CHAPTER 1

What is off-label medication, and how prevalent is it?

The practice of medicine has been regulated since Hippocrates, who first told doctors (physicians, clinicians, general practitioners [GPs] and so on) how they should behave with regard to their patients. His Oath, written nearly 2500 years ago, is the most famous text in Western medicine. Though most people do not know exactly what it says, they believe it to say something along the lines of ‘Doctor, do no harm’. That is only partly true, as I shall now explain.

But before I do, there are actually many versions in the public mind of what Hippocrates said, including the view recounted by one UK doctor of an elderly patient who believed the Oath instructed doctors never to tell patients the truth. This book will describe circumstances in which this patient is often correct, namely, that GPs do not tell the truth to their patients, but of course incorrect in that Hippocratic Oath does not say that.

The Oath starts: ‘I swear by Apollo the physician and by Asclepius and Hygieia and Panacea... to bring the following oath to fulfilment’. According to Greek mythology, Apollo is the god of healing, Asclepius is his son and Hygieia and Panacea are his granddaughters. As with Zeus his father, Apollo had many love affairs with goddesses and mortals. One of his amours was Coronis, who was the daughter of the king of the Lapiths. Dwelling on a higher plane, Apollo was not able to be beside Coronis on earth, so he sent a white crow to look after her. Unfortunately, while she was pregnant by Apollo, Coronis fell in love with another man, and the crow informed Apollo of the affair. Appalled at her infidelity, in his anger, Apollo turned the crow black.

Artemis, Apollo’s twin sister, shot an arrow to kill Coronis. While Coronis’ body was burning on the funeral pyre, Apollo removed the unborn child, who was called Asclepius and became the god of medicine. When he grew up, Asclepius had two daughters, Hygieia, the goddess of health, and Panacea, the goddess of cures: medicine ran in the family. The words ‘hygiene’ and ‘panacea’ clearly have their etymological origins in these mythological figures.

According to legend, Hippocrates was a descendant of Asclepius; this gives more weight to Hippocrates’ proclamations, particularly when he pronounces on medical matters. Part of the Oath instructs the doctor to treat his teachers as his parents and to pass on the art of medicine to the next generation of healers. This is clearly relevant to Hippocrates’ ancestry, going all the way back to Apollo. But it is the next part of the Oath that is most relevant to this book and indeed to the practice of medicine.

It continues: ‘And I will use treatments for the benefit of the ill in accordance with my ability and my judgment, but from what is to their harm and injustice I will keep them’.

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It is the two words, ‘harm’ and ‘injustice’ which I ask you to bear in mind as we go forwards.

What is ‘off-label’ medicine?

Today, medicines are regulated for their efficacy and safety, and once licensed for sale, they can be marketed for certain uses as justified by the data. Regulatory bodies in developed countries are constituted by legal statute and operate as parts of government, ostensibly in the interests of the people as patients. But once approved, medicines can be used for any purpose the prescriber sees fit and appropriate for the patient. In other words, regulatory authorities are the gatekeepers to prevent the medical use of unapproved products, but then leave the gate entirely wide open regarding unapproved indications or uses of approved products. To be succinct, medicinal products require regulatory approval, but the practice of medicine does not. There remain restrictions on the marketing of these products, but these are considerations for the producer, not the prescriber. Later on, I will explain the nuance that distinguishes between the marketing and the use of medicines and how, in my opinion, pharmaceutical companies.game the system.

The ways in which medicines are prescribed, and administered, outside the terms of the marketing authorisation are called ‘off-label’ uses. They have not been justified by the regulatory authorities, which determine the label for the product, hence the title of this book. As was said, a ‘general off-label use of drugs is the death of the idea of regulation’ [3]. The importance of the regulatory justification is not merely because these public authorities spend a lot of time, money and manpower examining the evidence behind the safety and efficacy of the medicines we take: it is because these authorities are put in place to implement certain standards to which the patient expects his or her therapy to accord. The regulatory approval is also the patient’s approval, the basis for their consent to being treated with the prescribed medication. Drug regulation is a complex decision about the balance of safety and efficacy,¹ benefit and risk – a world of shades of grey, not black and white. In the real world, the prescribing doctor has a lot of flexibility as to what s/he can prescribe; that flexibility can be put to good use, but patients are rarely aware that their off-label medicine has not been approved for their affliction, with consequences to the quality of their care.

So, off-label prescriptions are not illegal, and from the doctor’s perspective, they may not even be seen as unethical; in fact, according to the Hippocratic Oath, they may fulfil a doctor’s moral imperative, for instance, in situations of rare diseases where there is no approved product. However, the evidence behind off-label medicine rarely fulfils the patient’s expectations that a formal regulatory assessment of safety and efficacy has been performed, and this is the first sense in which I mean off-label medicine seems to be unjustified. Later, in Chapter 6, I shall deal with other consequences, such as who pays for the medicine, and what happens in cases where things go wrong. But before doing so, let us consider the scale of the issue.

There are lots of examples of secondary uses for existing drugs. The story of how a proposed treatment for angina and heart failure ended up as the world’s first treatment for erectile dysfunction is well known. The company behind the drug (Pfizer), now known as Viagra™, recorded that when the product, then known as

¹Clinicians and policymakers often differentiate between efficacy and effectiveness, where the latter relates to how well a treatment works in the practice of medicine, as opposed to the former, which measures how well treatment works in clinical trials or laboratory studies.
What is off-label medication, and how prevalent is it?

UK-92480-10, or sildenafil, was first tried on male volunteers in a Welsh clinic, they reported physical excitation on seeing the nurses in the ward, requiring them to roll on their stomachs. In this case, the intended development for cardiovascular diseases was curtailed, and the product entered into medical practice for the treatment of erectile dysfunction instead (and in 2012, generated over $2 billion in revenue for Pfizer). Because the decision to develop for erectile dysfunction occurred before Viagra was approved for any use, this is not an example of off-label medication. However, even though this story is somewhat anecdotal, it does show that drugs often do more than one thing. In fact, there is a sequel to the first approval indication for sildenafil, in which it was subsequently developed for a second indication (or third, depending on how you look at it), as we shall see in Chapter 2.

