Evidence-based Dermatology
Third edition
Dedication

We, the editors, dedicate this book to our patients who have helped us to understand what it is really like to have a skin disease, and who have helped us to identify the questions that matter to them. Evidence-based dermatology starts with patients and ends with patients. If we lose our compassion for patients, we become a sounding brass or a tinkling cymbal.
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Foreword

Twenty-eight years ago, when drafting an introductory chapter for a book on the effects of care during pregnancy and childbirth [1], I decided to use contrasting quotations from a distinguished statistician and a distinguished dermatologist. In 1952, Austin Bradford Hill had written [2]:

In my indictment of the statistician, I would argue that he may tend to be a trifle too scornful of the clinical judgement, the clinical impression. Such judgements, I believe, in essence, statistical. The clinician is attempting to make a comparison between the situation that faces him at the moment and a mentally recorded but otherwise untabulated past experience.

Twenty years later, Sam Shuster coined the memorable phrase [3]:

Lies, damned lies and clinical impressions.

My draft went on to discuss the fundamental importance and great dangers of clinical impressions: in obstetric practice they have led both to important therapeutic discoveries and to iatrogenic disasters. I doubt that people treating skin disease have the capacity to do unintended harm on the scale achieved by obstetricians and neonatologists, but I also doubt there is any justification for complacency in matters of dermatological therapy.

The huge variability that exists in the management of common chronic skin diseases is clear evidence of collective uncertainty about the effects of alternative management strategies, even if a majority of individual clinicians are certain that they are doing the right thing. For example, I gather that fumaric acid esters have been used widely to treat psoriasis for over 40 years in Germany and the Netherlands, but that, although their use is supported by good evidence [4], they have hardly been used at all anywhere else. Some patients with warts are being put to the inconvenience (and expense) of attending hospital for cryotherapy; yet there is no strong evidence to suggest that they would be worse off treating their warts at home with salicylic acid paints [5]. Topical corticosteroid preparations like bethamethasone valerate are traditionally used twice daily, yet there is no good evidence to show that twice-daily applications are more effective than once-daily applications. Furthermore, once-daily applications are easier for people with eczema, they may result in fewer side effects, and they are also less costly [6]. As professionals are concerned to do more good than harm to their patients, all who treat skin disease have a duty to reduce uncertainty about the relative merits of alternative treatments by paying attention to the results of well-designed research.

To do right by their patients, people treating skin disease need to know what they know and what they don’t know. This book tries to help them. Unlike traditional textbooks, it contains a toolbox section that describes the methods that have been used to review the evidence upon which conclusions about the effects of treatments have been based, and gives references to more detailed reports of the systematic reviews on which much of the text has drawn.

There is no consensus about the materials and methods that should be used to assemble evidence to support treatment recommendations published in textbooks and review articles, nor even about the principles of systematic reviews. One senior dermatologist, for example, has written [7]:

The idea of a systematic review is a nonsense, and the sooner those advocates of it are tried at the International Court of Human Rights at the Hague (or worse still, sent for counselling), the better.

Unfortunately, those who express reservations about applying systematic approaches to the synthesis of research evidence tend not to outline the alternative strategies that they implicitly deem preferable. This is a serious matter because it has been shown that reviews using explicit methods reach conclusions that differ from traditional reviews, with implications that can be matters of life or death [8]. In dermatology, too, the conclusions of reviews in which efforts have been made to reduce biases and the effects of chance can differ from those reached in traditional reviews [9], and Cochrane systematic reviews have been shown to be higher quality than other systematic reviews [10]. In the light of this evidence, I believe that continued acquiescence in reviews that have not attempted to minimize biases and, where possible and appropriate, the effects of chance is not only scientifically unacceptable but also ethically highly questionable [11].

The contributors to this book have tried to control biases and – where they judged it appropriate – they have also reduced the effects of the play of chance by using statistical synthesis to analyze the results of similar but separate studies. As ways of improving the materials and methods used in such research synthesis are developed further, researchers will apply them, taking advantage of the potential offered by electronic media to publish full and transparent accounts of their work, and to respond to new data and suggestions for improving their analyses.

This third edition of Evidence-based Dermatology has extended coverage of topics from the second edition to include several additional and important skin disorders, such as molluscum contagiosum, pityriasis versicolor, onychomycosis, and vulval lichen sclerosus. And in the introductory section of the book, there are new chapters on outcome measures and qualitative research.

In laying bare just how much cannot be known on the basis of reliable evidence, the contributors to this book have also posed a very great challenge to everyone involved in treating skin disease. Can it be that a modest reduction in “doctor-assessed itch” is really the only demonstrable beneficial effect of the widespread use of evening primrose oil for people with eczema [12]? The book exposes the dearth of reliable studies addressing questions and outcomes that matter to patients, and it reveals the extent to which perverse incentives distort the dermatological research agenda. Those suffering from skin disease have every right to expect more from clinicians, researchers, and those who fund research. This book should help to provoke them to do better.

Professor Sir Iain Chalmers
Oxford, UK
2014
References

When I started with the first edition of this book in 2001, evidence-based dermatology was a risky and controversial subject. It was new and threatening to some, and the topic was barely mentioned at large dermatology meetings where the case report was still king. Nowadays, everyone seems to be blurring out the word “evidence” in every other sentence. But what does it really mean in relation to good clinical dermatology care?

I am confident that this book will help you to make that bridge between good external evidence and the care of individual patients. Such integration is not easy in the messy realities of everyday life – the key is to try and to continue to enjoy lifelong learning.

