authorisation.

This process works well and produces information which companies, regulators and clinicians trust. Lack of efficacy and gross toxicity are the main reasons that prospective drugs fail to be marketed. For example, one-third of pharmaceuticals which are withdrawn at the development stage have inappropriate pharmacokinetic properties, e.g. poor absorption (Prentis et al., 1988). It is understood that even the largest clinical trials will only identify the most common ADRs.

There are calls, particularly in the US, to reduce regulatory delay, which prevents early marketing of useful drugs and discourages the entry of new research led companies into the drug market (Lenard et al., 1995; Green, 1995). The market may, or may not, be best placed to judge the acceptability of a drug's *prima facie* toxicity profile relative to its clinical benefits, with due regard to the seriousness of the medical condition and the alternative treatments available (including non-drug intervention). This issue is explored in more detail in Chapter 6.

b) Post-marketing

ADR signals to feed into national reporting schemes are generated by (see Gruer, 1991):
- spontaneous reporting;
- phase 2 and 3 clinical trials that continue post-marketing for new indications or patient groups;
- phase 4 trials of safety and efficacy in authorised indications;

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- company-sponsored safety assessment of marketed medicines (SAMM, post-marketing surveillance studies);
- epidemiological studies (cohort and case-control).

There is much debate about the proper structure and role of post-marketing studies, pharmacovigilance (monitoring and assessing ADRs) and the diffusion of pharmaceutical information. The main aim of all types of post-marketing study should be to gain as much accurate information on pharmaceutical use and effects as quickly as possible. This will maximise the benefits and minimise the costs of drug utilisation (see Crooks and Mooney, 1978, and Chapter 6 below).

Different types of post-marketing study have their own strengths and weaknesses:

- clinical trials are expensive but necessary to provide new efficacy data;
- cohort studies require large numbers of patients but can identify many outcomes (including ADRs) in those taking a particular medicine;
- case-controlled studies (e.g. based around one adverse reaction) can confirm causality when there are many factors influencing the treatment of a relatively small patient group;
- company sponsored SAMM is sometimes seen as little better than promotion or advertising (La Puma, 1995).

Venning (1983b) identified the study designs which generated the first alerts of 18 important post-thalidomide ADRs. These were: anecdotal and single case reports (13); valid case studies (2); and cohort studies (3). Venning (1983c) believed that, in order of relative efficacy, there were four approaches to earlier discovery of ADRs:

- record linkage with data on incidence of ADRs and prevalence of pharmaceutical usage;
- review of published first alerts, with prompt case-control studies for verification;
- post-marketing surveillance of cohorts of pharmaceutical users;
- voluntary reporting systems.

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An assessment of record linkage was carried out in Tayside, Scotland (McDevitt et al., 1987). The study was able to take advantage of Scotland's unique patient identifiers – the community health index number - and central hospital admission records, to link prescribing data to morbidity and mortality data. In this particular case no new data collection was required. However, the resources needed for the organisation of record linkage on any scale would be great.

Current developments in pharmacovigilance revolve around the harmonisation of spontaneous reporting systems in the EU (Charlesworth, 1993; Danan, 1994; Bénichou, 1994b). However, the only great advance over the past 25 years has been the dramatic increase in the data handling capacity of computers (Edwards, 1994). Using such power for the modelling of drug structure at one end of the drug development process and record linkage at the other may yield great benefits (Edwards, 1994).

New European arrangements for pharmacovigilance have clarified the respective responsibilities of pharmaceutical companies, Member States and the EMEA. More rapid open communication should have benefits. One practical outcome is that pharmaceutical withdrawal from European markets may be more harmonised than in the past (Steward and Wibberley, 1992; Spriet-Pourra and Auriche, 1994). However, given the heterogeneous nature of medicine utilisation and disease patterns, in the short to medium term sharing information is likely to raise more questions than it answers (see Griffin, 1987). Do variations in patterns of ADRs result from genuine differences in morbidity and the need for health care services, or from a failure to apply knowledge of pharmaceutical action appropriately (see Anderson and Mooney, 1990)?

5.4 Conclusions

The majority of ADRs require little treatment; a smaller number will need symptomatic treatment or require a change in pharmaceutical therapy; and a small minority of serious ADRs are untreatable. It is important that clinicians are able to distinguish the effects of a drug

from that of the disease (i.e. to identify an ADR) and to then choose the appropriate course of clinical action to deal with the ADR.

In terms of prevention of ADRs, specific advice is available concerning pharmaceutical therapy in the elderly as a group, and the properties of the most troublesome medicines are well known. Medicines with teratogenic effects (causing abnormal fetal growth) or those associated with grossly unacceptable risks should never reach the market place. Careful monitoring of new pharmaceuticals should aid the accurate quantification of known type A reactions and thus lead to more appropriate use if the knowledge can be disseminated. To gain a deeper understanding of the issues there is unlikely to be any substitute for fundamental clinical research.

However, we cannot maximise the health gain from pharmaceutical use by having no ADRs. In the next chapter a possible framework for reconciling our desire to enjoy the clinical benefits of pharmaceutical use without unacceptable levels of ADRs will be discussed.

6 ECONOMICS

6.1 Introduction

The preceding chapters have adopted a clinical focus. That is, they are primarily concerned with the impact of ADRs on health status. Risk-benefit analysis is about judging the probability of a medicine doing more good than harm when given to a patient, that is, the balance between efficacy and safety. In this chapter, the cost of producing health using medicines will also be considered. So far, important questions have been raised, such as:

- how much information is needed before a pharmaceutical receives marketing approval?
- what type of post-marketing surveillance should be in place?
- given the risk of ADRs, how much pharmaceutical treatment should be employed?

Economists argue that it is best to address these questions by explicitly considering the costs (resource use) and consequences[1] (health effects) of pharmaceutical treatment and ADR detection alongside each other. This chapter, therefore, explains the basic principles of economic evaluation and then applies them to the question of ADR detection and management. Section 6.2 describes the basic principles of economic evaluation and explains how it differs from clinical evaluation.

Section 6.3.1 outlines the costs and consequences of pharmaceutical treatment once a product has been granted marketing approval. It is argued that, if we wish to have clinical benefit from pharmaceutical treatment, then ADR toxicity must be accepted. Economic analysis indicates that maximising health gain from drugs involves accepting a non-zero level of ADRs. Ideally, it would be possible to reduce the negative effects of drug therapy while maintaining the positive benefits. However, reducing ADRs (by, for example, increased monitoring of treatment or acquiring additional information about its

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[1] Throughout this chapter the term 'consequences' (beneficial and harmful health effects) is used to describe what economists would usually call 'benefits'. This is to distinguish consequences from the benefits (beneficial health effects only) in risk-benefit analysis.

effects) requires the use of resources which could be used to achieve health gain in other ways. Whether it is worthwhile to devote these resources to the prevention of ADRs depends on the health gains thus forgone. Both too many and too few ADRs can each indicate that alternative levels of pharmaceutical treatment would be more socially desirable. In Section 6.3.2, a case study of treatment with NSAIDs shows how society could gain if the number of associated ADRs were to decrease and a case study of asthma treatment shows how society could gain even if the number of associated ADRs were to increase.