I have strong interest in this area, having investigated this area of secondary uses for existing drugs, now called drug repurposing, for over 15 years. I have collated over 2300 proposed new uses for existing drugs, either marketed products or investigational compounds. This is freely accessible on the internet at http://www.drugrepurposing.info. But the level of support for such new uses can vary enormously. In some cases, we have human data, such as clinical trials to support the effect. In many others, there is only information from experiments in vitro (literally ‘in glass’, this refers to test tube experiments) or in vivo (in animals). Some information even derives from a computer assessment of the shape similarity of drugs, but predictions like this based on in silico analysis are merely hypotheses, starting points for research programmes lasting years or even decades to deliver validation in regulatory studies that would be needed for market approval. As we shall discover in Chapter 4, most of the normal scientific hypotheses upon which drug discovery programmes are based turn out to be wrong.

We now realise that there are very few, if any, drugs with only one activity and/or only one conceivable therapeutic use. But even though there is vast promise from making better use of the drugs we currently have on hand, most of the early-stage predictions fail to be realised in practice. Sometimes this is for commercial reasons, but it is also for experimental reasons of safety or efficacy. As this area becomes more widely used as a means to discover new therapeutics, it is all the more likely that the current medicines that we all use will become increasingly investigated for new uses. New discoveries of this kind can be enormously helpful to the armoury of therapeutics available to the patient. However, it is unsafe to suppose that a theory deriving from an animal experiment, or anecdotal case report from one patient, really translates into a safe, efficacious treatment of general merit: it needs to be proven. Prescribers have enormous freedom to uncover whether the early science suggestive of a human benefit really works in a patient. As this book will show, the current legal framework, regulatory controls and ethical norms in medicine do not provide the best environment for delivering such new therapeutics to patients, and the consequences of its misapplication can be gravely injurious.

There are two main types of off-label medicine: use of drugs for unapproved diseases or conditions (which, in the medical profession, are called ‘indications’), and use of drugs for unapproved patient groups. Off-label use can also include prescribing different dosages, lengthening or shortening the interval between treatments or using different routes of administration from those indicated on the drug label.2

2A word about semantics. There is a difference between the terms ‘unapproved drug’ or ‘unlicensed drug’ and ‘unapproved medicine’. The word ‘drug’ implies the active ingredient in the therapy, whereas ‘medicine’ connotes the entire formulation (including dose, frequency, etc.), its use and the type of patient.
There are three main areas of therapy where off-label medicines are most widely used. The first is the use of products licensed for adults, on the basis of clinical trials in adults, for children. The second is of psychiatric medicines, and the third is in oncology treatment. We started with a broad statement that off-label use constitutes ‘20% of all prescriptions’, but the prevalence varies enormously, and among these broad classes lie salient examples where off-label use reaches staggering proportions. Getting consistent statistics can be difficult: a review of international studies in ambulatory care reports rates of 13.2% and 29%, in paediatric wards between 18% and 60% and in neonatal units between 14% and 63% [4]. Another international literature review reports that rates for off-label medicine use vary between 11% and 80% [5]. A study from the Netherlands reports that 44% of all prescriptions in a paediatric ward are off-label [6]. In Germany, around 40% of under 18s were prescribed at least one off-label medicine among a study of 17 000, with no significant differences according to region, urbanity, migrant background and social class [7].

To summarise these figures, one could say that higher rates are seen in younger patients and in hospital settings, and that a figure of 20% lies at the lower end of these reports. However, consistent estimates of the prevalence of off-label use are made more difficult because they are often not recorded in a patient’s notes; this in turn may reflect the fact that they are associated with increased liability for physicians. Thus, it is quite possible for an audit of physician practice to deliver a result indicating a falsely low rate of off-label prescriptions and, where there is a range of figures, to suspect the higher proportion to reflect more accurately the real situation [8].

In fact, in many areas, off-label use is more common than use according to the approved label, bringing to mind the point that in such circumstances the pharmaceutical regulatory system is not fit for purpose. But also, even though this is clearly a very large issue, getting hold of reliable statistics is something of a problem in itself. Off-label medicine is not universally shady, but it does have shady patches, and few practitioners will admit to having participated in the darker regions of the practice any more than they absolutely have to. So there are questions about the statistics, but if they are wrong, one would suspect them to be under- rather than overestimates. Very few doctors would voluntary admit to prescribing off-label when they have not. That also tells you something about the perceived ethics involved. Nevertheless, to avoid criticism, I have erred on the side of caution in my overall statement that it constitutes ‘20% of all prescriptions’. A widely referenced article looked in detail at the issue and came to a similar conclusion; they also assessed the proportion of off-label use by therapeutic class [9] (Figure 1.1).

To give you some simple examples, the prescription of antibiotics for colds and flu is almost entirely without patient benefit but at significant cost to the NHS in the United Kingdom (and equivalent payers in other countries) and raises concern in an era of increasing bacterial resistance; the prescription of antipsychotics to dementia patients without their consent and at their increased risk is a scandal that led to a recent UK government report and action; and the prescription of antidepressants to children and adolescents when they had only been licensed for adults revealed age-related increases in suicide risk, with increasing risk for young patients but not for old.

Off-label medication is not always a bad thing, and it would be a grave mistake to ban the practice entirely. I certainly would not advocate its prohibition, far from it. In my work on the area of secondary and tertiary uses for existing drugs, I have come to realise the huge potential of this area of study. A main purpose of this book is to ensure that the beneficial discoveries made by doctors in the privacy of their patient consultations are properly validated and widely disseminated. The advantages of this approach are shown clearly by the story that follows, representing one of the
What is off-label medication, and how prevalent is it?

strangest examples of a bad drug made good through off-label prescription, coupled with a strong element of serendipity.

The drug is thalidomide, a name which connotes some of the worst aspects of pharmaceutical industry misbehaviour and patient harm. Thalidomide was first introduced in 1957 by the West German company Chemie Grünenthal GmbH with the trade name Contergan, a potent and apparently safe sleeping pill. In laboratory rodents, unlike barbiturates – with which it was compared at the time – thalidomide proved remarkably ‘safe’, insofar as it was almost impossible to administer a single lethal dose. As we know now, these tests were insufficiently broad to cover the full range of toxicological consequences of the drug’s long-term administration. Clinical testing in Germany was unsystematic, with pills distributed to employees and samples given to local doctors. With its apparent safety advantages compared to other sleeping pills like barbiturates, which can be lethal at small multiples of their therapeutic dose, thalidomide gained widespread popularity in Europe and Canada; it could even be purchased without a prescription. This was an era of burgeoning use of pharmaceuticals, and their use in psychiatric conditions, as the Rolling Stones recognised so acutely in ‘Mother’s Little Helper’, a song about the widespread use of diazepam (Valium™). It was also an era of minimal regulatory supervision of the pharmaceutical industry. Later on, in addition to its use as a sleeping pill, thalidomide also became popular in the treatment of pregnancy-related morning sickness.