For those of you new to *Evidence-based Dermatology*, you will find it a different sort of book to the usual textbook. Different in that we start the book by providing you with a detailed “toolbox” to help you understand the basic rudiments of practicing evidence-based dermatology. Our clinical chapter contributors then follow a common structure when summarizing the evidence base for different skin diseases. That structure begins with a clinical scenario, followed by clinical questions that lead to an evidence summary, based on the best possible evidence, such as systematic reviews and randomized controlled trials. Each summary includes a description of the possible benefits and drawbacks of individual treatment approaches followed by a view on the clinical implications of that evidence. It is a lot more work to write in this way than to let experts write what they like, but the success of the first two editions of this book suggests that you, the reader, appreciate such an approach. We have taken care, where possible, to separate the evidence found in studies from our opinions about that evidence, and we have tried to help the reader by summarizing the key points at the end of each chapter.

For those of you familiar with the first and second editions of *Evidence-based Dermatology*, welcome back. In addition to providing evidence updates to chapters from previous editions, several new chapters appear in this third edition. In the toolbox section, there is now a chapter explaining all about comparative effectiveness research, another on outcome measures, and another describing qualitative research.

In the clinical section, there are new evidence summaries on molluscum contagiosum, pityriasis versicolor, onychomycosis, dermal fillers and wrinkles, and vulval disorders.

This third edition of *Evidence-based Dermatology* has been a labor of love for me, my associate editors, and chapter contributors, and I wish to thank them all for their efforts. None of us have contributed to this book for the money, but because of our motivation to create a stable record of what evidence-based dermatology is and how it can be applied to clinical practice. We have strived to keep the book as patient based as possible by discussing the evidence around commonly encountered patient scenarios. At the end of the day, it is patients who are at the heart of evidence-based dermatology. Please use this book in your clinic, rather than the library. If the book ends up dirty, torn, and fingered from daily use, we will be delighted.

Hywel Williams
March 2014
Evidence-based Dermatology: Companion Website
Additional resources to accompany this book are available at:

www.evidencebasedseries.com/dermatology

Included on the site:

• Extra tables of trial results
  Web Table 19.1 Retinoid RCTs.
  Web Table 19.2 BP versus placebo/retinoid RCTs.
  Web Table 19.3 Azelaic acid RCTs.
  Web Table 19.4 Oral antibiotics versus placebo RCTs.
  Web Table 19.5 Head to head oral antibiotic RCTs.
  Web Table 19.6 Topical versus vehicle antibiotics.
  Web Table 19.7 Topical versus topical antibiotics.
  Web Table 19.8 Oral versus topical antibiotics.
  Web Table 19.9 Combination antibiotic RCTs.
  Web Table 19.10 Antibiotic/retinoid combination RCTs.
  Web Table 19.11 BP/antibiotic combination RCTs.
  Web Table 19.12 Oral isotretinoin RCTs.
http://www.evidbasedderm.com
  Web Table 24.1 Emollients for the treatment of atopic eczema.
  Web Table 24.2 Topical steroids versus placebo in atopic eczema: results of RCTs.
  Web Table 24.3 Oral antihistamines for atopic eczema.
  Web Table 24.4 RCTs of dust mite reduction for the treatment of atopic eczema.
  Web Table 24.5 Table of elimination diets in the treatment of those with established atopic eczema.
  Web Table 24.6 Randomized controlled trials of probiotics in the treatment of atopic eczema.
  Web Table 24.7 Randomized controlled trials that have evaluated treatments for clinically infected atopic eczema.
  Web Table 24.8 Randomized controlled trials that have evaluated antiseptics for atopic eczema.
  Web Table 24.9 Randomized controlled trials that have evaluated topical steroid/antibiotic combinations for non-infected atopic eczema.
http://www.evidbasedderm.com
  Web Table 74.1 Table of systematic reviews included.
  Web Table 74.2 Skin conditions included.
http://www.evidbasedderm.com

• Glossary of terms
PART I

The concept of evidence-based dermatology

Andrew Herxheimer, editor
CHAPTER 1
The field and its boundaries

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Introduction
Evidence-based medicine (EBM) represents the best way of linking and integrating clinical research with clinical practice. The results of clinical research should inform clinical practice. Ideally, whenever a clinical question has no satisfactory answer it should be addressed by clinical research. Since clinical questions are innumerable and resources are limited, the process needs some control, and priorities should be set using explicit and verifiable criteria. The public and purchasers have to be involved at this stage, and health needs and expectations in any given clinical area should be analyzed and taken into account. In many instances, confirmatory studies are needed and systematic reviews can be used to summarize study results, or to explore results in specific subgroups with a view to further research. The results of clinical research should be applied back to the individual patients in the light of their personal values and preferences. Communicational skills and patient understanding are key issues in this respect. In the real world, forces other than those involved in such an ideal process often distort research priorities and questions. For example, strong industrial and economic interests partly justify the lack of data on rare disorders or on common disorders if they occur mainly in poorer countries. This book may help to identify the more urgent questions that lack a satisfactory answer by summarizing for physicians (and patients) the best evidence available for the management of a large number of skin disorders – excluding sexually transmitted diseases, which are not regularly cared for by dermatologists. It can be thus be a starting point for rethinking the clinical research priorities in patient-oriented dermatology.

What is special about dermatology?
The skin is not a simple inert covering of the body but a sensitive dynamic boundary and is an important organ of social and sexual contact. Body image is deeply rooted within the culture of any given social group and is profoundly affected by the appearance of the skin and its associated structures. The role skin appearance plays in any given society is best understood from an anthropological perspective and using a narrative qualitative approach. This area is rather neglected in dermatological curricula.

Extensive disorders affecting the skin may disrupt its homeostatic functions, ultimately resulting in ”skin failure,” needing intensive care. This is rare, but may happen, for example, with extensive bullous disorders or exfoliative dermatitis. The commonest health consequence of skin disorders is connected with the discomfort of symptoms – such as itching and burning or pain, which often accompany skin lesions and interfere with everyday life and sleep – and with the loss of confidence and disruption of social relations that visible lesions may cause. Feelings of stigmatization and major changes in lifestyle caused by a chronic skin disorder such as psoriasis have been repeatedly documented in population surveys [1,2].