In addition to measures which can be taken in clinical practice to optimise drug treatment, we may also consider the way in which pre-marketing research is carried out. Section 6.4.1 applies the principles of economic evaluation to pre-marketing detection of ADRs. The costs and consequences of gaining information on pharmaceutical action are outlined. The section shows how health care purchasers, pharmaceutical companies and patients may each prefer to have different amounts of information before marketing approval is granted. Section 6.4.2 discusses a general approach to estimating the value of further research (which could be conducted pre- or post-approval). In Section 6.4.3, post-marketing surveillance is discussed in general terms. It is argued that the primary role of post-marketing surveillance is not ADR prevention, but the continuing provision of information, which in turn influences clinical decision making and modifies pharmaceutical use. Section 6.4.4 presents evidence on the cost-effectiveness of interventions which can be used to reduce the number of ADRs in the clinical environment.

The lexicon of medicine safety is confusing, and it is clear from the literature that the same terminology is often used with different (though equally precise) meanings. Therefore, in this chapter the term 'adverse drug reaction' (ADR) is used to describe an adverse event, according to the appropriate official definition, causally related to the administration of a medicine within its normal dosage range, but sometimes inappropriate for a particular patient. We do not include the failure of a medicine to accomplish its intended purpose as an adverse event.

6.2 Clinical and economic evaluation

Economic evaluation compares the *costs* and consequences of alternative health care interventions, whereas clinical evaluation considers only consequences. Two basic principles form the foundation of much economic analysis: 'opportunity cost' and 'the margin'. Whenever we commit resources (chiefly skilled people and the equipment and space they need) in a particular way, we forgo the opportunity to use those resources in other alternative ways.

Therefore, cost is the sacrifice of consequences in the best alternative use of resources. For example, the opportunity cost of using more of the cardiac services budget for extra heart transplants may be the health consequences arising from the reduction in the number of bypass grafts performed. Resources are always scarce relative to the number of alternative uses for them. Economic analysis aids the efficient allocation of resources, by examining whether the health gain produced by one pattern of resource use is greater or less than that generated by alternative uses and whether or not a re-allocation of resources will serve to increase health gains.

This process usually involves changes 'at the margin' to existing patterns of allocation. For example, the average cost of heart transplants is not as important as the *additional* (marginal) costs of *additional* operations. These are the resources that have to be found from elsewhere e.g. by reducing the provision of bypass grafts.

To compare costs and consequences each must be identified, measured and valued. The example given in Box 6.1 illustrates the difference between considerations of risk-benefit and cost-consequence with reference to the testing of blood donations for HIV (Holmes, 1996).

Concluding that the new HIV test described in the box is not justified on cost-consequence grounds makes certain important assumptions:
- that there is a fixed budget for saving lives;
- that given this fixed budget, $10 million is too much to pay (give up) to save a life;
- that it does not matter *whose* life is saved, so long as the total number of lives saved is maximised.

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> **Box 6.1:** **Testing blood for HIV: risk-benefit and cost-consequence**
>
> In this example, every unit of blood collected is tested for HIV antibodies. Infected blood is thrown away. People who have been recently infected with HIV may not develop detectable antibodies for up to 22 days. They remain infectious during this 'window phase'. In the US around 35 HIV infections per year are caused by the transfusion of blood collected from infected patients during the window phase. A new test is available which can detect HIV in blood sooner after infection. It is thought that if every unit of blood in the US was subjected to this new test (in addition to the old one which is still necessary) then 10 extra HIV infected units would be detected each year. On the grounds of risk-benefit, the FDA have told blood banks they must use the new test after it has been approved.
>
> However, the new test will cost an extra $40-$100 million dollars per year, or up to $10 million dollars per infection prevented. An American virologist has calculated that after accounting for the health status of those receiving transfusions the extra HIV test will cost $2.2 million per extra life-year saved. In fact $100 million is equivalent to the entire AIDS prevention budget of the US Centers for Disease Control. It is highly likely that spending the $100 million on something other than an extra HIV test would save more life-years. On cost-consequence grounds the use of the new test cannot be justified.
>
> *Source:* Holmes, 1996.

At a population level these assumptions may be reasonable. For example, when considering road safety improvements, the UK Department of Transport values a 'statistical life' at about £1 million ($1.7 million, €1.4 million). However, many, perhaps most, people would wish to modify the distribution of resources implied by the pursuit of efficiency in order to take account of social justice or equity. At the very least, policy decisions influenced by cost-consequence analysis must be seen as acceptable by those who implement them and by those people likely to be affected. Of course patients can influence the benefit-risk trade-off to themselves by refusing treatment if they do not share society's (and their doctor's) view of risks worth taking to achieve the health gain on offer. However,

it is much harder for them to gain access to a medicine that their doctor, health care purchaser, or the licensing body, does not think has an acceptable benefit-risk trade-off.

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6.3 The costs and consequences of pharmaceutical treatment

6.3.1 An economic approach

An assessment of the scale and nature of ADRs caused by marketed pharmaceuticals was presented in Chapter 3. Economic evaluation requires that costs and consequences are identified, measured and valued at an acceptable level of accuracy. Serious attempts have been made to measure and value the costs and consequences of pharmaceutical treatment.

Ernst and Grizzle (2001), updating a study by Johnson and Bootman (1995), estimated the direct health care costs of drug-related morbidity and mortality (including ADRs and therapeutic failure) in the US to be $177.4 billion in 2000. This estimate relates to health care costs as a result of negative therapeutic outcomes in ambulatory populations. The authors considered any departure from an optimal outcome of drug therapy, namely treatment failures (TFs), new medical problems (NMPs) and a combination of TFs and NMPs. Hospital admissions were estimated to account for $121.5 billion, long term care admissions for $32.8 billion, physician visits $13.8 billion, emergency department visits over $5.8 billion and additional treatment more than $3.5 billion. The total of 177.4 billion represents over 20% of US health care expenditure in 2000.

Dukes (1992) suggested valuing the clinical harm done by ADRs by using compensation awards for loss of life, limb or amenity ('implied values'). This would in principle combine consequential health care costs with the impact on earnings and on enjoyment of life. However, calculating the implied value of human life from social decision making (whether from court awards or other sources such as the premiums in wage rates for dangerous occupations) produces

Table 6.1: **Valuing the costs and consequences of minor illness (1984 prices)**

Symptom severity	Sample	Value of consequences* (US$)	Value of costs¢" (US$)
Heavy drowsiness	5	142.00	1.80
Headaches	46	108.71	3.45
Nausea	17	47.88	2.50

*Amount that would be paid to avoid one extra day of the symptom.
¢"Per diem expenditure on doctor visits and medicines plus lost earnings.

Source: Berger et al., 1987

results that vary greatly between countries and sectors of the economy. Attempts have been made to value the costs and consequences of minor illness directly, i.e. from peoples' stated expenditure and preferences rather than compensation awards (Berger et al., 1987). These estimates are therefore additional to the health care costs identified by Ernst and Grizzle (2001) above. Table 6.1 lists peoples' valuations for three minor illnesses that are also commonly experienced as ADRs. Notice that although the private cost of illness was small in all cases, subjects valued the relief from minor symptoms relatively highly. Thus, if even a small proportion of patients experience a trivial ADR following pharmaceutical treatment the effect on their welfare may be considerable.