The first ‘thalidomide’ baby was born on Christmas Day, 1956, before the drug went on the market; she was born with no ears as the daughter of an employee of Chemie Grünenthal who had given his pregnant wife some of the free tablets. Around the same time, physicians and neurologists reported an increased incidence of peripheral neuritis (tingling hands and feet) in adult patients who were taking the sedative. The connection between these cases and the use of thalidomide was not yet clear, but the neuritis effect prevented the approval of the drug by the Food and Drug Administration (FDA) in the United States.

The Australian obstetrician William McBride was instrumental in connecting the use of thalidomide with its toxicity to the unborn child (teratogenicity). He prescribed the drug for women suffering from morning sickness and then suspected a causal link in the malformed babies he delivered months later. McBride led the uncovering of the scandal, which included overcoming the initial intransigence of
the drug companies that were involved and the important role of journalists in securing proper compensation for the victims. One estimate is that thalidomide caused malformations in between 8000 and 12 000 infants, 5000 of whom lived to adulthood. In addition, over 40 000 people suffered from peripheral neuritis. Thalidomide was banned by the World Health Organization (WHO) in 1962 and withdrawn from the market in Europe and Canada, and one would have thought that would be the end of its medical life.

But in 1964, a critically ill patient with erythema nodosum leprosum (ENL), a complication of multibacillary leprosy, was referred to Dr. Jacob Sheskin, who was at Hadassah University in Jerusalem by the University of Marseilles, France. The story is brought to life in the eminently readable *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine*, by Trent Stephens and Rock Brynner [10]. Leprosy (Hansen's disease) is a chronic, infectious disease of human beings that primarily affects the skin, mucous membranes and nerves. This bacterial disease is caused by *Mycobacterium leprae*, and is normally contracted through the respiratory tract and is similar to the bacillus that causes tuberculosis.

‘My discovery’, said Dr. Sheskin,

came about only by chance. In 1964, we had a letter from the University Hospital in Marseilles saying that a Moroccan immigrant from the Atlas Mountains on his way to Israel had been hospitalized there with Hansen's disease. They requested permission to allow the patient to continue his travels to Israel [11]. Through the Jewish Agency we answered that since the man was a Jew he was entitled to return to Israel. A separate plane was hired, and the patient, his wife, a son of a previous marriage also suffering from Hansen's disease, and several children of the wife's previous marriage were put on the plane in isolation and sent to Israel.

The patient arrived in a terrible state, suffering from extreme lepra reaction with all the classical symptoms. I have never seen a leper in worse condition. For 19 months he had been bedridden and had not slept for more than 2–3 hours during the course of any 24 hours. The pain he was suffering was unbearable. He had cachexia\(^3\) and was on the verge of death. I had read in the literature that women mental in-patients were being given thalidomide to make them sleep, and that the drug was effective where nothing else had helped. Since the patient was in such a hopeless state, I decided to try thalidomide to sooth him.

After 1 day of the thalidomide – two pills – he slept for about 20 hours without waking. When he woke he said he felt so much better that he wanted to get off the bed to go to the toilet! I only had 20 thalidomide tablets: the drug had already been condemned all over the world and had been withdrawn from the market. I gave him two more pills and made him stay in bed for another 24 hours. This time, the pain, which had been so great, had disappeared almost entirely. After another 3 days of treatment, I decided to stop the pills to see what would happen.

All the symptoms returned, the pain, the insomnia, and the inflammation of the eyes. So I started the pills again. Once again, his condition improved dramatically. I then knew that it was not by chance that he had gotten better but because of the thalidomide. I secured more thalidomide and started to give other patients in the Hospital suffering from extreme lepra reaction the thalidomide treatment. All recovered dramatically.

\(^3\)Cachexia, otherwise known as the wasting disease, involves the loss of muscle and other bodily tissues in response to severe chronic conditions, particularly cancer, heart failure and emphysema.
Because of the disastrous effects of thalidomide on foetuses, we did not give the drug to fertile women lepers. We did not want any more deformed thalidomide babies. So we gave the pills only to women rendered infertile. But there are still about 12 million lepers in the world, half of whom are not being treated at all. Much remains to be done to reach them.

To confirm his findings, Sheskin needed to travel to Venezuela, where there were many more lepers and where thalidomide was still available. There he conducted clinical tests with patients whom he had treated in the past and for whom he had records. He ended up treating 173 patients, and over 90% were symptomatically cured. His unexpected discovery led to further research on the discredited drug; scientists began to ask if it could be useful in other inflammatory conditions? In so doing, they revealed that thalidomide could modify certain immune reactions and could be useful also for those infected with HIV/AIDS and in other autoimmune conditions. More widely, research in cancer revealed that it could inhibit the proliferation of blood vessels associated with the development of tumours, thus slowing tumour growth. This effect paralleled the original effects of the drug on the growing foetus, where it was shown to interfere with the blood supply to the developing limbs of the foetus. We seem to have a common mechanism for the teratogenicity and the oncological activity.

As far as leprosy was concerned, the development was taken up by the US pharmaceutical company Celgene, and after some confirmatory placebo-controlled trials, thalidomide was finally approved in 1997 by the FDA for treatment of ENL. It subsequently became approved for cancer of the bone marrow, or multiple myeloma. To enhance its safe application and use, a special educational booklet was created, called System for Thalidomide Education and Prescribing Safety, to which patients must adhere. As a further indication of its concern about safety and to remind patients of the terrible former history of the new treatment, Celgene wanted to retain the name ‘Thalidomide’ as a trade name for its product, so that people would recognise its potential problems and avoid them.

This is a remarkable story, elements of which I shall refer to in later parts of this book. Firstly, it is profoundly apposite for my subject matter, since off-label uses refer to the use of medicines outside regulatory purview. Thalidomide was the reason why our current system of medicines regulation exists. Regulatory bodies around the world were drastically strengthened after the tragedy in order to prevent it happening again. A whole range of additional preclinical toxicology tests became necessary before experimental drugs could be first tested on humans. Drug regulation nowadays is all about risk and reward, safety and efficacy. It is a complex process, and enormous amounts of information are accrued and evaluated in order to make the assessment as accurate as possible. However, we recognise that no drug is perfect, and all have side effects. We need to minimise the risk and optimise the reward, but we are never going to have a completely safe or a completely efficacious treatment. It is a balance, infinite shades of grey. The system got it wrong with the first life of thalidomide, but got it right in the second.