A vast array of clinical entities
Unlike most other organs that usually count around 50–100 diseases, the skin has a complement of 1000–2000 conditions, and over 3000 dermatological categories can be found in the International Classification for Disease version 10 (ICD-10). Part of the reason is that the skin is a large and visible organ. Beside disorders primarily affecting the skin, many major systemic diseases (e.g., of vascular and connective tissue) have cutaneous manifestations. Currently, the widespread use of symptom-based or purely descriptive terms, such as parapsoriasis or pityriasis rosea, reflects our ignorance and limited understanding of the causes and pathogenetic mechanisms of a large number of skin disorders. We still lack consensus on a detailed lexicon of dermatological terms for use in research and everyday clinical practice.

The ICD-10 revision dates back over 20 years to 1990. The new ICD-11 version due in 2014 should improve consensus. This review capitalizes on what three significant initiatives have achieved: (1) the Dermatologischer Diagnosenkatalog published in German-speaking countries by the Deutsche Dermatologische Gesellschaft and in English by the International League of Dermatological Societies; (2) the British Association of Dermatologists’ diagnostic
index, first published in 1994 and updated annually since then; and (3) the Dermatology Lexicon Project, developed with a grant from the US National Institutes of Health, first published in 2005 and now supported by the American Academy of Dermatology [3].

**Extremely common disorders**

Skin diseases are very common in the general population. Prevalence surveys have shown that they may affect 20–30% of the general population at any one time [4]. The most common diseases are also the most trivial ones. They include such conditions as mild eczematous lesions, mild to moderate acne, benign tumors and angiomatous lesions. More severe skin disorders that can cause physical disability or even death are rare or very rare. They include, among others, bullous diseases, such as pemphigus, severe pustular and erythrodermic psoriasis, and such malignant tumors as malignant melanoma and lymphoma. The disease frequency varies according to age, sex, and geographic area. In many cases, skin diseases are trivial health problems compared with more serious medical conditions. However, as already noted, because skin manifestations are visible they may distress people more than do more serious medical problems. The issue is complicated because many skin disorders are not a yes or no phenomenon but occur in a spectrum of severity. The public’s perception of what constitutes a “disease” requiring medical advice may vary according to cultural issues, the social context, resources, and time. Minor changes in health policy may have a large health and financial impact simply because many people may be affected. For example, most of the campaigns conducted to raise public awareness of skin cancer has greatly increased in the number of people having benign skin conditions such as benign melanocytic nevi evaluated and excised [5].

**Large variations in terms of health-care organization**

Countries differ greatly in the way in which their health services deal with skin disorders. These variations are roughly indicated by the density of dermatologists ranging, in Europe, from about 1:20000 in Italy and France to 1:150000 in the UK.

In general, only a minority of people with skin diseases seek medical help, while many opt for self-medication. Pharmacists have a key role in advising the public on the use of over-the-counter products. Primary care physicians seem to treat most of those seeking medical advice. Primary care of dermatological problems is ill defined and overlaps with specialist activity. Everywhere the dermatologist’s workload is concentrated in the outpatient department. Despite the vast number of skin diseases, just a few categories account for about 70% of all dermatological consultations [6].

Generally speaking, dermatology requires a low-technology clinical practice. Clinical expertise depends mainly on the ability to recognize a skin disorder quickly and reliably, which, in turn, depends largely on awareness of a given clinical pattern, based on previous experience and on the practiced eye of a visually literate physician [7]. The process of developing “visual skill” and a “clinical eye” is poorly understood, and these skills are not formally taught.

**Topical treatment may be possible**

A peculiar aspect of dermatology is the possible option for topical treatment. This treatment modality is ideally suited to localized lesions, the main advantage being the restriction of the effect to the site of application and the limitation of systemic side effects. A topical agent is usually described as a vehicle and an active substance, the vehicles being classified as powder, grease, liquid, or combinations such as pastes and creams.

Much traditional topical therapy in dermatology has been developed empirically with so-called magistral formulations. Most of these products seem to rely on physical rather than chemical properties for their effects, and it may be an arbitrary decision to consider one specific ingredient as the “active” one. Physical effects of topical agents may include detergency, hydration, and removal of keratotic scales. The border between pharmacological and cosmetic effects may be blurred, and the term “cosmeceuticals” is sometimes used [8]. In addition to drug treatment, various non-drug treatment modalities exist, including phototherapy or photochemotherapy and minor surgical procedures such as electrodessication and cryotherapy. Large variations in treatment modalities for the same condition mainly reflect local traditions and preferences [9].

**Limitations of clinical research**

As in other disciplines, the last few decades have seen an impressive increase in clinical research in dermatology. However, the upsurge of clinical research has not been paralleled by methodological refinements; for example, the quality of randomized control trials (RCTs) in dermatology seems to fall well below the usually accepted standards [10]. Innovative thinking is needed in dermatology to make clinical research address the important issues and not simply ape the scientific design.

**Disease rarity**

In at least 1000 rare or very rare skin conditions no single randomized trial has been conducted. These conditions are also those carrying a higher burden of physical disability and mortality. Many of them have an annual incidence rate of below one case per 100000 and frequently below one case per million. International collaboration and institutional support are clearly needed, but so far such efforts are very few.

