PART 1

Introduction

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CHAPTER 1

Evidence-based medicine: its contributions in the way we search, appraise and apply scientific information to patient care

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Terms of reference

Reflections and elaborations about how evidence-based medicine (EBM) has been, and will increasingly be, able to influence clinical practice and the teaching of medicine abound, and it is very hard to try to say something original that is not already available [1]. This book, as Livia Candelise states in her introduction, is an attempt to summarize and compile examples of the contributions that a systematic approach to the search, identification and critical appraisal of scientific information can bring as an added value to the appropriate care of a patient with neurological problems/diseases. It is, therefore, very likely that this book will be read and used mostly by clinicians that – with different level of appreciation of the EBM approach – will seek information useful for their daily practice. The benefits, however, of putting together an account of what we know and do not know about the best ways to diagnose and treat neurological diseases are that one can see how far we are from being able to properly address patients problems and, more importantly, whether the ways in which the many uncertainties that still surround the care of patients with neurological disorders are being addressed in a proper way.

In short, the purposes of this chapter are:

(a) To revisit what EBM is and is not in the light of the strong positive, as well as negative, feelings that its appearance has brought about.

(b) To discuss the fact that the term 'evidence' itself is not so simple as it is sometimes portrayed, and try to see the extent to which this is at the heart of the controversial feelings about EBM.

(c) To summarize what the steps recommended by an 'EBM approach' are and exemplify the different ways in which users can take advantage of it.

In the concluding part of this chapter an attempt to reflect of who are the 'enemies' of EBM and how EBM itself has raised our awareness of the challenges that are ahead of us in terms of clinical practice, clinical research and health care policies will be attempted.

The EBM movement has provoked strong restatements from within the clinical world about the essence of the patient–clinician relationship and the balance between scientific approach and personal experience.

Some commentators saw the movement partly as an attempt by clinicians to keep control of decision making in the face of governments set on increasing intervention in the previously relative autonomous professions. Health policies worldwide, however, reveal the growth of mechanisms aimed at establishing parameters for acceptable clinical practice and a range of apparatus for monitoring and enforcing these parameters. On another track, some critics have questioned the movement's sometimes exclusive focus on one particular research design (i.e. the randomized controlled trial, RCT) as unnecessarily narrow and reinforcing the cultural and political values of particular research groups. Also embedded in this phenomenon is a staging of the confrontation between science and progress on one hand and myth and reaction on the other.

Whether the current debate addresses the real issues or is rather confounded by extraneous factors is the main 'file rouge' that the reader will recognize within this chapter. Our personal conviction is that in the current debate there is a mixture of epistemological confusion about the proper definition of 'proof' and 'evidence', resistances to cultural and professional changes from within the medical profession, misplaced criticisms from EBM scepticists and, to some extent, over-enthusiasm and reductionism from those that fail to recognize EBM's practical and methodological limitations.

What is EBM and what it is not?

The term EBM, as we use it nowadays, was introduced in 1992 by the same group of people that, years before, started

the discipline called 'Clinical Epidemiology' (CE) [2]. CE stemmed essentially from the idea of adapting and expanding epidemiological methods to medical and health care decision making; CE was in fact defined as 'the discipline dealing with the study of the occurrence of medical decisions in relation to its determinants' [3].

CE has been very successful in illustrating new ways of teaching medicine and training health professionals and positioned itself around the notion of 'critical appraisal skills' as yet another essential ability that – in addition to the interpersonal, diagnostic and prognostic ones – a good doctor should master. An important CE's by-product was the documentation that much of the available evidence on diagnosis, prognosis and treatment of diseases was of poor methodological quality and quite often of dubious transferability to everyday clinical practice.

This led to a strong call for improving the scientific basis of clinical practice that was seen as too often dominated by practices of unproven effectiveness. This was the background for the 1992 *Journal of American Medical Association* (*JAMA*) article that first used the term 'Evidence-Based Medicine' [2].