So secondly, this story makes another important point. We should recognise that thalidomide’s old uses, for inducing sleep and for morning sickness, are troublesome for those affected, but not more than this: they are hardly life-threatening. People who are not treated are likely to be more tired, or nauseous, but these are natural processes which to a certain extent are self-correcting. Patients with insomnia eventually fall asleep; pregnant women with morning sickness eventually move into their third trimester, and the symptoms normally resolve. In comparison, leprosy and multiple myeloma are very serious conditions. They do not self-correct; left untreated, patients with these conditions often die as a result of them. This difference is vital if
we are fully to understand and find better systems to deal with off-label uses for existing drugs.

But in another respect, this is a good demonstration of off-label prescription leading to patient benefit, rather than the reverse. So, where then is the harm?

**Scope of the issue**

Clear from the thalidomide example, serendipity plays a central role in the history of the development of medicines. Indeed, Dr Sheskin’s motivation for prescribing thalidomide to the leprous patient was to enable him to sleep, given that the patient had not been able to do so before coming into his care. Long before the modern era, treatments were often applied to patients in all sorts of conditions in order to discover whether they worked. If you look at the potential uses proposed for herbal medicine, which often derived from folk medicine, you can see the huge range of ailments which they are proposed to work for.

In William Withering’s *An Account of the Foxglove*, written in 1785, the author is a practising doctor who tries his treatment on all sorts of patients. Included in the account are examples of diseases we can recognise, like asthma or gout, as well as ones which are difficult to decipher, like dropsy (an old word for oedema, or swelling) or anasarca (which is extreme generalised swelling). These latter two are symptoms of a number of possible illnesses. He informs us in particular that the preparation has beneficial effects on urine production. In days of bladder stones and other urinary problems, the delivery of ‘a healthy flow’ was generally considered a very good thing. It would particularly be so for patients with extreme general swelling, which could be due to liver failure, kidney failure, heart failure as well as severe malnutrition or protein deficiency. Nowadays, we recognise the active ingredient of the foxglove (*Digitalis purpurea*) to be digoxin, which is used both directly and as its derivative, digitoxin, for the treatment of heart failure. But it is not useful for liver failure, or malnutrition, and when used in excess, digoxin and digitoxin are both poisonous.

The story of *Digitalis* shows how one herbal product was generally used in a number of indications, but over the years, its utility focussed upon one indication. The evidence base closed in around heart failure. Dr Withering, in the late eighteenth century, played his part in this process by providing a written account of his experiences. Nowadays, drugs are subjected to randomised, controlled trials to find out whether they actually do any good and then first introduced for one indication alone, to be given to a specified patient population, at a specified dose and in a specified form. Subsequent to that introduction, experimental efforts are made to expand the limits of these specifications. Sadly, unlike Withering’s treatise, not all of the experiences in that process of expansion are documented in modern medical practice. Generally, the prescription of a drug in an off-label fashion, based as it is on limited evidence, does not itself result in the enlargement of the evidence base; the result of the prescription is not written and disseminated for future cohorts exposed to similar treatment. This problem is further dealt with in Chapter 8, where I discuss whether it is right that off-label medication should be categorised as different from a clinical trial, as it currently is, and how we can routinely document off-label uses, so that we can build the evidence base for safety and efficacy upon which future prescribers can depend.

One of the major classes of off-label drug use is for paediatric therapy. For legal, ethical or practical reasons, clinical trials are usually not performed on children (nor are they routinely conducted on other patient groups, such as pregnant women or
What is off-label medication, and how prevalent is it?

Senior citizens). In paediatric respiratory care, many drugs are not available in formulations suitable for infants and toddlers, having been tested predominantly on older children. However, respiratory drugs are frequently used in children for common diseases like asthma, upper and lower respiratory tract infections, rhinitis (allergies) and sinusitis. Three-quarters of marketed prescription drugs have no labelling indications for children, although their inclusion in clinical trials is enlarging [12]. Among medicines which were newly licensed by the European Medicines Evaluation Agency (EMA) between 1995 and 2005, only one-third was specifically licensed for children [7]. Thus, off-label use is particularly widespread in paediatric situations, and over half of children in Europe who are prescribed medicines in hospital receive a medication that is either ‘unlicensed’ or ‘off-label’ [13]. Other studies put the figure at 40%, 45% or 76% [6,7,14], and the area has been comprehensively reviewed [15]. To summarise these statistics, the younger the patient and the more critical and rare their illness, the more likely they will be treated off-label. This may be because the licence is for older children, whereas the prescription is for a younger child. It may also be for a different use than that on the approved label; or it may be because the dose is different or its schedule of administration is different from the approved use. Commonly, it is believed the problem is that the drug is approved for adults, having been tested only in adults. There are regulatory incentives available to producers through the regulatory system, and the extent to which this can be improved is dealt with more thoroughly in Chapter 7.

So what? Do these statistics amount to anything of real patient import, or am I just demanding unrealistic standards of pointless box-ticking by our medical practitioners? Of course, if there were no adverse consequences, there would be little to complain about (apart from the waste of money). So, for one thing, let me point out that there is an increased rate of adverse drug reactions (ADRs) associated with off-label use. A study from France in paediatric care showed that there were over three times as many ADRs associated with off-label medication as with ‘on-label’ alternatives [16]. The relationship does not just apply for ADRs overall; it is particularly concerning that a Swedish study showed that off-label drug use in children was associated with a significantly higher number of serious adverse reactions [17]. A study from Liverpool, United Kingdom, also showed that the rate of adverse reactions associated with off-label medication, at 6.0%, was significantly higher than on-label comparators, at 3.9% [18]. Another report from Derbyshire, United Kingdom, cited two studies, one of which suggested that five out of eight severe ADRs were associated with the off-label use of a medicine. This study suggested that the percentage of unlicensed and off-label drug use was significantly associated with the risk of an ADR. The other study found that 14 of 19 drug prescriptions associated with 17 severe ADRs were either unlicensed or off-label [19]. In a study of ADRs in children and adolescents over a 10-year period in Denmark, 60% of ADRs reported for medicines prescribed off-label were serious, and, in contrast, 35% of ADRs reported for ‘on-label’ medicine use were serious. Thirteen of the off-label serious ADRs resulted in a fatality [20].