**Patients’ preferences**

One alleged difficulty with mounting randomized clinical trials in dermatology is the visibility of skin lesions and the consideration that, much more than in other areas, patients self-monitor their disease and may have preconceptions and preferences about specific treatment modalities [11]. The decision to treat is usually dictated by subjective issues and personal feelings. There is a need to educate physicians and the public about the value of randomized trials to assess interventions in dermatology. Motivations and expectations are likely to influence clinical outcomes of all treatments, but they matter more in situations where “soft end-points” matter, as in dermatology. Commonly, more than 20% of patients with psoriasis entering randomized clinical trials “improve” on placebo independently of the initial disease extension [12]. Motivations are equally important in pragmatic trials evaluating different packages of management, such as in the comparison of a self-administered topical product for psoriasis with hospital-based therapy like phototherapy. Traditionally, motivation as a characteristic of the patient that is assumed not to change with the nature of the intervention. However, it is more realistic to view motivation in terms of the “fit” between the nature of the treatment and the patient’s wishes and perceptions, especially with complex interventions requiring the patient’s active participation [13]. The public is
inundated with uncontrolled and sometimes misleading or unreal-
istic messages on how to make the body look better. The design and
analysis of clinical trials must properly consider patients’ motiva-
tions and what they are told.

The use of placebo in randomized control trials
Too many placebo-controlled RCTs are conducted in dermatology
even when alternative therapies exist [14,15]. As a consequence,
many similar molecules used for the same clinical indications can
be found in some areas; for example, topical steroids. Many regula-
tory agencies still regard placebo controls as the “gold standard.”
There is a need to establish criteria for the use of placebo in der-
matology. They should be used with the active and informed par-
ticipation of the public and should be considered by ethics
committees and regulatory agencies. “Pragmatic” randomized trials
conducted under conditions close to clinical practice and contrast-
ing alternative therapeutic regimens are urgently needed to guide
clinical decisions.

Long-term outcome of chronic disorders
Several major skin disorders are chronic conditions where no
cure is currently available. Whenever a definite cure is not reason-
ably attainable, it is common to distinguish between short-term, inter-
mmediate (usually measurable within months), and long-term
outcomes. Long-term results are not simply predictable from short-
term outcomes. Many skin disorders wax and wane over time, and
it is hard to define what represents a clinically significant long-term
change in the disease status. This is even more difficult than defin-
ing outcome for other clinical conditions, such as cancer or ischemic
heart disease, where death or major hard clinical end-points (e.g.,
myocardial infarction) are of particular interest. In the long term,
the way the disease is controlled and the treatment side effects are
vitaly important, and simply and cheaply measured outcomes
applicable in all patients are more appropriate. These may include
the number of patients in remission, the number of hospital admis-
sions or outpatient consultations, and major disease flare-ups.
Drop-outs merit special attention since they may strongly reflect
dissatisfaction with treatment.

Self-control design
Study designs that are often used at a preliminary stage in drug
development are within-patient control studies; that is, crossover
and self-controlled studies or simultaneous within-patient control
studies. In dermatology they are also used, albeit improperly, at a
more advanced stage. In a survey of more than 350 published RCTs
of psoriasis, a self-controlled design accounted for one-third of all
the studies examined and was relied on at some stage in drug
development [14]. The main advantage of a within-patient study
over a parallel concurrent study is statistical. A within-patient study
attains the same statistical power with far fewer patients, and at the
same time reduces variability between the populations ‘confronted’
[15]. Within-patient studies may be useful when studying condi-
tions that are uncommon or show high degree of patient-to-patient
variability. On the other hand, within-patient studies impose
restrictions and artificial conditions, which may undermine validity
and generalizability of results and may also raise some ethical
concern. The washout period of a crossover trial as well as the treat-
ment schemes of a self-controlled design, which entails applying
different treatments to various parts of the body, do not seem to be
fully justifiable from an ethical point of view. Clearly, the impracti-
cal treatment modalities in self-controlled studies or the washout
period in crossover studies may be difficult for the patient to accept.
Drop-outs may have more pronounced effects in a within-patient
study than in other study designs because each patient contributes
a large proportion of the total information. The situation is com-
pounded in self-controlled studies, where the dropping out from
the study may be caused by observing a difference in treatment
effect between the parts into which the patient has been “split up.”
In this case, given that drop-outs are related to a difference in treat-
ment effect between interventions, the effect of the intervention is
liable to be underestimated.

The increasing role of industry-sponsored trials
The pharmaceutical industry’s influence on medical research
has increased enormously in the last decades. Dermatology is no
exception. As indicated by the European Dermatoepidemiology
Network psoriasis project, only a quarter of all randomized clinical
trials published on psoriasis from 1977 to 2000 have been con-
ducted without direct pharmaceutical companies’ sponsorship, and
the proportion of sponsored trials has increased dramatically in
more recent years [14,16]. Evidence from systematic reviews show
that published studies funded by pharmaceutical companies are
several times more likely to have results favorable to the company
than studies funded from other sources [17].

Selective presentation of scientific data, statements by opinion
leaders in sponsored symposia and involvement of patient organi-
izations in sponsored campaigns are among the promotional strate-
gies adopted to expand the market once limited clinical evidence
has been collected on a new agent. Heavy marketing competition
has been paralleled by a cycle of increasing collusion between phy-
sicians, academic opinion leaders, patients’ organizations, research-
ers, and industrial interests [18,19].

The recognition of the problems involved with new drug registra-
tion and the lack of long-term data on effectiveness and safety have
prompted the starting of registries and postmarketing surveillance
programs closely linking prescription to the provision of patient
data at first drug prescription and on a regular basis subsequently
during a predefined follow-up period. Psoriasis registries are a suc-
cessful example [20].