In essence, proponents of EBM said that 'all medical actions of diagnosis, prognosis and therapy should rely on solid quantitative evidence based on the best of clinical epidemiological research'. Also they stated that 'we should be cautious about actions that are only based on experience or extrapolation from basic science'. Indeed this is not a new concept as recent research into the history of medicine has documented [4]. Vandenbroucke recently discussed the well-rooted historical precedents for the CE and EBM movements in the history of methodological research in medicine quoting, among others, Alexandre Louis who led in 1830 in France an initiative called 'Medicine d'Observation' [4]. Finding, not surprisingly, strong resistance from his fellows' environment, Louis stated that 'physicians should not rely on speculation and theory about causes of disease, nor on single experiences, but they should make large series of observations and derive numerical summaries from which real truth about the actual treatment of patients will emerge'.

Parallels and differences between now and then are worth noting here. In the early 1800s proponents of 'Medicine d'Observation' were reacting against a kind of medicine that derived its theories from many things that we would consider 'nonsense' by today scientific standards. Today EBM acts in the context of a very different environment where modern medical basic science has a solid experimental background. We now know that 'Medicine d'Observation' shortly after its appearance failed. A strong reaction from the medical profession together with the absence of contextual conditions account for this unfavourable outcome. Will EBM experience a different outcome as it leaves in a more scientifically oriented medical world? In many ways a similarly strong negative reaction has emerged today against EBM. No doubts that one of the reasons of such a negative reaction against EBM has been the fact that it was labelled as a 'shift in medical paradigm' [2,4]. Such a definition would imply that EBM means scientific medicine and that all medicine practised before it was unscientific. This is not only simplistic but, to any closer scrutiny, profoundly wrong. The difference between the pre- and post-EBM era is not that before it people did not use the evidence. Rather, the real failure was the lack of a framework and set of rules to use the evidence in a systematic and explicit fashion.

Seen in this way the current fight around EBM and its nature could be advanced by moving the discussion from principles into a more pragmatic perspective where the attention is centred on a 'better use of evidence in medicine'. This would have the distinct advantage of indicating that it is the way and the rules according to which we use and interpret evidence that needs to be changed.

In contrast with the traditional wisdom of clinical practice, stressing the need for a 'better use of evidence in medicine' would indicate that that intuition and unsystematic clinical experience as well as pathophysiological rationale are insufficient ground for clinical decision making. On the contrary, modern practice of medicine finds its way on formal rules aimed at interpreting the results of clinical research effectively; these rules must complement medical training and common sense of clinicians whose uncontrolled dominance is no longer ethically and scientifically acceptable.

Struggling for a better use of evidence in medicine has also other important advantages. It challenges the paternalistic and authoritarian nature of much medical practice and helps understanding that – even when based on scientific methods – there is a selective and structural imbalance in the nature of the evidence that is available. This is skewed and biased towards therapeutic versus preventative interventions and towards simple pharmacological versus complex behavioural/social care. Acquiring critical appraisal skills – one of the most important tenets of the EBM movement – is the necessary (though not sufficient) best immunization against ignoring that there is a structural imbalance in the research agenda. An imbalance that should be overcome in order to make fully available the sort of evidence that is needed to provide effective and comprehensive health care to all patients [5].

The many faces of evidence (proof, causality and uncertainty) and their implications for clinical decision

Having set this background it should be clear that some definition of 'proof' is also needed to distinguish between scientific medicine and charlatanism. Pathophysiology – that is the reference to a mechanism to support the introduction of a new drug – is a criterion that has failed several times in the past: for example, the widespread practice of phlebotomy in 18th century medicine had some 'pathophysiological'

basis, but no effectiveness at all. To define what we accept as a proof is clearly a problem of transparency of medical practice.

Our thesis is that, unfortunately, the 'evidence/lack of evidence balance' is not a black/white one for several reasons:
(a) For many clinical practices, even if we have well-conducted RCTs, all we can achieve is a 'weight-of-evidence' overall evaluation, because we face conflicting results from RCTs.
(b) In other instances RCTs are not available simply because they have not been conducted, and we only have access to observational investigations.
(c) The quality of the RCT is poor, so that a meta-analysis is not easily interpretable.
(d) RCT cannot be easily conducted for practical or ethical reasons.
Of course, we also have clear instances in which systematic reviews and meta-analyses contribute in an unequivocal way to the adoption or banning of a treatment.

In addition, we need to integrate the scientific evidence with the patient's preferences, with economic constraints, with the health care organization, with ethical obligations … This kind of integration is the object of clinical guidelines, in which ideally evidence is a necessary but insufficient component.