So, safety in paediatric medicine is something that we will need to pay close attention to as we go forwards in our consideration of patient consent and the ethics of off-label medication (see Chapter 3), especially as safety is a paramount consideration when children are concerned, and consent often has to be given by the patient’s parents, most of whom are acutely sensitive to safety concerns.

Psychiatric care is another common area of off-label use. A US study looked at psychotropic drugs over a decade-long period from 1998 through 2009: the average proportion of all uses that occurred off-label was 23.3% for antidepressants, 60.7%
for antipsychotics and 54.2% for mood stabilisers [21]. At these high levels, there are more drugs being prescribed off-label than in accordance with the regulatory approval; in this situation, this ‘is the death of regulation’ [3]. But it gets worse, as we now see.

In November 2009, the UK Department of Health issued a report on the prescribing of antipsychotic drugs to people with dementia [22]. With a rare exception, no antipsychotic is licensed in the United Kingdom for treating the behavioural and psychological symptoms of dementia; the approved label is generally limited to the treatment of schizophrenia and bipolar disorder. This therefore constitutes off-label medication except in the rare and unfortunate event that the demented patient also has a co-morbid psychotic illness. The report had been commissioned in recognition of widespread concern about the overprescription of antipsychotic drugs to patients with dementia, a concern felt particularly among patients and their families who had not been consulted before such antipsychotic treatment began; neither were they aware that the prescription was being administered in an off-label fashion. Subsequently, the UK National Institute for Health and Care Excellence (NICE) conducted its own evaluation [23]. It was suggested that up to a quarter of people with dementia had been prescribed antipsychotics in addition to their normal medication, up to 180,000 people at a cost of £90 million a year. In formal care, the proportion of dementia patients being prescribed antipsychotics rose to nearly a half [24]. The vast majority of these, 8 out of 10, derived no benefit from antipsychotic treatment, and NICE advised against the use of any antipsychotics for non-cognitive symptoms or challenging behaviour of dementia unless the person is severely distressed or there is an immediate risk of harm to them or others.

Moreover, not only are these drugs ineffective, but they are dangerous in older patients. There is an approximately threefold increased risk of cerebrovascular adverse reactions (in other words, stroke) that have been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole and olanzapine. As a result, NICE worked out that for each 100 patients treated with atypical antipsychotics over a year, one of them died prematurely and a similar additional number suffered non-fatal cerebrovascular events, such as stroke (around half of which may be severe) as a result of adverse side effects. In the context of longer-term treatment, there were estimated to be 167 additional deaths among every 1000 people with dementia treated with antipsychotics over a 2-year period. A similar situation pertained in the United States, where the Department of Health and Human Services found that in a 6-month period in 2007, 14% of nursing home residents were given antipsychotics, presumably with similar adverse outcomes [25]. Of course, stroke is not the only side effect of antipsychotic drugs: they also produce over-sedation, which may result in falls or in patients to become ‘like zombies’ [24], and worsening of cognitive function, which is exactly the opposite of what medical treatment of dementia sufferers is supposed to achieve.

Antipsychotic prescribing is also a surprisingly common practice for active duty troops in the US military, even though psychotic illness itself would presumably not be desirable, and should have been screened out as part of the selection process. Nevertheless, antipsychotic prescription is a growing trend: it was reported [26] there has been a 682% increase in the number of psychoactive drugs – antipsychotics, sedatives, stimulants and mood stabilisers – prescribed to US troops between 2005 and 2011, despite a steady reduction in combat troop levels since 2008. Some of the off-label uses for which these drugs have been prescribed include insomnia, anxiety and aggressive behaviour. They have also been used to treat post-traumatic stress
disorder (PTSD), even though the evidence for efficacy in this area is weak (for instance, one antipsychotic risperidone failed in a clinical trial examining its use as add-on treatment of PTSD symptoms [27]). Certainly, by comparison with antidepressants, which are demonstrably effective in PTSD, antipsychotics are very much the inferior option. In addition to the nearly sevenfold increase in the use of antipsychotic drugs, there has been an even bigger increase in the use of sedating anticonvulsants, an increase that is not matched in the general population, and, perversely, a decrease in the use of antidepressants. Given the comments earlier about PTSD and depression, which are both likely outcomes of active duty, the decline in antidepressant use is disturbing if they are being substituted by less efficacious antipsychotic alternatives, with consequently poorer therapeutic outcome. It is particularly disturbing given that untreated PTSD and depression are both associated with increased rates of suicide, and in soldiers involved in the Iraq war and Afghanistan mission, suicide is a greater risk than death in combat.

The overall prevalence of off-label prescribing in psychiatry is high. A study from 2000 reported that 65% of psychiatrist respondents had prescribed medication off-label within the past month [28]. A German prescription survey from 2000 reported that antipsychotic drugs were being prescribed in older patients (aged 49–70 years) almost exclusively for off-label indications [29]. Another study found the off-label use of Eli Lilly’s atypical antipsychotic Zyprexa (olanzapine) to be 45% [30]. However, one of the problems in psychiatry is the complexity and specificity of the diagnosis, together with an increasing specificity of the label. It may be helpful to think of a spectrum of use of licensed psychotropic drugs in unlicensed applications, with some off-label prescribing being nearer the label than others. Because of this very fine level of diagnostic specificity, there may be no regulatorily approved treatment for the specific condition to be treated [31]. To address this problem, I came across a blog post in the course of researching this book [32] advocating that psychiatrists should formally diagnose in accordance with the approved label in order to avoid their prescription being regarded as ‘off-label’, whatever the real patient diagnosis. The [anonymous] author of this blog appears to be a pharmaceutical industry insider or a medical professional. It is not clear whether this is a serious proposal or to what extent if reflects widespread, if unspoken, attitudes among medical professionals for their patients. However, other reports have used the term ‘diagnosis shifting’, to indicate physician behaviour in cases where they are aware that prescribing practices are being monitored. For example, when treating a patient with sinus congestion but prescribing antibiotics, a clinician might be more inclined to write it up as sinusitis, an antibiotic-appropriate diagnosis, instead of nonspecific upper respiratory infection, an antibiotic-inappropriate diagnosis [33].