The limitations of systematic reviews
The large number of clinical studies in dermatology and the lack of
consensus on the management of many skin disorders point to
systematic reviews as a way to improve the evidence and guide
clinical decisions. However, systematic reviews alone cannot be
expected to overcome the methodological limitations in dermato-
logical research we have pointed to. On the contrary, there are
some indications that systematic reviews, if not properly guided
by important clinical questions, might amplify the unimportant
issues and may result in a rather misleading scale of evidence
to guide clinical decisions. Since most RCTs are performed by
pharmaceutical companies, it is quite plausible that data-driven
systematic reviews will reflect the priorities as perceived by phar-
maceutical companies and not necessarily by the public and clini-
cians. Without a change in regulatory procedures, pharmaceutical
companies will continue to pay little attention to comparative RCTs
and will continue to assess drugs for indications which are worth
the financial investment, neglecting rare but clinically important
disorders [21].

Systematic reviews alone cannot fill the gap, and we urgently
need primary research and high-quality and relevant clinical trials.
In recent years, the problem has been acknowledged, and we have
seen the upsurge of initatives in our discipline to develop independent clinical trial research networks [22–24] and, more recently, the promotion of an international federation of these networks to promote collaboration and to improve the quality and reporting of clinical research at an international level.

Evidence-based medicine: where do we go from here?

An EBM approach should permeate medical education and inform academic medicine. Only if such a change is promoted can EBM become central to clinical practice and not trivialized to “cookbook” medicine. If EBM is successfully integrated into everyday practice it may become easier to conduct primary clinical research based on clinical needs rather than on commercial interests.

In primary research, more imaginative and effective research instruments are needed, and research strategies should be developed that take account of the peculiarities of dermatology compared with other disciplines. Qualitative research should not be neglected. It is the key to understanding what matters to patients, the intercultural variations in body image and how health needs for skin diseases are expressed and perceived in different situations.

References


Other useful resources

http://www.ifdctn.org (The International Federation of Dermatology Clinical Trials Networks).
http://www.ukdctn.org/ (The UK Dermatology Clinical Trials Network).

CHAPTER 2
The rationale for evidence-based dermatology

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What is evidence-based dermatology?
Definitions
Sackett, a clinical epidemiologist and one of the founders of modern evidence-based medicine (EBM), defined the latter as "the conscientious, explicit and judicious use of current best evidence about the care of individual patients" [1].

Sackett’s definition is still one of the best, because it reflects a number of key concepts:

• "Conscientious" implies an active process that requires learning, doing, and reflection.
• "Explicit" implies that we can describe and replicate the process that is used to practice EBM.
• "Judicious" denotes the need for clinical judgment in applying evidence.
• "Current" implies being up to date.
• "Best" implies that we should seek the most reliable evidence source to inform practice.

As Chapter 18 elaborates, perhaps the most important and frequently forgotten phrase in this definition is "the care of individual patients." The place for EBM is not in trying to score intellectual points in the literature or in humiliating colleagues at journal clubs; it is at the bedside or in the outpatient consulting room. As Chapter 75 emphasizes, EBM is a way of thinking and working, with improved health of patients as its central aim.

Nowadays, the term “evidence-based practice” is often used instead of EBM. The term “evidence-based practice” is a good phrase as it emphasizes the doing rather than talking about EBM, and may be defined as integrating one’s clinical expertise with the best external evidence from systematic research [2]. Evidence-based dermatology (EBD) simply implies the application of EBM principles to people with skin problems [3].

What evidence-based dermatology is not
Despite the above clear definitions, the purpose of EBD is often misunderstood in the literature [4]. Some of these misinterpretations are shown in Box 2.1. First, EBD does not tell dermatologists what to do [1]. Even the best external evidence has limitations in informing the care of individual patients. To use R.E. Clerk’s metaphor, external evidence is just one leg of a three-legged stool – the other two being the clinician’s expertise and the patient’s values and preferences. Take one of those legs away, and the stool falls down. Clinical expertise and discussion of what matters post to patients in their choice of treatment options will always be at the heart of applying evidence during a dermatology consultation. EBD is not a cookbook of recipes to be followed slavishly, but an approach to medicine that is patient driven from its outset. Patients are the best sources for generating the important clinical questions, answers to which then need to be applied back to such patients [5].

Just as ordinary patients are at the heart of framing evidence-based questions, so too are ordinary clinical dermatologists at the heart of the practice of EBD [6]. EBD is not something that only an exclusive club of academics with statistical expertise can understand and practice, but rather it is something that all dermatologists can practice with appropriate training. Being able to critically appraise a published clinical trial or systematic review about a new dermatological treatment is a core competency that is as basic to being a dermatologist as the ability to examine, diagnose, or perform a skin biopsy.

Contrary to popular belief, the prime purpose of EBD is not to cut costs. Like any information source, selective use of evidence can be twisted to support different economic arguments. Thus, the relative lack of randomized controlled trial (RCT) evidence for the efficacy of methotrexate in psoriasis should not imply that methotrexate should not be used or purchased for patients with severe disease...
when there is so much other evidence and long-term clinical experience to support its use. But this is not to say that a clinical trial comparing methotrexate against other systemic agents, such as acitretin or fumarates, would not be desirable at some stage [7]. It was heartening, for example, to see a trial of a biologic for psoriasis compared against methotrexate as an active comparator [8], rather than the usual profusion of placebo-controlled studies that leave doctors confused about which treatment is best.

EBM should not be viewed as a restriction on clinical freedom, if clinical freedom is defined as the opportunity to do the best for your patients, as opposed to making the same mistakes with increasing confidence. Searching for relevant information for your patients frequently opens up more rather than fewer treatment options [9]. Shared decision-making through a physician–patient partnership is free to choose or discard the various options in whatever way gives the most desirable outcome.