The model we can use comes from a different field, causality, and has been suggested by the philosopher John Mackie. Mackie claims that causality cannot be reduced to single necessary and sufficient causes, but rather should be described in terms of elements that he calls INUS (Insufficient Non-redundant component of an Unnecessary Sufficient complex). In his example, why did the house burn? The causal complex is formed by the association of fire in the fireplace, a strong wind, a defect in the alarm system and the fact that the house is wooden. If we analyse each component, none of them is a single sufficient cause, but only their conjunction gives origin to an overall sufficient complex. However, the complex is not necessary, because the house could burn in many different ways (e.g. because I put it deliberately on fire). According to Mackie, although none of the elements are sufficient, at least one is necessary (non-redundant), that is in its absence the complex would be ineffective (in the example: eliminating the fire in the fireplace would make the whole complex ineffective). Let us try to apply this same reasoning to medical decision. The physician has to integrate several elements into a decisional complex. Consider, for example, the prescription of interferon in patients with a diagnosis of relapsing–remitting multiple sclerosis (MS). According to the systematic review in the Cochrane Library, there are only seven trials including approximately 1200 patients with reliable information only on short-term follow-up (i.e. up to 2 years; example in the Appendix). The evidence overall suggests some advantage associated with interferon but results are hampered by the high proportion of drop-outs and the type of outcome measures chosen. Should the neurologist decide to prescribe interferon? Instead of being an exception, the example is the rule. In other words, we often face 'grey' areas and the practicing neurologist might decide that, based on the Cochrane Review, the weight of evidence is quite strong or can reason exactly in the opposite way considering the relatively short follow-up, the questionable methodological quality of the studies and the important side effects. In other words, the weight of the empirical evidence can determine the ultimate therapeutic choice depending on the array of factors that, in the face of the same empirical evidence, a practitioner will consider.

Having said that it is important to perceive correctly one important feature of Mackie's definition of INUS, that is that at least one component is necessary (non-redundant). This component is evidence and without evidence there will never be good and justifiable clinical decision.

If we accept that evidence is a necessary component, still how to weigh the evidence depends on the definition of effectiveness one adopts. Effectiveness, like disease, is a 'fuzzy' concept. Concepts are almost never sharp, that is defined on the basis of a single property, but they tend to be fuzzy. In particular, the concept of effectiveness cannot be defined on the basis of a singular property (reducing mortality, disability, etc.), but of several properties that are partially overlapping in the actual instances: for some people effectiveness is mainly subjective, for others it is mainly objective, and no single definition is the right one. In summary, we have to face that effectiveness is a 'fuzzy' concept. This means that we cannot use the results of clinical trials (or of their synthesis in the form of systematic reviews or meta-analyses) as the only source of information and decisions about care: the work of the physician consists just in integrating different kinds of knowledge, although evidence is a necessary component.

Different modes of developing and using EBM skills and their ability to bring about evidence-based practice

The rapid spread of EBM has arisen from two main awareness:

1 The need for valid information about diagnosis, prognosis, therapy and prevention.

2 The inadequacy of traditional sources for this information because they are out of date (textbooks), frequently wrong (experts), ineffective (didactic continuing medical education), or too overwhelming in their volume and too variable in their validity for practical clinical use (medical journals).

Until recently, coping with these problems was impossible for full-time clinicians. However, developments in the 'technology of EBM' have permitted a change in this situation:

- The development of strategies for efficiently tracking down and appraising evidence (for its validity and relevance).
- The creation of systematic reviews of the effects of health care (see the Cochrane Collaboration).

• The creation of evidence-based journals of secondary publication and of evidence-based summary services such as clinical evidence.
• The creation of information systems for bringing the foregoing to us in a timely fashion.

The essence of the EBM approach to patients care comprises four steps [6]:

• *Step 1*: Transforming the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc.) into an answerable question.
• *Step 2*: Locating the best evidence with which to answer that question.
• *Step 3*: Critically appraising the evidence for its validity (closeness to the truth), impact (size of the effect) and applicability (usefulness in our clinical practice).
• *Step 4*: Integrating the critical appraisal with our clinical expertise and with the patients characteristics, values and circumstances.