Some of the harm caused by drugs is doubtless avoidable, and Section 6.4 will consider ways in which ADRs might be prevented. However, any level of drug treatment will always be associated with some ADRs. Therefore, when drugs are used optimally, (i.e. at a cost-effective level given net health gains) there will be an associated level of ADRs. Reducing drug utilisation, and thus the number of ADRs, below this level is inefficient just as increasing the level of utilisation, and the level of ADRs, is inefficient. Optimising drug treatment may require

targeting treatment on sub-groups of the general population of patients who could benefit. Whether the level of utilisation, and thus the level of ADRs, is too high or too low will be determined on a case by case basis.

The following case studies give an example of underutilisation and one of overutilisation.

6.3.2 Case studies

a) Non-steroidal anti-inflammatory drugs (NSAIDs)

As a general rule, the more clinically effective NSAIDs produce more ADRs as a result of their principal pharmacodynamic effect: inhibition of prostaglandin production, which both reduces inflammation in the joints and makes the stomach more susceptible to ulceration. The most common ADR to NSAIDs is dyspepsia. The most common (but relatively rare) serious ADRs to NSAIDs are, in rank order: peptic ulceration, renal effects, skin reactions and CNS effects. Recent data have shown that even small doses of the most well known NSAID, aspirin, (taken to prevent heart attacks) increase the risk of peptic ulcer bleeding (Weil et al., 1995). In this case, the benefits of prophylactic aspirin (to reduce the incidence of heart attacks) were considered likely to outweigh the possible risks. However, such findings indicate that not even the smallest doses can be considered completely safe. There is a direct linear relationship between daily dose of NSAIDs and the risk of GI complications for people of any age (Garcia Rodriguez and Jick, 1994).

When NSAIDs use is high they may be the direct cause of 20-30% of all cases of complications of peptic ulcer disease (Brooks and Day, 1991; Langman, 1987). Although the risk associated with an individual prescription may be only one in 10,000, in the UK this equates to at least 2,000 hospital admissions annually (Langman, 1987). Meta-analysis of clinical trial data shows that taking an NSAID increases the risk of upper GI bleeding by about 3.5 times (Belton et al., 1994). Replacing the observed pattern of pharmaceuticals in use with those with the lowest relative risk could halve the number of

upper GI ADRs, and the risk could be cut further by only prescribing the lowest effective doses of NSAIDs, according to Langman et al., 1994.

Thus the literature suggests that NSAID prescribing results in an excess ADR rate, where the clinical benefits of treating a group of patients with a pharmaceutical are outweighed by the risk of ADRs, i.e. on balance patients' health status is reduced by treatment. If prescribing could be restricted to more appropriate patients, then the number of ADRs associated with NSAIDs could be reduced, patients' health status improved and resource use reduced.

It is possible to quantify the effects of such a shift in prescribing. Bloor and Maynard (1995) reviewed the toxicity and cost of (non-aspirin) NSAIDs, which accounted for 3.5%-4% (about 25 million) of UK prescriptions. On the basis of the UK's 1994 expenditure on NSAIDs of around £175 million, their illustrative model showed that if prescribing were reduced by 25%, average dose reduced by 10%, and patients were switched to less toxic medicines, up to £86 million could be saved. In addition, the number of serious ADRs and serious GI complications could be reduced without compromising the quality of life of patients using the drugs.

Recently, the introduction of Cox II selective NSAIDs has, on the basis of a review of the evidence for the National Institute for Clinical Excellence (NICE, 2001), presented the possibility of reducing the incidence of gastrointestinal adverse events while maintaining efficacy equivalent to established NSAIDS. An economic evaluation referred to by NICE (pre-publication) has suggested that, in patients at high risk of GI events, Cox II inhibitors may provide greater health benefits at a lower cost than an established NSAID combined with an anti-ulcer drug (Maetzel et al., 2002).

b) Asthma treatment

Asthma affects 5% of adults and up to 20% of children in the UK, and its prevalence has risen over time (Thomson, 1995). The Audit Commission (1994, p.16) reported that asthma has been under-

diagnosed. Patients' lack of compliance with all types of prescribed asthma medication has also been a significant problem (Thomson, 1995). Asthma relieving medication tends to be more popular with patients because of its immediate beneficial effect. In contrast, asthma preventing medication will reduce the frequency of attacks and possibly hospital admission but has no immediate tangible effect. It calculated that if GPs were to prescribe half as many steroids as bronchodilators (1:2 ratio), the additional pharmaceutical costs of £75m for the more expensive bronchodilators would be outweighed by savings to the NHS (Audit Commission, 1993).

6.4 The costs and consequences of ADR detection

6.4.1 Pre-marketing

Marketing approval is granted when a pharmaceutical's quality, safety and efficacy have been established to the satisfaction of the regulatory authorities. The length of time a new pharmaceutical should be held from the market by testing and the process of approval have been matters of debate on both sides of the Atlantic but particularly in the US (Anon, 1995; Lenard et al., 1995).

The FDA in the US and MHRA in the UK are essentially concerned to avoid 'type 1' errors, i.e. approving a drug and subsequently discovering the risk of ADRs outweighs the clinical benefit. Historically, it was the cautious nature of the FDA that saved the US from the worst of the thalidomide tragedy; US approval was delayed for long enough for major problems to be noticed in European markets. The cost of the drug *per se* is not an explicit concern of pharmaceutical regulation authorities. In some countries, as a separate matter, drugs must demonstrate economic efficiency before the state will approve reimbursement at the public's expense.

Pharmaceutical companies and patient groups are more concerned with 'type 2' errors, i.e. failure to gain marketing approval for a beneficial product or, in the 'least worst' case, its delayed introduction.

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The general public's attitude towards risk is less clear, but if possible it should influence policy. If a medicine for an already well-treated illness has its marketing approval delayed, then the forgone clinical benefits are likely to be small. In such cases, when assessing the balance between risks and benefits, we may be quite cautious and demand better evidence of safety. Anecdotal evidence would seem to suggest, not surprisingly, that people suffering from diseases with a poor prognosis are prepared to accept greater risks than the general population. Examples are those who have AIDS, someone with a disease for which there is only experimental treatment (Price, 1996) and sufferers of multiple sclerosis.

The regulatory authorities may, as a consequence, also have a variable approach to risk. Medicines for poorly treated conditions (especially those which are life threatening or chronically debilitating) are sometimes fast-tracked by regulatory authorities, and patient pressure groups clamour for their release on to the market.

Table 6.2 lists the main costs and consequences of delayed pharmaceutical marketing, according to where the economic burden falls. From each actor's individual perspective their own net financial burden will be considered most important. The costs of reducing the level of ADRs by increased pre-market testing (so enabling drugs to be better targeted, doctors to be warned about potential ADRs or for the drug not be approved) are borne by the pharmaceutical company (increased trials and testing) but may be passed on to payers in the form of higher prices for pharmaceuticals generally. The biggest cost to the company is lost revenue from the new product. The purchaser is not having to pay for the new treatment or for corrective treatment of extra ADRs, but is incurring the costs of treating the disease in other ways. Patients are denied the benefits of effective treatment (no new medicines) but may suffer fewer ADRs, and additionally they may try alternative non-NHS therapies/self-help to alleviate their condition.

