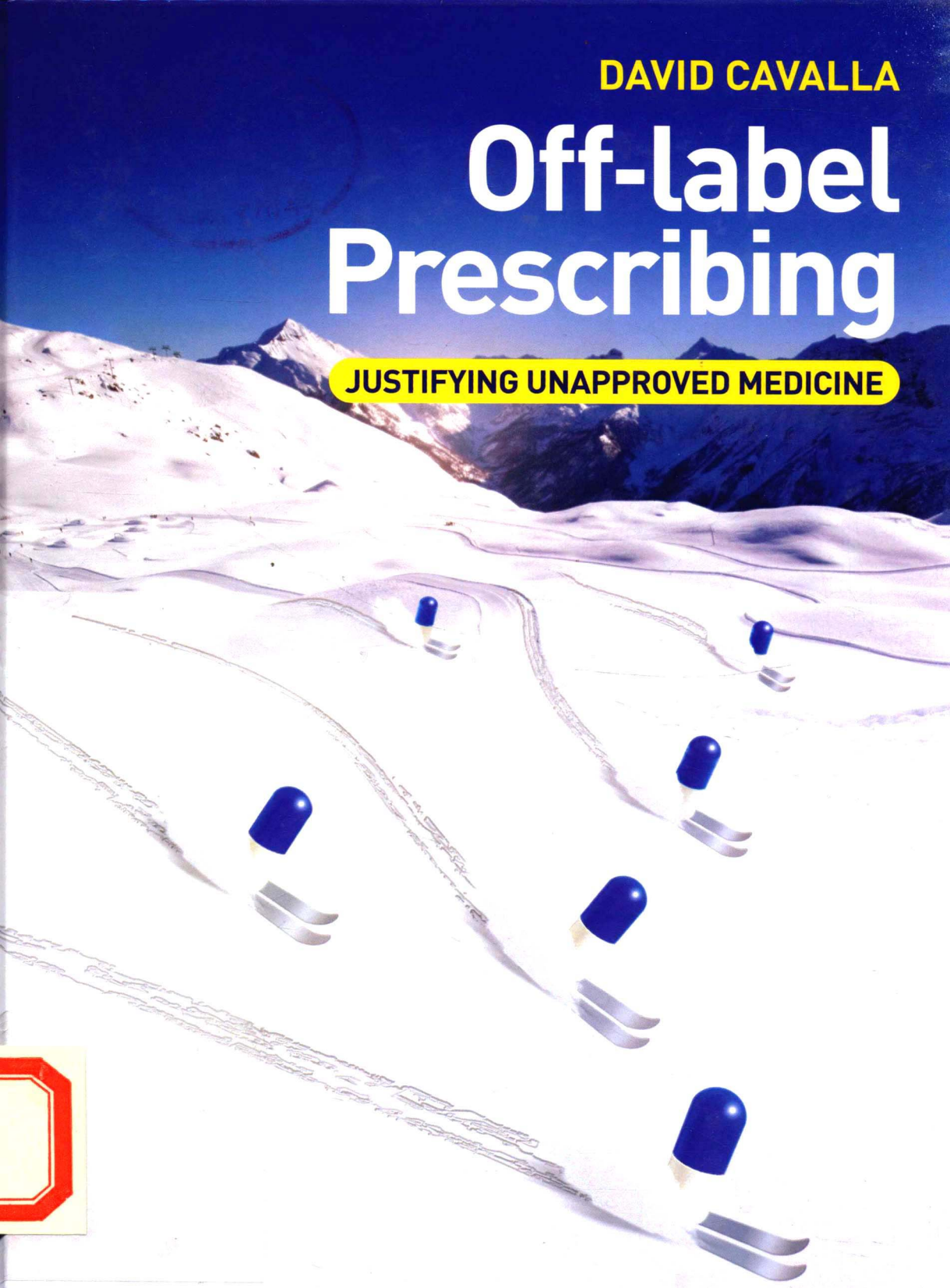
DAVID CAVALLA

Off-label Prescribing

JUSTIFYING UNAPPROVED MEDICINE



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Off-label prescribing – Justifying unapproved medicine

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This book is for patients, who for too long have been misled about the fact that many of the prescriptions that are written for them are for unapproved for their circumstance. We are all patients, or potential patients, so really this book is for everyone.