Part of the problem is lack of awareness among prescribers about exactly what drugs are approved for what indications. A US survey of nearly 1200 physicians (599 primary care physicians and 600 psychiatrists) showed widespread ignorance of what drugs were actually approved for. The study was conducted in 2007–2008 and included 22 drug–indication pairs. The indications varied in their FDA approval status from on-label use, to off-label use supported by medical evidence, to off-label use deemed to be ineffective. In the area of psychiatric care, 13% of all physician respondents erroneously believed that quetiapine (Seroquel®) was FDA approved for dementia with agitation; an even higher number, 19%, had prescribed quetiapine for dementia with agitation, suggesting that roughly one-third of doctors had prescribed this indication pair knowingly off-label, with roughly two-thirds having prescribed it unknowingly [34]. These two groups may be categorised, somewhat unkindly, but not inaccurately, as the ‘ignorants’, those that do not know, and the
‘insouciants’, those that do not care. In this case, it is difficult to know which group to be most concerned about.

A common form of off-label medication in psychiatry is the prescription of drugs at higher than their approved dosage ranges. While potentially offering greater efficacy, for instance, in patients not well treated for depression, the likely adverse consequences of this practice on safety are obvious. Another factor which seems to be more prevalent in psychiatry is that the approved indications change over time, with some new uses being added to the list of approved indications (such as the expanding uses beyond depression for serotonin uptake inhibitors, [SSRIs] for anxiety and obsessive compulsive disorder), while sometimes the approved uses can be reduced (for instance, the use of fluoxetine for depression in children and adolescents) [35]. So, we need to reflect that the situation is complex and nuanced, but that in itself is not a good reason for an abandonment of concern over the scope of off-label medication in psychiatry [36].

When we put paediatric and psychiatric use together, as in paediatric psychiatry, off-label prescribing is even more common, and other concerning facets arise. In the United States, it has also been estimated by the American Medical Association that although certain atypical antipsychotic drugs are FDA approved for specific uses in paediatric patients, the majority of prescribing (70–75%) is off-label for these drugs in this patient group.

One of the additional concerns with atypical antipsychotics involves their adverse metabolic effects. Because the risk of childhood obesity is inversely related to socio-economic status, low-income children who are already at high risk for obesity and related metabolic disorders may be especially vulnerable to the adverse effects of weight gain from atypical antipsychotics. Children treated within the Medicaid programme, that is, publicly funded healthcare for the poor, were four times more likely to receive antipsychotics than children treated privately [37,38].

A substantial proportion of paediatric psychiatric prescriptions are written to control violent behaviour, rather than address the root cause of the violence, which would require more expensive psychotherapeutic intervention. The inference is that the expensive, non-medicated option is only available for private (non-Medicaid) care, and this explains the fourfold lower rate of antipsychotic prescription in these patients. Some of the prescriptions were written for very young children: for example, some children between ages 1 and 2 received antipsychotics for conditions such as autistic disorder and attention deficit disorder (ADD) with hyperactivity. In this context, we should note that between 1994 and 2003, reported diagnoses of paediatric bipolar disorder increased 40-fold, from about 20 000 to approximately 800 000. That diagnosis was associated with the claim that extreme irritability, inattention and mood swings were actually due to paediatric bipolar disorder that can occur before age 2. This increase in incidence seems difficult to reconcile with a real change in psychiatric disorder, but of course, once a diagnosis associated with bipolar disorder is reached, it is much easier to prescribe an antipsychotic, albeit one that is not specifically approved for paediatric use. In 2008, an estimated $6 billion was spent on off-label antipsychotics in the United States, of which $5.4 billion was for uses based on uncertain evidence [39].

The US Department of Health and Human Services recently reviewed antipsychotic drug use by Medicaid recipients of age 17 and under, focussing in particular on the newer ‘atypical’ antipsychotics, which include AstraZeneca’s Seroquel (quetiapine), Eli Lilly’s Zyprexa (olanzapine), Johnson & Johnson’s Risperdal (risperidone) and Otsuka Pharmaceutical’s Abilify (aripiprazole). Medicaid spends more on antipsychotics than on any other class of drugs, and there is evidence that 70% of the
cost of these drugs in the United States was paid for by Medicaid and other government programmes. In 2013, aripiprazole became the top-selling drug in the United States, reaping revenues of $6.3 billion for the Japanese pharmaceutical company Otsuka in that year.

The last general area where substantial off-label use exists is in oncology. The levels in this area has been estimated at between a third [8] and a half [40], with another study suggesting that 50–75% of all uses of drugs in cancer care in the United States are off-label [41]. In terms of cost, in 2010, $4.5 billion was spent on off-label chemotherapies compared to an overall bill of $12 billion. It has been estimated that 62% of cancer patients use drugs off-label. In cancer, although regulatory approval is generally given for a specific type of cancer, it is a reasonable and frequently valid hypothesis that efficacy crosses into other types. Moreover, given the seriousness of the condition, there is much public sympathy for the widest possible armoury of therapies to be available to the patient, regardless of actual regulatory status. The European Society for Medical Oncology, for instance, is dedicated ‘to promote equal access to optimal cancer care of all cancer patients’ in its mission statement. In reflection of this sentiment in the United States, in 2008, Medicare rules were changed to cover more off-label uses of cancer treatment drugs (the issue of drug reimbursement is dealt with fully in Chapter 6). A 2008 study found that 8 out of 10 cancer doctors surveyed had used drugs off-label. Studies have reported that about half of the chemotherapy drugs used are given for conditions not listed on the approved drug label. Nevertheless, the evidentiary support for such off-label use is very variable in quality, and always less than would be required for a formal regulatory approval [42].

In most cases (not just in cancer), adequate research evidence to support off-label prescribing is lacking. A survey of 150 million off-label prescriptions in the United States found that 73% had little or no scientific support, even when sources other than the product information were searched [9]. A similar percentage, 79%, of off-label medicines were found to lack scientific support from a survey in Canada [43]. Similarly, in Australia where the prevalence of off-label prescribing overall is between a wide range of 7.5% and 40% in adults and may be up to 90% in some hospitalised paediatric patients, there is a lack of evidence to support prescriber’s off-label choices [44]. As a consequence, only a minority of off-label prescribing can be said to be scientifically justified. When analysed by therapeutic area, a similar if not more alarming situation pertains (see Figure 1.2). In terms of cost, Stafford et al. looked at the expenditures on off-label antipsychotics in the United States over the period to 2008 and found a huge increase in poorly evidenced use that reached $5.5 billion a year by the end of the period, relative to $4 billion of on-label use and around $0.7 billion of well-supported off-label use (see Figure 1.3) [45]. This matter is further dealt with in Chapter 4.