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Table 6.2: **The marginal costs and consequences of delayed drug marketing**

Actor	Costs	
	Expenditure	**Savings**
Company	Trials and testing, plus delay adding to opportunity cost of R&D cost already spent	Drug production but more than offset by lost revenues
Purchaser	Existing treatment if available	ADR treatment; drug purchase, administration and dispensing
Patient	Complementary therapies (non NHS)	
	Health consequences	
	Positive	**Negative**
Patient	No ADRs¢"	Disease less well treated¢'

¢"Money value given by patients' willingness-to-pay to avoid ADRs.
¢'Money value given by patients' willingness-to-pay for therapeutic effect.
Source: Adapted from Lumley et al., 1986.

Pedroni (1984) presented a model to demonstrate the costs of detecting ADRs prior to marketing (Table 6.3). The main assumptions she made were: a cost of US $150 for the surveillance, control and evaluation of the data on one patient during the testing phase; a potential market of one million patients; and that the costs of detection are equal to the costs of prevention (i.e. detecting ADRs is identical with preventing them). The figures in Table 6.5 are illustrative and show that, as trial size is increased, the number of ADRs prevented will increase. The additional number of ADRs prevented is the extra ADRs prevented for the trial being considered over and above the next largest trial. Correspondingly, the costs of conducting a trial increases as its size increases. Whether it is worth

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increasing the size of a trial can be assessed by comparing the additional cost of enlarging the trial with the added benefits of doing so. The final column in Table 6.3 shows the additional cost of preventing one ADR by increasing the number of trial subjects from one level to the next.

The main point Pedroni made was that at a high cost (US $4 million per prevented ADR) manufacturers could achieve extremely high levels of safety for 'drug X' but that these high costs would reduce the incentive to conduct research on 'drug Y'. The resulting opportunity cost is clear: the health care purchaser pays higher prices for drug X and patients lose the health gain from future drugs that are no longer developed. Devoting those resources to ADR detection would be at the cost not only of forgone health gains now but also in the future. Pedroni stated that the choice of research programme therefore depended on the type and gravity of ADRs expected, i.e. an assessment of consequences alongside costs. However, as it is impossible to anticipate every relevant treatment population and conceivable pharmaceutical or disease interaction during testing, monitoring must continue in the marketing phase where ADR detection takes place in more realistic circumstances.

This point is reinforced by questioning Pedroni's assumption that detection costs and prevention costs are equal. Showing that ADRs
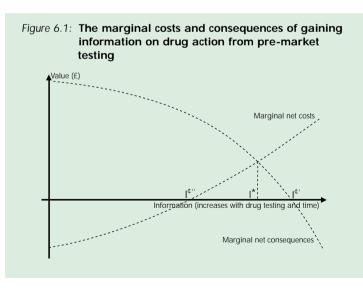
Table 6.3: **The cost of detecting ADRs by pre-market testing**

Design	ADR incidence	Number of trial subjects	Additional cost of trial (million US$)	Additional no. of ADRs prevented	Marginal cost of prevention (US$ per ADR)
A	1:100	271	0.04	10,000	4
B	1:1,000	2,723	0.37	1,000	368
C	1:10,000	29,773	4.06	100	40,600
D	1:100,000	297,755	40.2	10	4,020,000

Source: Pedroni, 1984.

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occur at a certain incidence does not in fact prevent them from happening. Thus, prevention costs must be incurred in addition to detection costs. This will add to the marginal cost of prevention figures in the final column of Table 6.3. Once identified in a research population, by what mechanism are these adverse events to be prevented in a clinical population? Of what use is the information that one in 10,000 patients will suffer an ADR? Will it change the way a pharmaceutical is initially used, or negate the need for astute clinical observation? Additionally, whilst the pharmaceutical is being tested, potential benefit is denied the clinical population. There is a need to question the wisdom of using a large amount of resources to detect rare adverse drug reactions and explicitly ask: what are the costs and consequences of gaining information on drug action?

In principle, it is possible to assess the value of a trial (or trials programme) by investigating what happens to the costs and benefits of the trial as the number of patients is increased. The more patients in the trial, the greater the number who will benefit from treatment but the more that will suffer adverse reactions. However, compared with the exposure that would have resulted from releasing the drug into clinical practice earlier, without the trial, which would have involved many more patients receiving the drug in the time period over which the trial will be conducted, some adverse events will be avoided and some benefits lost. The knowledge gained in the trial can be used once the drug is released into clinical practice in order to improve the targeting of treatment, enhance benefits and reduce ADRs. By assigning monetary values to positive and negative health effects (as illustrated in Table 6.1) and to the impact of the trial on resource use, the marginal costs and benefits of recruiting further patients into the trial can be estimated. These marginal effects are the additional costs and benefits of recruiting an additional patient (or group of patients) into the trial.

In Figure 6.1, as information from pre-market testing is gained, the overall effect of each increase in patient numbers in pre-market trials is that it increases knowledge about both good and bad health effects so increasing the potential for positive health effects as well as

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reducing the likelihood of creating negative health effects. ADRs are avoided, initially in large numbers and subsequently in declining additional numbers. However, gathering information pre-market launch takes time and so delays gaining the beneficial effects from routine clinical use in suitable patients. The curve labelled 'marginal net consequences' shows the changing balance between positive and negative health effects. The curve marked 'marginal net costs' shows the change in overall resource use. Figure 6.1 illustrates that as an effective drug's properties are discovered and appropriate indications identified, increased testing:

- prevents suitable patients being treated whilst not making further significant reductions in ADR avoidance in any time period. The marginal value (net consequences) of delay to gain information falls and eventually becomes negative. In other words there are decreasing returns from information gained from additional investment in testing;

- increases the cost of refining indications (marginal net costs rise) as proportionately more testing is needed to gain each increment of information.
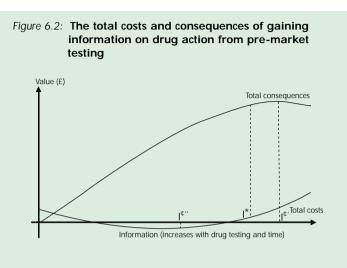

Figure 6.1: **The marginal costs and consequences of gaining information on drug action from pre-market testing**

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We now explore the assumptions behind the Figure and the implications in more detail.

Considering consequences alone, waiting until the level of information reaches $I^{c'}$ ensures that as many patients as possible benefit from treatment without allowing the adverse consequences of recruiting additional subjects to outweigh the extra benefits. This point may be preferred by patients and health care professionals.