Foreword

NORD (The National Organisation for Rare Disorders) estimates that 25 000 000 Americans, 8% of the population, have a life-altering disease for which there is no currently effective therapy. Globally, 8% of the population would yield over 500 000 000 people similarly affected. Yet, under the current system, with all the knowledge, technology and money we have to invest in this problem, most people with diseases for which there are no, or only poor, treatment options have little hope of receiving an effective treatment in their lifetimes. Healthcare costs round the world keep rising, and a significant portion is spent on palliative care for diseases with no truly effective treatment. Those costs, plus lost productivity costs and the emotional trauma for patients and their families, directly or indirectly impact all of us.

The for-profit medical research industry is our current 'solution', but it can only work for some patients, and many serious conditions are left unaddressed. The major pharmaceutical companies invest more than US$ 70 billion per year in R&D to bring to market about 30 new drugs or drug improvements annually. Development takes 10–14 years and costs US$ 1.5 billion or more per new drug. Industry generally makes a lower investment in rare diseases, acute diseases, prevention and diseases of the poor where it cannot make a suitable profit. This is essentially a market failure, which restricts many patients from receiving solutions to their medical problems, and makes it unlikely that the for-profit system can conquer most of the 7000 diseases waiting to be addressed.

Other factors compound the problem. Academic research for diseases of the poor and rare diseases receive limited funding. Researchers often cannot or would not collaborate due to intellectual property and authorship concerns, so the limited funds that are available are not leveraged by collaboration. And philanthropic and venture funders are often stymied in their efforts to find the best treatment ideas and creating the research partnerships required to create treatments for these underserved patients and diseases.

Physicians, patients, payers, government and industry are all searching for solutions to this gaping treatment hole. One stopgap measure employed with regularity around the globe is to use drugs approved for one disease to treat another disease for which formal approval has not been obtained: this is called 'off-label' medicine. While on the surface repurposing of our existing therapeutic armoury has great appeal, when one examines this in more detail, significant peril is exposed. In practice, the freedom to prescribe off-label has often been abused by prescribers and industry: products have been used with inadequate evidence for trivial conditions, and commercial interests have trumped patient welfare. In order to sort this out, we need to differentiate the acceptable off-label uses from the unacceptable. But how?

David Cavalla examines, in great detail and with clear support, the issues of off-label drug prescribing. His evaluation is both broad and deep. He notes the value and the pitfalls of the practice, and offers cogent and feasible solutions to create greater value for patients. Most importantly, while sharing his expertise, he gives the reader the chance to draw his or her own conclusions. This is a very important book, because catastrophic diseases do or will impact many of us. At some point in each of our lives, we are likely to be faced with the need to find a medical solution to an unresolved

disease, either for ourselves or for someone we care about. And that solution might involve what David Cavalla calls 'An Unapproved Medicine'. Armed with the knowledge in this book, you might make a different set of decisions or make the same decision better informed.

Dr. Bruce E. Bloom
President and Chief Science Officer,
Cures Within Reach

Acknowledgement

In writing this book I would like to thank all of the people who have given me help and advice, including specifically my wife, my daughter Anna and father John, who read and reviewed the early draft of the manuscript. I am also most thankful for the expert advice from Drs David Erskine, Janice Steele and Michael Clementson from the delivery end of medicine, as pharmacists and practitioners.

Author's note on the cover design

Off-label medicine is the technical term for medicines which have not been approved for the therapeutic purpose for which they are prescribed. It is a term with which most patients are unfamiliar, yet it can be likened to something with which is much more recognisable: off-piste skiing. The likeness, depicted on the cover of this book, extends on the one hand to the fact that neither practice is strictly illegal, and on the other to the fact that both practices are less safe and well-described than the authorised alternatives. Off-label uses of medicines are not regulated, so we have much less information about the safety and efficacy of the treatments. But sometimes, like off-piste skiing, there is no other way to travel.

To justify the use of an off-label treatment, there is one and only one person to bear in mind: the patient. But disposing of the other interests in the delivery of medicine, for example the pharmaceutical company that makes the product, the doctor who prescribes it and the government or insurance company who pays for it, is not an easy task.

Introduction

When becoming authorised to practise, the Hippocratic Oath requires a doctor to swear to '...use treatments for the benefit of the ill...but from what is to their harm and injustice...[to]...keep them'[1].

It is common knowledge among the medical profession and the public at large that the Oath requires the doctor to essentially 'Do no harm'; however, the requirement to keep their patients from injustice is much less appreciated. This book will identify issues that relate to the justice of the relationship between doctor and patient, as well as a wider consideration of other aspects of the complex ways in which medicines travel from scientist's bench to the bedside.