Guidelines are not the same as EBM, although the two are frequently confused [10]. Guidelines may or may not be evidence based, but guidelines are just that – guidelines. Many dermatology guidelines now incorporate a grading system that describes the quality of evidence used to make recommendations and their strength [11]. Many guideline development groups use methods that combine the strength of available external evidence based on the hierarchy described more fully in Chapter 7 sometimes using specific criteria such as those as recommended by the Grading of Recommendations Assessment, Development and Evaluation working group [12], plus some method for suggesting whether a recommendation is a strong one such as the Strength of Recommendation Taxonomy system suggested by Ebell et al. [13]. Striking a balance between only recommending expensive new treatments based on high-quality placebo-controlled clinical trial evidence conducted by the pharmaceutical industry instead of other long-established treatments simply because they pass the “level A” evidence hurdle is a difficult one for guideline developers to get right [14].

**Problems with other sources of evidence**

**Working things out on the basis of mechanism and logic**

Many physicians base clinical decisions on an understanding of the etiology and pathophysiology of disease and logic [15,16]. This paradigm is problematic, because the accepted hypothesis for the etiology and pathogenesis of disease changes over time, and so the logically deduced treatments change too. For example, in the past 20 years, hypotheses about the etiology of psoriasis have shifted from a disorder of keratinocyte proliferation and homeostasis, to abnormal signaling of cyclic adenosine monophosphate, to aberrant arachidonic acid metabolism, to aberrant vitamin D metabolism, to the current favorite: a T-cell-mediated autoimmune disease. Each of these hypotheses led to logically deduced treatments. The efficacy of many of these treatments has been substantiated by rigorous RCTs, whereas other treatments are used even in the absence of systematically collected observations. We thus have many options for treating patients with severe psoriasis (for example, ultraviolet B, Goeckerman treatment, psoralen–ultraviolet A, methotrexate, ciclosporin, and at least six biologics) and mild to moderate psoriasis (for example, dithranol, topical corticosteroids, calcipotriol, and tazarotene). However, we do not know which is best, in what order they should be used, or in what combinations.

Treatments based on logical deduction from pathophysiology can have unexpected consequences. For example, the observation that antiarrhythmic drugs could prevent abnormal ventricular depolarization after myocardial infarction logically led to their use to prevent sudden death after myocardial infarction. However, RCTs showed increased mortality in patients treated with antiarrhythmic drugs in comparison with placebo [17,18]. So, although patients’ electrocardiograms looked a lot happier and smoother, more people died whilst on treatment. This example highlights the dangers of using surrogate outcome measures, such as electrocardiograms, for more meaningful outcomes, such as disability or death, simply because the surrogate measurements are easily made. The challenge with surrogate outcome measures is to ensure that they measure important things rather than trying to make measurable things important. Another classic example of the dangers in basing our treatments on empirical observations of “scientific” mechanisms is the clinical trial of thalidomide for toxic epidermal necrolysis (TEN) [19]. On the basis of observations that TEN is associated with high levels of tumor necrosis factor-α (TNF-α), a trial of thalidomide (a drug that inhibits the actions of TNF-α) was commenced. The trial was stopped early because 10 out of 12 patients in the thalidomide group died, in comparison with three of 10 on placebo treatment. It was also found that those in the thalidomide group had an unexpected increase in TNF-α levels during treatment.

Some “designer” drugs, such as topical tazarotene, were promoted on the basis of their molecular mechanisms of action and may have appeared attractive at launch, but have been less exciting when tested in practice [5]. It might also be argued that the frequent narration of the superantigen story as a mechanism for antistaphylococcal treatments for atopic eczema is a smokescreen that obscures the real lack or uncertainty of evidence of clear benefit for such agents [20].

Given these lessons, many dermatologists have become less interested in how treatments work and are now daring to ask questions such as: “Does it work?” and – more important than a demonstration of statistically significant efficacy in comparison with placebo – “How well does it work in comparison with existing, more established treatments?”

**Personal experience**

Although personal experience is an invaluable part of becoming a competent physician, the pitfalls of relying too heavily on personal experience have been widely documented [21–23]. These include:

- overemphasis on vivid, anecdotal occurrences and underemphasis on statistically significant strong evidence;
- bias in recognizing, remembering, and recalling evidence that supports preexisting knowledge structures (for example, ideas about disease etiology and pathogenesis) and parallel failure to recognize, remember, and recall evidence that is more valid but does not fit preexisting knowledge or beliefs;
- failure to characterize population data accurately because of ignorance of statistical principles – including sample size, sample selection bias, and regression to the mean;
- inability to detect and distinguish statistical association and causality;
- persistence of beliefs despite overwhelming contrary evidence [23].

Nisbett and Ross [24] provide examples of these pitfalls from controlled clinical research, and simple clinical examples abound. Physicians may remember patients assuming that those who did not return for follow-up improved, and conveniently forget the patients who did not improve. A patient treated with a given medi-
clication may develop a severe life-threatening reaction. On the basis of this single undesirable experience, the physician may avoid using that medication for many future patients, even though on average it may be more efficacious and less toxic than the alternative treatments that the physician chooses. Few physicians keep adequate, easily retrievable records to codify the results of treatments with a particular agent or of a particular disease, and even fewer actually carry out analyses. Few physicians make provisions for tracking those patients who are lost to follow-up. Thus, statements made about a physician’s “clinical experience” may be biased. Finally, for many conditions, a single physician sees far too few patients to draw reasonably firm conclusions about the response to treatments. For example, suppose a physician who treated 20 patients with lichen planus with tretinoin found that 12 (60%) had an excellent response. The confidence interval for this response rate (i.e., the true response rate for this treatment in the larger population from which this physician’s sample was obtained) ranges from 36% to 81%. Thus, the true response rate might well be substantially less (or more) than the physician concludes from personal experience [15,25].

Personal experience alone is also unlikely to pick up smaller treatment differences between active treatments. A new treatment must be substantially better than an existing treatment for a physician to notice. If, in the above example of lichen planus, standard treatment with topical corticosteroids resulted in a response rate of 55%, then the physician would need to treat 20 patients on average (number needed to treat equals the reciprocal of 60% minus 50%) to notice one additional success from tretinoin.