Considering costs alone, the greater the number of patients recruited into the trial, the greater the costs of that trial. Proportionately more patients are needed to gain each increment of additional information, as indicated in Table 6.3. However, in this simple example, these extra costs are in part counterbalanced by savings elsewhere. Firstly, it is assumed that, in the absence of the trial, the new treatment would immediately be received by a given number of patients. The effect of the trial is that those potentially eligible patients not enrolled in the trial will receive an existing therapy, assumed to be less costly, while the trial is being undertaken and thereafter will receive the new therapy. However, there is also an opportunity cost in terms of the already sunk R&D cost having to wait longer before it achieves a return on investment.

The costs of recruiting additional patients are offset, up to a point, by reduced treatment costs for the duration of the trial and, subsequent to the trial, by a (temporarily) reduced number of ADRs requiring treatment as a result of the information generated by the trial. However, there will be some fixed costs (including the opportunity cost of already sunk R&D cost) associated with conducting the study, that is, costs which are incurred before any patients are recruited and which remain constant regardless of the level of recruitment in that time period. These are allowed for in Figure 6.2, which shows the total costs and consequences curves. In this illustration, negative marginal costs initially serve to generate cost savings (falling total costs) over a range of levels of patient recruitment, savings being maximised at $I^{\dagger}$ in Figure 6.1 where marginal costs change from being negative to positive. After this point, increasing the sample size adds to costs,

Figure 6.2: **The total costs and consequences of gaining information on drug action from pre-market testing**

patients suffered from delayed access to a more suitable or effective treatment. How regulators undertake this risk – benefit calculation is being increasingly debated by regulators, companies, patient groups, academics and other stakeholders.

In the presence of a regulatory authority, companies would hope for quick regulatory approval leading to early market access. Companies may therefore seek to move the regulator towards $I^{¢"}$ in Figure 6.1, at which point the cost savings from testing are maximised, i.e. to have less testing than the socially efficient solution of I^*. This will in part depend on the extent to which reputation and legal costs may be incurred by a company as a result of a drug leading to ADRs. Marketing with limited information may be in the purchasers' interest if the disease to be treated currently gives rise to large non-drug costs, which could be substantially reduced. For patients, the information required is likely to depend on the severity of their disease and the prognosis. No single actor is motivated to argue for a socially optimal level of pre-marketing information although, arguably, this should be the brief of the regulatory body. Recognising the basis of actors' disparate incentives should help to develop policies to change their behaviour and move towards this goal. We should note, however, that the "efficient" solution may not be that chosen by the regulator since the implicit weighting it gives to ADRs as opposed to health gain in its risk-benefit calculation may not reflect the views of society or those of the patients eligible for a particular treatment.

The cost and consequences curves plotted in Figure 6.1 and Figure 6.2 have been generated using some simplifying assumptions concerning numbers of patients, efficacy and ADR rates, monetary values of health benefits and ADRs, ability to extrapolate beyond the trial, and costs per patient of the trial and of treating ADRs. Key variables are the relative monetary values of health gains and ADRs and the relative efficacy and ADR rates. If efficacy or the value of health benefits is relatively high, additional pre-marketing trials may not be worthwhile because of the lost health gains of those who might otherwise have received the drug as a result of an earlier launch. If ADR rates are potentially high and clinical benefit is low, then releasing the drug into

primarily because the number of additional ADRs prevented for each increase to the size of the trial diminishes.

From the societal perspective, we find the optimal amount of information (I^*) at the point where the distance between the total consequences and total costs curves is greatest. This equates to the point where the marginal costs and consequences curves meet in Figure 6.1. Up to this point, the additional benefits from increasing sample size are greater than the additional costs, so a net benefit can be achieved by increasing sample size. In contrast, beyond this point, additional costs are greater than additional benefits, so there is a net cost from increasing trial size. At the point of intersection, net benefits are maximised. We assume that the societal perspective is the one adopted by the regulator. However, there may be pressure for the regulator to "play safe" and push for information up to point $I^{¢'}$, particularly if the costs are largely incurred by the company and because it may be easier for the regulator to identify patients harmed by an ADR and to quantify the effect than it is to work out how many

clinical practice may involve a net loss, in which case the drug would require further testing and may not be licensed.

Although these illustrative cost and consequences curves are abstracted from reality, it seems plausible that the more research is undertaken, the lower the benefits from undertaking additional research. Since the added costs of research will always be positive, research funds should ideally be allocated up to the point at which the additional benefits of that research are just equal to its additional costs. How the cost and consequences curves appear when considering a new piece of research will depend on where the origin lies, that is, the extent of current knowledge.

6.4.2   *Value of information analysis*

An economic method which formally considers the value of acquiring additional information, given current knowledge, is described by Claxton (1999). The starting point for this approach is that treatment decisions based on mean net benefit[1] are uncertain. This is because of the uncertainty surrounding net benefits. We do not know in advance for certain what the treatment costs and health benefits (net of any adverse health effects) will be in routine clinical practice. There is a chance that we may adopt a treatment in the expectation that it is cost-effective but then find out subsequently that it is not, or vice versa, i.e. not use a treatment because we believe it not to be cost-effective only to find out subsequently that it is. Additional research to inform the treatment decision will be of value because it will reduce this uncertainty. The cost of uncertainty is the probability that the wrong decision is made and the magnitude of the benefits forgone if the wrong decision is made (failure to choose the treatment with the greatest net benefit). This cost can also be interpreted as the expected value of perfect information (EVPI), since having perfect information (which would require an unlimited sample) would remove uncertainty about the correct decision.

[1] Net benefit is defined as the monetary value of the net health benefits of treatment (i.e. health gains less the health impact of any adverse health effects associated with the treatment) less the costs associated with treatment.

The EVPI represents the maximum it would be worth investing in additional research. In an Alzheimer's disease example, Claxton et al. (2001) estimated an EVPI of $339 million for the US population assuming that a quality adjusted life year (QALY) is valued at $50,000. This suggests high uncertainty relative to the potential scale of use of the product. Since the fixed costs of additional research are likely to be below this figure, extra research is potentially worth undertaking. In this example, EVPIs associated with each of the model inputs were reported, indicating for which variables more precise estimates would be most valuable.

To ascertain if extra research is justified requires consideration of the costs and benefits of gathering information on a sample of patients. The costs of sampling will be comprised of the additional treatment cost of the intervention being assessed relative to current practice and any marginal reporting or information gathering and analysis costs (Claxton, 1999). Analogous to the EVPI, the expected value of sample information (EVSI) is the reduction in the cost of uncertainty around the treatment decision from a study of a certain sample size. The sample size yielding the maximum expected net benefit of sampling (ENBS), where ENBS equals EVSI less the cost of sampling, gives the optimal sample size for the additional study. If ENBS is positive and greater than the fixed costs of research, then the additional trial is worth undertaking. The costs of research would take account of the appropriateness of different research designs for different variables. Where selection bias is expected to be an important issue, such as in the estimation of the health effects of treatment, an experimental design would be indicated. For other variables, observational data may be sufficient.