Aside from the general therapeutic areas, there are some specific cases where off-label rates are shockingly high. A particular example is NovoSeven, marketed by Novo Nordisk A/S of Denmark; it is a bioengineered form of factor VIIa, a critical protein involved in the coagulation of blood [46]. Factor VIIa is approved by the FDA for patients with certain forms of haemophilia or congenital deficiencies in the protein, for whom it can prevent potentially fatal episodes of bleeding. But an anecdotal story emerged involving a soldier that had received life-saving treatment of a battlefield wound. In June 1999, an Israeli doctor, Uri Martinowitz, injected two doses of factor VIIa into a 19-year-old Israeli soldier who was shot through the abdomen with a high-powered rifle; it was the first reported use of the drug in a non-haemophiliac
and, according to Martinowitz, caused the bleeding to ‘stop immediately’. Between 2000 and 2008, industry-sponsored research revealed that factor VIIa could also prevent bleeding in heart surgery, trauma or haemorrhagic (i.e. bleeding) strokes. As a consequence, annual usage soared 140-fold (while use in haemophilia increased less than fourfold), from about 125 to a total of more than 18 000 cases; over the total 8-year period, it is estimated that factor VIIa was used in more than 70 000 hospital cases in the United States [46].

By 2008, the latest year studied, researchers found that off-label uses accounted for 97% of orders for the drug, total global sales of which amounted to $1.43 billion. The figure reflects the high cost of the drug, which can result in hospital costs of up to $650 000 for a single patient at the highest doses [47]. Part of the reason for the high cost is the way it is manufactured, using biotechnology rather than large-scale chemical reactors, but drug costs also increased because recommended dosages

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**Figure 1.2** Levels of off-label use and scientific evidence, by therapeutic area. Graph drawn from data in Ref. [9].

**Figure 1.3** Costs associated with the prescribing of antipsychotic medications in the United States, 2002 through 2008, categorised by off-label status and level of supporting evidence. Reprinted with permission from Ref. [45]. © Nature Publishing Group/Macmillan. (See insert for color representation of the figure.)
What is off-label medication, and how prevalent is it?

Increased. Factor VIIa is a complex biological protein that is made in hamster kidney cells that have been genetically engineered to secrete factor VIIa; the protein is harvested outside the cell and purified from the extracellular serum. The cost of factor VIIa, though high, is similar to other biological drugs, which are often produced by expensive manufacturing processes.

So far, then, the argument is that this drug is hugely costly and widely sold by means that make a mockery of the drug regulatory system. But a further key question is, ‘Does its off-label use nevertheless benefit patients?’ The clinical evidence in favour of most of the off-label use of NovoSeven is weak and disrespected. In 2011, researchers from Stanford University in California published a systematic review of the benefits and harms of factor VIIa when used for five off-label, in-hospital indications [48]. These were cardiac surgery, intra-cerebral haemorrhage, liver transplantation, prostatectomy (prostate removal) and trauma. They identified all the available evidence that addressed this issue and found 64 reports worthy of review. Only 16 were randomised, controlled trials; the others were observational studies that compared the treatment with another approach or had no comparator group. The authors concluded that limited available evidence for these five off-label indications suggested no mortality reduction with factor VIIa use. An editorial that accompanied this article stated that overall, there was no evidence that factor VIIa reduced mortality for any off-label use; however, it did increase the risk for thromboembolism, in other words a blood clot resulting in a heart attack or the kind of stroke where blood flow to the brain is interrupted. In plain English, off-label factor VIIa does not work and caused harm to patients when so used. Their findings are compatible with other recent studies. The editorialists noted that ‘allowing physician autonomy to choose medications is appealing, but not when it results in unhelpful, dangerous, and costly decisions’ [49]. This is an example where for every three prescriptions written in 2008 in accordance with the regulatory approval generated from the producer Novo Nordisk’s submitted data, the company sold 97 off-label doses. That’s a pretty interesting ratio, particularly if, as stated earlier, these 97 doses caused no benefit and harmed patients, but still cost thousands of dollars each.

A second example is bone morphogenetic protein 2, or BMP-2. This product has been approved for orthopaedic usage in the United States and Europe in a medical device, rather than as a drug per se. Bone morphogenetic proteins are growth factors that promote bone formation. BMP-2 is a particularly powerful bone growth stimulator, but more than that is thought possibly to be also involved in all kinds of biological processes involving changes in bodily form and structure. There are many roles for dysregulated BMP signalling in pathological processes, including cancer; over-activation of BMP signalling is instrumental in the development of adenocarcinoma in parts of the gastrointestinal tract. Medtronic is the producer of a medical device called InFuse, composed of a collagen sponge containing BMP-2 for the treatment of certain types of spinal fusion procedures in adults with degenerative disc disease, and at one time achieved close to $1 billion in annual sales.

Originally approved in 2002, a series of complications and side effects have grown in magnitude since that time. Many of them occurred when BMP-2 was used in an off-label manner, which was estimated to be about 85% of the time [50]. Medtronic found in a clinical trial of BMP-2 in a type of spinal fusion surgery that there were troubling findings of bone formation in the spinal canal (i.e. outside the area of fusion) of 75% of the BMP-2 patients. The trial was halted, but the results were not published until 2004, 5 years after the trial was conducted. Other cases of ectopic
bone formation\textsuperscript{4} were observed in a trial of cervical spine fusion. In some cases of cervical spinal fusion, there have been alarming reports of head and neck swelling, resulting in the compression of the airway and neurological structures of the neck. In other reports, there is an increased level of cancer reported in patients treated with BMP-2, particularly when administered in higher doses, and debate as to whether this is causally related.

In 2013, the US Senate Finance Committee published a report on Medtronic’s product [51]. The part relating to off-label uses of InFuse reads:

The FDA’s 2002 approval of InFuse was limited to spinal surgeries using the anterior lumbar inter body fusion (ALIF) technique...The Agency for Healthcare Research and Quality (AHRQ) estimates that...’at least 85% of InFuse use is now off-label.’ In 2008, the FDA published a public health notification linking the off-label use of InFuse in the cervical spine with life-threatening swelling in patient’s [sic] throats and necks. The Wall Street Journal reported at the time that ‘the agency... received 38 reports over four years of side effects, mainly swelling of neck and throat tissue, which resulted in compression of the airway and other structures in the neck.’ In addition, the Wall Street Journal reported that ‘at least three-quarters of the roughly 200 “adverse events” reported to the FDA involve off-label uses of InFuse’.