Most importantly, it will deal with the way in which around one in five of prescriptions today are written outside regulatory purview – in other words, the treatments have not been approved by the regulatory agencies. This is what I mean by unapproved medicine. Given that there were over four billion prescriptions written in the United States in 2011 [2], it is a very significant issue.* In certain areas, the proportion of unapproved prescriptions is much higher even than this, reaching three quarters or even 90% of prescriptions in some types of patients or with certain conditions.

At this point, you, the Reader, will surely say: No, he is wrong. This cannot be. We have a highly regulated and legally constituted system by which the safety and efficacy of medicines is ensured before they are taken by patients. I do know that medicines sometimes have side effects, sometimes do not work and sometimes even the regulators get it wrong, but I simply cannot believe that prescriptions cannot be written without regulatory say-so. And on this scale, it beggars belief!

You will also say: How can I not have heard of this before? If it is true, why have the press not highlighted it more? What is the point of medicines regulation when nearly a quarter of prescriptions are not regulatorily approved? Being perhaps well read in this area, you may also say: I have heard there are issues of data being hidden from the public by pharmaceutical companies, but I thought companies were obliged to have all their products approved by regulators before they are dispensed. And, you go on: if this is so, why are regulators not more stringent with the rules, to prevent it happening?

If this is your response, please do read on, because what I say is true. And, for the most part, it is all perfectly legal. It is my intention that by the end of the book, readers will be able to judge whether, from the patient's perspective, our current

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*Using data from the OECD (OECD Health Policy Studies Pharmaceutical Pricing Policies in a Global Market; OECD Publishing, 2008. DOI: 10.1787/9789264044159-en), the relative volume of pharmaceutical utilisation can be obtained across the OECD countries. This is then normalised according to the population and the known number of prescriptions in the United States in 2011, which is 4.02 billion according to Ref. [2]. The total number of prescriptions across the United States, Japan, France, Germany, Spain, the United Kingdom, Italy, Korea, Canada, Australia, Mexico, Poland, the Netherlands, Sweden, Portugal, Austria, Hungary, Czech Republic, Switzerland, Norway, Finland, Denmark, Ireland, Slovakia, New Zealand and Iceland is then estimated to be 10.85 billion. Twenty-one per cent of this is over two billion prescriptions per year, a number I shall refer to later in the book.

practice of medicine and its prescription meets the standard of justice espoused in the Hippocratic Oath.

This book explores the nooks and crannies of our medicated lives, where drug regulation runs up against medical practice, and concerns the use of a drug that has been approved for one use (in medical parlance, 'indication') being used for a different indication; alternatively, being used on a different set of patients from the ones it is approved for, or at a different dose. It is now time to shed some light on this somewhat dark area. As you will see, not only does this mean that the evidence base for the drug's benefit is suspect, but there are safety issues too. Usually the patient is unaware of what is going on, having not been informed by their doctor of this aspect of his or her prescribing choice. I will tell you what the various medical professions have to say about this, how they respond to regulatory bodies and how pharmaceutical companies benefit by moving into this poorly regulated area. The issues are complex and resist simplistic headline-grabbing sound bites; but I hope you will persist to the conclusion of this book, since, in addition to pointing out the problems, by the end I will also leave you with some proposals to improve the way medicines are prescribed and evidence gathered to support the ways they are used.

Contents

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'.

Off-label Prescribing – Justifying Unapproved Medicine, First Edition. David Cavalla.

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

[1]Clinicians 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.

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]

[2]A 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

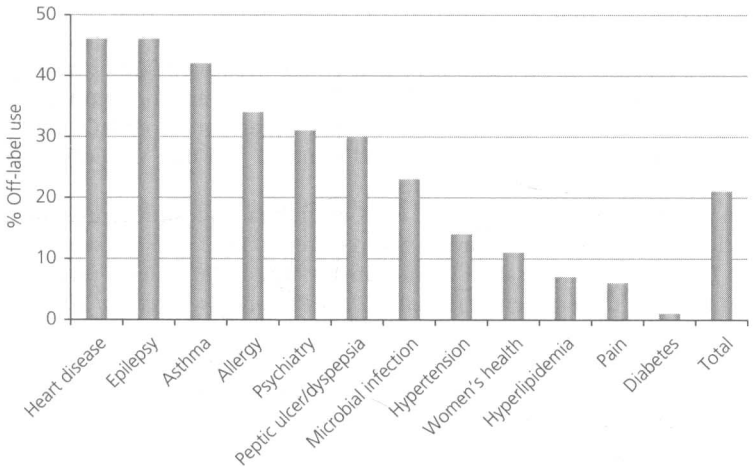

Figure 1.1 Off-label mentions by therapeutic class. Graph drawn from data in Ref. [9].

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