Claxton (1999) argues that this framework could be used to inform the regulation of new pharmaceuticals, in place of the current approach based on arbitrary significance levels and power calculations. Indeed, he suggests that the US FDA has recognised that evidential standards should vary according to the technology under consideration, depending on the costs and benefits of acquiring additional information. However, he develops this approach in the context of FDA regulation of cost-effectiveness claims by companies

when products are being marketed, rather than in the licensing process to determine the extent of pre-market trial work that should be undertaken in order to get the right risk-benefit decision in terms of health benefits and ADRs. In this context he proposes that the FDA deem a cost-effectiveness claim to be substantiated when the societal benefits of acquiring additional information are no longer justified given the costs of doing so.

Of perhaps more obvious relevance for this approach is its potential use by reimbursement authorities and organisations such as the National Institute for Clinical Excellence (NICE) formulating guidance for the health service on the basis (at least partly) of cost-effectiveness. As Claxton et al. (2002) point out, the current information requirements of regulatory authorities for drug licensing purposes differ from the needs of health care decision makers concerned with questions regarding the best use of available resources. However, the value of information approach can be applied to the licensing decision. Indeed the approach we have set out in Figures 6.1 and 6.2 is based on a similar framework for assessing the costs and benefits of collecting additional information on ADRs given the potential cost in terms of running the trial and in terms of health gains forgone from delaying patient access to the drug. A value of information approach would look at the expected net benefits at any point in time from licensing or not licensing a product (similar to our marginal net consequences) and the degree of uncertainty around them. It would look at the costs of collecting additional information through another pre-market trial and the benefits that might accrue in terms of increased confidence that the right decision would be made as to whether or not to license the product. The two main differences between our approach and the Claxton model are that our focus:

- is on the trade-off of the potential impact of delayed access in terms of health benefits lost as compared to better information on the likely number and effect of ADRs over the lifecycle of use of the product;
- seeks to include the broader societal impact of delayed use (in our marginal net costs) whilst the Claxton model focuses on trial costs and information gains.

The Claxton approach could in principle be adapted to include a time dimension and a broader definition of costs. A key issue of principle for the Claxton approach, however, is the use of expected net benefit for decision making. The application of the value of information approach in drug licensing would involve a conceptual separation of the licensing/not licensing decision from the decision as to whether additional research should be undertaken. The former should be based on the expected net risk-benefit taken from the pre-market information available. If expected risk-benefit is positive, but more information can be collected in a cost-effective manner to reduce uncertainty, then the regulator should license the product subject to the information being collected and a reassessment taking place at that point. We do not make an explicit assumption in our approach as to how the regulator assesses risk-benefit. Nor do we explicitly include in our consequences and costs the impact of collecting the information post-launch rather than pre-market. The overall messages from both approaches, however, are the same. Firstly, information has a value and a cost. Secondly, the risk benefit criteria used in licensing decisions need to be explicit. Thirdly, these criteria should take account of the lost health gain from delayed or non-licensing as well as the health loss associated with ADRs.

An important aspect of any decision as to how much information to require pre-marketing is to ensure efficient post-marketing data collection, which we now consider.

6.4.3   Post-marketing

Practically, it is not possible to detect rare ADRs in anything but the largest and most expensive clinical trials, which are unlikely to be an efficient (health maximising) use of resources. Within a clinical trial, pharmaceutical production costs are not directly borne by the health care purchaser, but wide human exposure to the medicine is still required to discover its full ADR profile.

The argument against greater regulatory delay before marketing authorisation delay rests on the assumption that it is prohibitively expensive, and perhaps technically impossible, to obtain a more complete ADR profile for a medicine, and thus an accurate assessment of its risk-benefit profile, prior to marketing. Drews (1994) argues that it is doubtful whether any extension of pre-marketing research and development would be financially or economically viable. This means that great care has to be taken post-marketing to ensure pharmaceuticals are used as appropriately as possible and that safety assessment must be an on-going exercise. The safety assessment of marketed medicines (SAMM) can be seen primarily as a means of avoiding ADRs. However, its proper role is to increase knowledge, thus moving us more quickly towards the level of drug utilisation where the perception of adverse effects is accurate (Crooks and Mooney, 1978). SAMM should aid accurate risk-benefit analysis and economic evaluation, so that the optimal level of pharmaceutical treatment can be determined.

Crooks and Mooney (1978) discuss how comprehensive SAMM should be. They assume that: a) the clinical benefits of ADR detection are directly related to a reduction in the number of years between initial marketing and ADR detection; and b) more comprehensive detection programmes would detect ADRs in a shorter period of time. This is illustrated in Table 6.4, which shows how the length of time (in terms of number of years) between initial marketing and the discovery of a particular ADR are reduced (in decreasing increments) by increasing expenditure on detection. In the table, A to E are increasingly effective ADR detection programmes. Programme A might be spontaneous reporting and programme E could represent record linkage. The main point is that both the marginal costs and consequences of detection must be considered. Increasing investments in detection, moving from basic to comprehensive SAMM, are likely to have decreasing returns in terms of the reduction in the number of years taken to discover ADRs. Thus, an ideal 'low-cost, high-detection' system is not feasible.

Table 6.4: **The cost of detecting ADRs by post-marketing surveillance**

Design of ADR detection programme	Reduction in number of years between product launch and ADR detection	Extra cost of increasingly comprehensive ADR detection programmes (£m)	Marginal cost per year saved
No SAMM	0	0	–
A	2	1	0.5
B	1	1	1
C	1	2	2
D	0.5	2	4
E	0.5	4	8

Source: Crooks and Mooney, 1978.

Venning (1983c) concluded that published anecdotal reports had provided the greatest number of early ADR warnings. Their importance has been confirmed by a review of the 3,252 citations drawn from the world literature on ADRs and drug interactions in the year 2000 for the 2001 Side Effects Annual (Aronson, 2001). 30% of citations were found to be anecdotes (case reports), second only in importance to major randomised controlled trials or observational studies (Aronson, 2003). In comparison, there were only 45 meta-analyses or other forms of systematic review. While trials can provide estimates of the size of benefits or adverse effects, Aronson (2003) supports the publication of anecdotes since they "call attention to potential adverse reactions or interactions, mechanisms, diagnostic techniques, or methods of management".

The effectiveness of spontaneous reporting is debatable and under-reporting is a considerable problem. However, it *offers* universal coverage, is relatively cheap and has also provided a number of important early warnings (CSM, 1994). Record linkage would perhaps be the most effective detection system but even with recent advances in computer technology its implementation would probably be very

expensive. Formal assessments of medicine safety sponsored by the pharmaceutical industry continue, therefore, to be valuable sources of information. However, such studies present the industry with a great conflict of interest. Although SAMM guidelines state that SAMM should not be conducted for the purposes of promotion (Joint Working Party, 1993), SAMM inevitably helps to raise product awareness, and some people see promotion as its primary purpose. In the US no guidelines exist and there are concerns that payments to doctors (for time and expenses) and the supply of free pharmaceuticals to patients act as incentives to prescribe (La Puma, 1995). In particular La Puma (1995) believed doctors should not be paid to recruit patients for SAMM (or 'seeding studies' as they are sometimes termed).