The risk and benefit of BMP-2 has been debated for over a decade. In what is probably a defining moment for the product, a report published by the widely respected Yale University Open Data Access Project in June 2013 in the \textit{Annals of Internal Medicine} detailed the results from two independent groups that ‘rhBMP-2 provided little or no benefit compared to bone graft and may be associated with more harms, possibly including cancer...’ [52]. The criticism applied to both off-label and on-label uses. Meanwhile, evidence continues to mount regarding the increasing adverse events attributed to utilising BMP-2 ‘off-label’ in spinal surgery [53]. It is a pity therefore that the off-label expansion of the approved use exposed approximately six to seven times as many patients to harm while not offering treatment proven to be effective.

The third example is that of niacin (vitamin B\textsubscript{3}), which is used for its ‘good’ cholesterol-raising properties. In a long-acting form as Niaspan\textsuperscript{TM}, it is indicated to reduce elevated total cholesterol and LDL (‘bad’) cholesterol and to increase HDL (‘good’) cholesterol. Whereas the mainstay of cholesterol therapy is based on the administration of the statin class of drugs, which have been shown both to control cholesterol levels and to reduce heart attacks and strokes in people with abnormal cholesterol levels, Niaspan and other drugs based on niacin have not demonstrated this functional benefit. In other words, they have only demonstrated an effect in reducing ‘bad’ cholesterol, not on the consequences of so doing. In 2012, 5.3 million prescriptions costing $1.1 billion were written for Niaspan, according to data provided by IMS Health, on the assumption of such a benefit. James Stein, a professor of cardiovascular medicine at the University of Wisconsin School of Medicine and Public Health, estimated that only about 25\% of Niaspan’s use was ‘proper’; by inference, the other $825 million spent was for ‘improper’ use of the drug [54].

However, in 2013, the results were reported of a large randomised trial testing the use of extended-release niacin for the reduction of major vascular events. It was called the Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study. The study found that not only did this special

\textsuperscript{4}Ectopic bone formation relates to bone being formed in an unwanted place, where it does not belong.
extended-release niacin formation not reduce heart attacks and strokes, it increased the risk of bleeding, infection and diabetes. This example indicates that sometimes the off-label use of a drug is a result of an improper inference based on a biomarker; in the case of niacin, it was assumed that the effects on cholesterol were functionally important in heart disease, but when this was tested, they were not. As in the previous example, there have been accusations of improper marketing by the pharmaceutical company (Abbott); but at the end of the day, it is the prescriber who has assumed, in this case falsely, that the effects on cholesterol would equate to a beneficial cardiovascular outcome, in advance of that outcome having been demonstrated.

Finally, we should recall the interesting story of modafinil. Modafinil was originally marketed in Europe by the small French pharmaceutical company Lafon for idiopathic hypersomnia (in other words excess sleepiness for unknown reasons); but in 1986, the US company Cephalon leased the US rights to the compound and obtained orphan drug designation and subsequent FDA approval to market the compound for narcolepsy, under the brand name Provigil. Orphan drug designation is a scheme put in place by many of the regulatory agencies worldwide to offer market inducements for rare diseases. We will talk about it more in Chapter 4. Narcolepsy is a chronic brain disorder that involves poor control of sleep–wake cycles. People with narcolepsy experience periods of extreme daytime sleepiness and sudden, irresistible bouts of sleep that can strike at any time. These sleep attacks usually last a few seconds to several minutes. Narcolepsy often occurs with cataplexy, a sudden loss of voluntary muscle tone while awake, that makes a person go limp or unable to move. Narcolepsy with cataplexy is estimated to affect about 1 in every 3000 Americans. Given the infrequency of the marketed condition, Cephalon led an astute campaign of increasingly wide regulatory approvals that established modafinil as a ‘wakefulness promoting agent’ rather than a classic amphetamine-like stimulant, and with those approvals came substantial commercial success, the product selling $744 million in the United States in 2007.

On the basis of this, Cephalon purchased Lafon, the originator of the product, and continued to seek further approvals for additional uses of the compound from the FDA. In the meanwhile, modafinil developed a wide range of additional off-label uses, so much so that its use grew almost 10-fold between 2002 and 2009. During the period from 2001 to 2006, Cephalon was specifically alleged to have illegally promoted modafinil for non-approved uses, for the treatment of sleepiness, tiredness, decreased activity, lack of energy and fatigue. Modafinil also became widely used for ADD (ADHD) and for non-therapeutic uses such as a cognitive enhancer to boost exam performance; it is a drug of choice for the competitive student around revision time or for the workaholic executive who needs to boost alertness after marathon sessions of work and travel. People who take it say it keeps them awake for hours or even days, maintaining most users in a refreshed and alert state but still able to go to bed when they are ready. It is widely available through Internet pharmacies. According to Barbara Sahakian, professor of psychiatry at the University of Cambridge, there is evidence that a staggering 90% of modafinil’s use is off-label [55]. The success of modafinil does not result solely from off-label uses, since Cephalon also filed for additional approved uses in order to expand the market for their product; and while much of the recent uptake of modafinil is a result of off-label use, Cephalon currently derives little benefit from this since the patents have expired and the product is mainly sold by multiple generic manufacturers.

Taking these individual examples together, in conjunction with the therapeutic area-wide assessments, it is clear that off-label use is a widespread practice, but with particularly common occurrence in specific hotspots. While prescribers sometimes
need to be able to find solutions for rare diagnoses that are not covered by the approved use of any individual drug, the practice of off-label medication goes much wider than that. There are concerns this raises both for the real level of efficacy of a treatment outside its regulatory approval, as well as the safety in the unapproved use or unapproved patient population. It crosses into dubious grey areas where pharmaceutical companies have been found guilty of improper marketing and, as we shall discover in Chapter 7, eye-watering fines. We will need to ask whether, and under what circumstances, reimbursement of prescription costs to the patient in respect of these off-label uses is appropriate. Having sampled the scope of the issue, we can also delve more deeply into these safety and efficacy aspects. But before we do, let’s understand why this practice has grown up, because there is a legitimate basis for finding drugs to work in more than one therapeutic use. Then once we have looked at some of these examples, we can ask, as I have, whether and how the current extent of off-label use can be justified.