**Expert opinion**

Expert opinion can be valuable, particularly for rare conditions in which the expert has the most experience or when other forms of evidence are not available. However, several studies have demonstrated that expert opinion often lags significantly behind conclusive evidence [21]. Experts suffer from relying on bench research, pathophysiology, and treatments based on logical deduction from pathophysiology, and from the same pitfalls noted for relying on personal experience [25]. Some have even questioned the value of content experts when producing systematic reviews of evidence [26].

Textbooks can be valuable, particularly for rare conditions and for conditions for which the evidence does not change rapidly over time. However, textbooks have several well-documented shortcomings. They tend to reflect the biases and shortcomings of the experts who write them. By virtue of the way in which they are written, produced, and distributed, most are at least 2 years out of date at the time of publication. Also, many textbook chapters are narrative reviews that do not consider the quality of the evidence reported [21,25,27].

**Uncontrolled data**

Empirical, uncontrolled and unsystematically collected data form the basis of much of dermatology practice. This situation is justified by its advocates by two erroneous assumptions. The first is that it is acceptable to use such data because better evidence is not available – an assumption that is often not true due to lack of training in searching for relevant information, as discussed in Chapter 6. There is a surprisingly large body of high-quality evidence that is useful for the care of patients with skin disease, as exemplified by the growing body of evidence-based treatments discussed in this book and by the exponential increase in systematic reviews of skin treatments [28]. The second erroneous assumption is that the majority of dermatologists already base their practice on the best evidence that is already available. The base of knowledge for the practice of medicine is expanding exponentially. It is estimated that, to keep up with the best evidence available, a general physician would have to examine 19 articles a day, 365 days a year [2]. Therefore, keeping up to date by reading the primary literature is now an impossible task for most practicing physicians [29]. The burden for dermatologists is no less daunting [5]. The challenge is to know how to find information efficiently, appraise it critically, and use it well. Knowing the best sources and methods for searching the literature allows a dermatologist to find the most current and most useful information in the most efficient manner, when it is needed. The techniques and skills needed to find, critically appraise, and use the best evidence available for the care of individual patients have been developed over two centuries. These techniques and skills are currently best known as EBM [2,15].

**The process of evidence-based dermatology**

Having discussed the definition and rationale of EBD, how does one actually do it? This process is best considered in five steps (Box 2.2), although in real life they tend to merge and become iterative [5]. These steps are elaborated in subsequent chapters.

**Step 1: asking an answerable structured question**

Developing a structured question that can be answered requires practice. An example of a useless question would be, “Are diets any good in eczema?” A better question, generated from a real clinical encounter, would be, “In children with established moderate to severe atopic dermatitis, how effective is a dairy-free diet in comparison with standard treatment in inducing and maintaining a remission?” Such a question includes four key elements:

- the patient population to which one wishes to generalize;
- the intervention;
- its comparator;
- the outcomes of interest and their timing that might make you change your practice [30].

Unless one uses such a PICO (patients, intervention, comparator and outcome) structure, it would be easy to waste time discussing and searching for data on the role of diets in preventing atopic disease, the effects of dietary supplements such as fish oil, studies that evaluate only short-term clinical signs, and those that deal with a “ragbag” of different types of eczema in adults and children. Bigby and Rzany discuss further examples of framing answerable questions in more detail in Chapter 5.

**Step 2: searching for the best external information**

Publication of biomedical information has now expanded so much that it is hard to contemplate searching for relevant information without some form of electronic bibliographic search, followed by reading the original key papers. Most of us (including the authors)
are not experts at performing complex electronic searches, and need to learn such skills. These skills are dealt with in more detail by Bigby and Corona in Chapter 6. As pointed out earlier, traditional expert reviews are risky, because often they have not been done systematically, and the links between the author’s conclusions and the data are often unclear [31]. Thankfully, many systematic reviews have now been done in dermatology, and those that have been done in atopic dermatitis and acne have been mapped in a publically accessible resource at the Centre of Evidence-Based Dermatology (http://www.nottingham.ac.uk/scs/divisions/evidencebaseddermatology/resources/index.aspx). In the absence of good-quality systematic reviews, then, one often ends up searching for individual randomized controlled trials. Searching for trials on the Medline and Embase databases is hazardous unless one is proficient, because simply searching by the “clinical trials” type can miss up to half of the relevant trials due to coding problems [32]. The world’s most comprehensive database of clinical trials is now the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) which can be found at http://www.thecochranelibrary.com and which contained 680,109 records in September 2012. Thankfully, it is also the easiest to search.

**Step 3: Sifting information for relevance and quality**

The usefulness of an article is a product of its clinical relevance, multiplied by its validity, divided by its accessibility [33]. Information sources need to be near the clinical area if they are to be used for patients. Becoming distracted by irrelevant but interesting citations is also a real hazard when reading search results. Two filters need to be applied if one is to keep practicing EBD: the first is to discard irrelevant information, and the second is to spend more time looking at a few high-quality papers. It is timely at this point to mention the concept of the hierarchy of evidence [34], which is discussed in more detail in Chapter 7. This means that if a randomized controlled trial is found that deals with the question of interest (for example, dietary exclusion in childhood atopic dermatitis), or better still a systematic review dealing with the same topic, one should critically appraise these sources rather than dilute what little time one has by reading lots of case series and case reports.

**Step 4: Applying the evidence back to the patient**

This is usually the most important step, although the least well developed in EBD. Key points to note here are:

- to consider how similar the patients in the studies are to the patient facing you now;
- whether the outcome measures used in those studies are clinically meaningful for both you as a practicing doctor and the patient;
- how large the treatment benefits were;
- what the drawbacks of the intervention were;
- how the evidence fits in with your patient’s past experience and current preferences.