It is difficult to decide on the proper balance between pre- and post-marketing safety assessment, particularly if some post-marketing research is of questionable quality. There is clearly scope for more efficient post-launch data collection. The availability of good quality post-launch data might reduce the requirements for pre-marketing data collection. Even if it can be demonstrated that the optimal amount of information required for marketing approval (I* in Figure 6.1), is less than the current amount, because it would be more efficient to collect information post-launch, there may be some resistance to reducing the extent of pre-launch testing. One possible solution to this problem maybe 'contingent licensing' for some products, whereby marketing approval is granted for a certain length of time and will be extended only if expected levels of effectiveness and safety in use (rather than efficacy and safety in further trials) are demonstrated. Companies could also contract with purchasers to meet some ADR costs as part of the information collection in this 'contingent' period.

6.4.4   Clinical interventions to reduce ADRs

Aside from the potential for monitoring systems to inform clinical behaviour, there may be a more direct role for clinicians, and especially pharmacists, to play in reducing ADRs. Schumock et al. (1996)

reviewed studies which investigated the cost impact of clinical pharmacy services. 89% of studies reviewed reported a beneficial financial impact, including 94% of those which considered the input costs of the service. Among those studies which estimated a ratio of cost savings to costs, the average was 16.7:1, implying that every $1 invested would yield a saving on average of $16.70. Only 18% of studies were classified as full economic evaluations, i.e. they considered two or more alternatives and assessed both input costs and outcomes. In general, there were deficiencies in study design, with 41% of all studies not including a comparison group. Of those studies which included a comparison group, a minority used a concurrent control group. ADRs were assessed in some studies but true patient outcomes were rarely considered.

Schumock (2000) reports some evidence of the potential impact of clinical pharmacy services on mortality. However, the studies cited simply observed a negative relationship between patient mortality and, in one case, the number of pharmacists employed by a hospital and, in the second case, four clinical pharmacy service interventions. The four interventions associated with a reduction in mortality were participation in clinical research, provision of drug information, provision of medication admission histories and participation in cardiopulmonary resuscitation teams.

Bond et al. (2000) used a multiple regression approach to investigate the relationship between clinical pharmacy services and severity of illness-adjusted total health care costs in US hospitals. They found that drug use evaluation, drug information, ADR monitoring, drug protocol management, medical rounds participation and admission drug histories were associated with a lower total cost of care and two (total parenteral nutrition team participation and clinical research) with higher costs of care. In the population of hospitals covered by the study, it was estimated that, in addition to yielding nearly $91 million savings in drug costs, pharmacist-provided drug information would result (as reported elsewhere) in 10,463 fewer deaths. The authors caution, however, that the study was designed to test association, not cause and effect.

An overview by Cotter et al. (1995) of clinical pharmacy services provided by NHS hospital pharmacies has identified shortcomings of the literature on patient outcomes and cost-effectiveness relevant to the UK. The conclusion of the review was that, although there is some evidence for the beneficial effects of pharmacists on the process of care, drug costs and possibly patient outcomes, the few studies conducted on the different types of pharmacy services have been limited in scope and their results cannot be generalised. The authors concluded that no sound economic evaluations have been conducted and few therapeutic drug monitoring evaluations have been published.

Economic aspects of therapeutic drug monitoring[2] have been reviewed by Schumacher and Barr (2001), who have similar reservations about the literature to those expressed by Cotter et al. (1995) for clinical pharmacy services. They conclude that there is much evidence for the beneficial impact of therapeutic drug monitoring on the structure and process of monitoring therapy but little to suggest that it improves patient response or quality of life. Nor could they identify any studies conducted over sufficiently long time periods to be generalisable. Although a few studies were considered to have been well designed, most were deemed to lack methodological rigour. What the authors were able to conclude from the literature is that therapeutic drug monitoring is justified for targeted populations but not in routine use. In the US, for example, they report that over 80% of serum concentration measurements involve aminoglycosides and vancomycin. Support for therapeutic drug monitoring in treatment with aminoglycosides was found in a few well designed economic evaluations and one "rigorous cost-effectiveness analysis" found a cost per case of nephrotoxicity avoided of $435 for vancomycin monitoring among patients with haematological malignancies.

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[2] Therapeutic drug monitoring measures the plasma concentration of a drug at the relevant effector sites, as an indirect measure of concentration in the tissue compartments of interest and thus of clinical response, rather than relying on dose since a given dose may result in widely varying plasma concentrations in different patients.

6.5 Discussion

Chiefly, this chapter has provided a theoretical basis for the consideration of marketing approval and pharmaceutical treatment. It was noted that drug treatment will always be associated with some ADRs and thus, when drugs are used optimally, there will be a corresponding level of ADRs. Inefficient usage could be associated with too many or too few ADRs. While some level of ADRs is inevitable, steps can be taken to limit their occurrence. At the stage of regulatory approval, the licensing authorities will weigh up measures of a drug's efficacy versus its ADRs to ensure that only those considered to have an acceptable balance of positive and negative effects are introduced into clinical practice. The appropriate balance between costs and consequences will vary depending on the type of medicine being used and/or the disease being treated. Collecting more data at the pre-marketing stage may detect more ADRs but may not affect the licensing decision or prescribing behaviour and will generate additional costs. From an economic perspective, the costs of acquiring extra data must be justified by the health benefits produced.

Value of information analysis has been used to identify economically efficient avenues for further research based on the degree of uncertainty around cost-effectiveness estimates derived from existing data. Such an approach can be used to identify the optimal additional information requirements for risk-benefit assessments by regulators when deciding whether or not to license a product. An important aspect of this is the potential loss of health gain arising from not licensing a product, or delaying licensing a product whilst additional trials are done. Another element is the extent to which data can be collected post-launch, once the product is licensed.

Once a drug has been released to the general population, a greater number of ADRs are likely to occur for several reasons. Firstly, pre-marketing studies will be insufficiently large to detect the less common adverse reactions. Secondly, the patients treated in clinical practice tend to be more heterogeneous than those recruited into phase III trials. Thirdly, the setting of a clinical trial requires monitoring of treatment to an extent not carried out under normal treatment conditions.

These ADRs can be identified in a variety of ways. In the first two cases, spontaneous reporting and other ADR reporting systems will be important to identify ADRs not observed in clinical trials, for example the rarer events that will only emerge from widespread use, contraindications or drug interactions.

In order for these systems to be effective in reducing or eliminating certain types of ADR, they must be followed up with measures that are capable of altering clinicians' behaviour. Short of withdrawing a drug from the market, there is little evidence on the effectiveness of communicating safety messages arising from ADR monitoring systems. Some anecdotal evidence suggests that safety warnings may not be effective. For example, Marwick (2003) reports that doctors prescribed cerivastatin together with gemfibrozil (this combination being associated with the adverse reaction of rhabdomyolysis, which led to cerivastatin's withdrawal from the US and Europe in August 2001), despite being warned by the manufacturer that this could cause adverse reactions. The cost-effectiveness of ways of communicating safety messages is an area in which further research would be of value.

The third difference between the trial setting and clinical practice, namely the tighter monitoring of therapy in the former compared with the latter, raises a number of issues. One, not addressed here, is the degree of compliance with therapy and the extent to which this is an important influence on ADRs. Another is the existence of interventions which attempt to ensure that drug therapy is adjusted to the requirements of the individual patient. This would encompass therapeutic drug monitoring and clinical pharmacy services. However, it seems that there is little evidence on their cost-effectiveness in the UK context and, in the wider context, few well designed economic evaluations with external validity appear to have been conducted. Further research is warranted to explore the potential of these interventions not only to reduce ADRs but also to assess their impact on the wider effectiveness of drug treatment.

7   CONCLUSIONS

Despite past failings, medicine safety is now well regulated. New drugs must undergo a lengthy process of evaluation for efficacy and safety but no drug will be entirely without risk. Exploiting the benefits of drugs entails accepting some adverse drug reactions (ADRs). ADRs refer to adverse effects resulting from the appropriate use of medicines, rather than those due to medical error. Effective medicines appropriately used will always have the potential to cause ADRs. These are generally distinguished from adverse drug events (ADEs), which are defined as injuries resulting from medical interventions related to drugs. Patient non-compliance and medical negligence are the biggest human causes of adverse drug events (ADEs).

Most ADRs occur in the community but serious ADRs are relatively rare compared to the extent of medicines usage. ADRs are implicated in 5% of hospital admissions and 10% of hospital in-patients may suffer an ADR. It has been estimated that hospital admissions due to ADRs and ADRs experienced by inpatients combined costs the NHS in England the equivalent of 15-20 400-bed hospitals, or about 4% of bed-days available. This compares with an estimated 24 400-bed hospital equivalents accounted for by hospital-acquired infections.

Most ADRs are Type A, or dose-related. Therefore, to minimise the risk of ADRs, greater attention should be given to individualising treatment with medicines. Tackling most ADRs requires no treatment other than adjustment of dose, discontinuation of treatment or switching to an alternative medicine. A minor ADR may be an acceptable inconvenience to achieve the benefits of treatment. A minority of ADRs will require multi-disciplinary assessment. Some medicines are known to be particularly toxic and must be used with great care. ADR prevention involves better application of knowledge about drug action and more research to gain knowledge of drug action.

Economic analysis can be applied both to the question of conducting more research and clinical interventions to optimise drug therapy. Prior to the launch of a new drug, the collection of additional data requires research resources and involves delaying the drug's availability to patients who could benefit, but it may help to prevent ADRs in clinical practice (or even suggest that the drug should not be licensed).

Prior to launch, knowledge about a drug's actions will be limited by the relatively small number of patients exposed to the drug during clinical trials compared with the eligible population of patients. Detection of ADRs relies heavily on spontaneous reporting systems, with the attendant problem of under-reporting. It has, however, been emphasised that the costs of additional data collection should be justified by the benefits generated.

An economic framework which formally considers and quantifies the costs and benefits of conducting extra research is that referred to as value of information analysis. This has been applied principally to the question of whether it is worthwhile collecting additional information about cost-effectiveness once approval has been granted and, if so, just what types of data are worth collecting. However, the value of information approach can be applied to the licensing decision and we develop a simple model as well as discussing the Claxton model. The overall messages from both approaches are the same. Firstly, information has a value and a cost. Secondly, the risk benefit criteria used in licensing decisions need to be explicit. Thirdly, these criteria should take account of the lost health gain from delayed or non-licensing as well as the health loss associated with ADRs.

A means of reconciling the need to collect additional safety data with a desire to avoid delaying patient access to a drug that offers health gain could be conditional licensing whereby drugs showing clinical effectiveness are approved for use subject to additional data being collected post-launch. Evidence on less frequent ADRs may only emerge after experience in a large number of heterogeneous patients. In some cases, the emergence of ADRs will give the regulatory authorities grounds for withdrawing a licence, perhaps influenced by the extent to which safety messages have an impact on clinical practice.

Enhancements to drug therapy require not only that information is collected on a drug's effects but that the information is acted upon. In the absence of routine measures of clinical benefit, the ADR rate is one way to monitor appropriate levels of medicine usage. Utilisation of cost-effective treatments will imply that the use of some drugs should increase, thus increasing the ADRs associated with those treatments,

and the use of others should be reduced, thus reducing the corresponding level of ADRs. Whether, overall, ADRs should rise or fall will depend on the ADR rates of less cost effective relative to more cost effective drugs.

Better use could be made of existing data on drug use and ADRs and therefore it is important that pharmaceutical companies, government and the medical professions share information openly. Regulatory organisations could be more explicit about the weighting applied to positive and negative effects when deciding to approve or not approve a new drug. It is currently unclear whether the implicit risk posture adopted by licensing bodies towards a new drug reflects the attitudes to risk of those patients for whom the drug is intended. Whereas cost-effectiveness considers the overall effect of a drug relative to its cost, regulatory decisions are based on judgements about the a balance between the risk of a drug causing harm and the chances of a successful outcome. While two treatments may offer the same aggregate or average benefits across a group of patients, their relative desirability from an individual patient's point of view will depend partly on the risks involved. For example, a given overall benefit could be the result of a relatively good chance of gaining some benefit, but with a high probability of harm or, alternatively, a more modest chance of benefiting against a lower risk of being harmed. Depending on attitudes to risk, the two options will not necessarily be equally preferred by individual patients even if they are equally beneficial for the group.

The risk-benefit balance an individual considers acceptable may conceivably vary according to disease severity, prognosis, alternative treatments available and other factors and may not coincide with the judgements made by a regulatory body. Although the regulator will no doubt take some of these factors into account, the criteria used and the weighting between them are not generally made public. Relative to the preferences of those who might be offered a particular treatment, it is possible that regulators are sometimes too lenient, approving some drugs with an unacceptable risk benefit balance and sometimes too strict, failing to approve a drug where the risk is acceptable. There will

often be a temptation to "play safe" which may lead to undervaluation of the lost health gain from delaying patient access to a new treatment, unless patient groups are actively pushing for early approval of a drug, in which case the temptation may be to go for less than optimal pre-marketing testing. Greater knowledge about the way in which licensing decisions are made – in particular more explicit risk-benefit criteria - and about patients' preferences for risks and benefits would help to make best use of the information that is collected about both the positive and negative effects of drug therapy.

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9 GLOSSARY

ABPI	Association of the British Pharmaceutical Industry
ADE	Adverse drug event
ADR	Adverse drug reaction
BNF	British National Formulary
CNS	Central nervous system
CSM	Committee on the Safety of Medicines (UK)
DRAPE	Drug-related adverse patient event
EMEA	European Medicines Evaluation Agency
ENBS	Expected net benefit of sampling
EU	European Union
EVPI	Expected value of perfect information
EVSI	Expected value of sample information
FDA	Food and Drug Administration (US)
GI	Gastrointestinal
GP	General practitioner (a family doctor in the UK)
ICU	Intensive care unit
JCAHO	Joint Commission on Accreditation of Healthcare Organisations (US)
MCA	Medicines Control Agency (UK)
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MIMS	Monthly Index of Medical Specialities (industry sponsored prescribing guide)
NICE	National Institute for Clinical Excellence (England and Wales)
NSAID	Non-steroidal anti-inflammatory drug
PEM	Prescription event monitoring (UK)
QALY	Quality adjusted life year
SAMM	Safety assessment of marketed medicines
WHO	World Health Organisation

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