This difficult area is discussed in more detail in Chapter 18.

**Step 5: Recording the information for the future**

Having done so much work pursuing the above “evidence-based prescription” from question to patient, it might be useful to others and yourself to make a record of that information for future use as a critically appraised topic (CAT), although this has a limited lifespan if not updated [2]. Such CATs could become the norm in dermatology journal clubs all over the world, replacing unstructured chats about articles selected for unclear reasons. Some dermatology journals have promoted the use of CATs as an educational tool [35,36].

The key point to remember about the process of EBD is that it **starts and ends with patients**. A problem highlighted during an encounter with a patient is the best generator of an EBM problem [37]. Even if one then searches and critically appraises the best data in the world, the utility of this exercise would be zero if it were not then applied back to that patient or other similar patients. Developing the skills to undertake evidence-based prescription requires practice.

Dermatologists will participate in the practice of EBD to different degrees depending on their enthusiasm, skills, time pressures, and interest [34]. Some will be “doers,” implying that they undertake at least steps 1–4 highlighted in Box 2.2. Others will be more inclined to adopt a “using mode,” relying on searching for secondary evidence sources such as evidence-based summaries – for example, systematic reviews that others have constructed – thereby skipping step 3, at least to some degree. Finally, some will incorporate evidence into their practice in a “replicating mode,” following decisions of respected leaders (i.e., skipping steps 2 and 3). These categories bear some similarity to those of deduction, induction, and seduction that Sackett used to describe the methods that physicians employ to make decisions about therapy [21]. Such categories are not mutually exclusive, since even the most enthusiastic EBM practitioners in “doing” mode will flit to “user” and “replicating” mode according to whether they are dealing with a common or rare clinical problem.

**Conclusions**

Few dermatologists would argue that their overarching professional role is to provide their patients with the best health care. To do so, a dermatologist must be able to assess the patient’s physical condition, know the best and most current information about diagnosis, prevention, therapy, prognosis, and potential harm, and then apply that knowledge of universals to the individual patients [38,39]. Medicine is advancing very rapidly, creating major changes in the way we treat our patients. It is imperative that we, as health-care professionals, keep up with such changes. We need to be up to date with such new external evidence. We frequently fail to do this if we rely on passive means or an occasional flick through the main journals, and our knowledge gradually deteriorates with time. Attempts to overcome this deficiency by attending clinical education programs fail to improve our performance, whereas the practice of EBM has been shown to keep its practitioners up to date. EBM is a way of thinking that is intended to help accomplish these objectives. If we stick to thinking about patients’ welfare when contemplating EBM, we are less likely to get things wrong [5,15].

**References**

CHAPTER 3

The role of patient and public involvement in evidence-based dermatology

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Introduction

Various terms are used to describe patients, carers, and members of the public involved in health care, particularly with regard to research. The term patient and public involvement (PPI) is now widely used, and we use it here. PPI means health professionals, patients, carers, and the public working together to improve the health of the communities they represent.

Compelling evidence shows that patients who take an active part in managing their own health care have better outcomes than those who are passive recipients. Increasingly, patients are active, informed people who want to know more about their condition and have more control over their own care. Education can help patients share responsibility for their own care. They also need access to trustworthy information to make important choices about their treatment. Easy access to relevant, evidence-based information will help them to choose the care they need and want.

Those involved in PPI in evidence-based dermatology are bringing their experience and perspective to the table. Their participation in activities such as the prioritization of research projects, through to proof reading of articles for public consumption will help to ensure that any work done is of interest and of use to all end users.

The many benefits and roles of patient and public involvement in health care

PPI can bring many benefits to health care, not least having better informed patients and carers as outlined above. Other benefits include improving the quality of health care and making better use of existing resources; this includes improving access to services and making monitoring and evaluation of services more effective.

The roles of PPI in health care are many and varied and are outlined below (several are discussed in more detail later):

• playing an active part in self care as far as possible;
• working with professionals to improve one's own care and that of other family members and those in the general community;
• to share personal experiences of living with a disease and to inform and educate other patients and professionals;
• assisting with the development and governance of health institutions and organizations;
• contributing to research policy and practice by helping to decide research priorities and funding and helping to improve the design of research;
• to support the recruitment of patients into research studies;
• helping to disseminate important research findings.

Such PPI can benefit all those involved in the health-care process in different ways. For example, patients will benefit from seeing their views considered and used to improve the quality of care for others, while health service managers will benefit from improved standards of more patient-friendly services. Health service researchers can benefit greatly, as working with patients, carers, and the public from the very start of their projects can much improve the quality of their research design and outputs.

The skin shows: it matters psychologically and socially

The roles of PPI in health care are generic across all clinical specialties. Skin diseases differ from other illnesses in being much more visible, whether through constant itching, visible patches on the skin, or flaking of the skin. In this crucial area, patients and carers can help professionals understand and learn what matters to people with various skin conditions; those unaffected may find these aspects difficult to understand and recognize appropriately.

Many people with skin disease experience significant psychological and social distress such as depression and fear of stigma [1]. A recent German study of patients with occupational hand eczema found a high prevalence of anxiety and depression among them [2]. Although recognized, this has rarely been addressed when considering treatment options, and a survey [3], conducted for the European Commission on public opinions, found that the patients they surveyed felt “doctors do not take account of the ‘psychological’ impact of treatments and their effects in day-to-day life.”

The extent of disease may not be the most important factor in considering a patient’s suffering. Self-esteem, self-image, the site of the lesions, how far the patient feels disabled, and the support networks available should all be considered. For example, an office worker may tolerate extensive psoriasis on covered areas of the body, but as soon as the psoriasis starts to affect “high expression” and visible areas, such as the face and hands, quality of life can drop drastically. More could be done to ensure that practitioners assess