Depending on her/his different needs each health professional will use all or part of the above steps in different modes.

First is the 'doer' mode, in which all the four steps above are carried out.

Second is the 'user' mode, where searches are restricted to evidence resources that have already undergone critical appraisal by others such as evidence summaries.

Third is the 'replicator' mode, where the decisions of respected opinion leaders are followed.

All three of these modes involve the integration of evidence (from whatever source) with patient's unique characteristics, values and circumstances, but they vary in the execution of the other steps.

An intuitively appealing way to achieve such evidence-based practice is to generalize EBM teaching and training so that all clinicians become able to independently find, appraise and apply the best evidence. This strategy, however, has limitations as attaining all the necessary skills requires favourable personal attitude(s) and predisposition(s), intensive study and frequent, time-consuming, application. It is neither realistic nor feasible to expect and pretend that all practitioners will get to this advanced level of EBM skills. It has been repeatedly shown that practitioners welcome the availability of evidence-based summaries generated by others and evidence-based practice guidelines or protocols as long as they see them as helping tools and not compulsory obligations for their practice [6].

Thus, producing more comprehensive and more easily accessible pre-appraised resources is a second strategy for ensuring evidence-based care. The availability of evidence-based resources and recommendations will, however, still be insufficient to produce consistent evidence-based care. Habit, local practice patterns and product marketing may often be stronger determinants of practice. Studies have shown that traditional continuing education has little effect on combating these forces and shaping doctors' behaviour [7]. On the other hand, approaches that do change targeted clinical behaviours include one-to-one conversations with an expert, computerized alerts and reminders, preceptorships, advice from opinion leaders, and targeted audit and feedback. Other effective strategies include restricted drug formularies, financial incentives and institutional guidelines. Application of these strategies, which do not demand even a rudimentary ability to use the original medical literature and instead focus on behaviour change, thus constitute the pivotal strategy for achieving evidence-based care [7]. Therefore, educators, managers and policy makers should be aware that the widespread availability of comprehensive pre-appraised evidence-based summaries and the implementation of strategies known to change clinicians' behaviour will both be necessary to ensure high levels of evidence-based health care.

Internal and external enemies of EBM

But the difficulties that hamper a prudent and systematic use of evidence come not only from its imperfect and limited nature and from the medical establishment's resistance to change. There are also 'internal enemies' (which we will call the 'enthusiasts' here) who seem to have limited understanding of EBM's structural limitations and are dominated by unduly (optimistic) expectations of its sufficiency to guide medical practice. We mention below some of the relevant problems that should be kept in mind before blaming EBM as the sole culprit of its limitations.

First is the bias in the research agenda and the lack of mechanisms to prioritize it with respect to health needs. The increasing commercial influences in health care have produced a structural distortion in the setting of the research agenda and we see today a systematic bias in research priorities with a lot of (often redundant) data on pharmacological treatments and a dearth of information on potentially very relevant non-pharmacological interventions. Only recently this is starting to attract attention but this is still far from what would be needed to bring about the necessary changes [8]. Health services, on the other hand, have not traditionally been interested in investing in research and with some noticeable recent exceptions (see the UK R&D programme as well as part of the NIH research programme in the US) this is still the case. Consumers' input into research agenda is far from systematic and often the role of patients' charities ends up with lobbying for a particular disease or health problem rather than for the advocacy of an open and transparent prioritization [5].

The lack of independence of medical information and the 'pollution' caused by the commercial interference in it is another key factor. The imbalance between commercial and independent information is so striking that it may be naive to imagine that EBM alone can maintain its credibility without structural and cultural investments. When relevant information is not properly disseminated and implemented it is

as if it would not exist. The recent example of the pharmacological treatment of hypertension is a case in point here: very expensive drugs have been for many years marketed without good evidence of their superiority to the equally effective and much less expensive old diuretics and only thanks to a publicly funded large scale trial [9] we now know that millions of dollars have been probably wasted without substantial benefits for patients. But lack of independence and monopoly of scientific information manifests itself also in the increasing medicalization of common problems and in the making of 'new diseases' as a way to make the health care market bigger and more profitable [10]. In this scenario as far as people identify as 'evidence-based' procedures and interventions for which studies exist and as 'non-evidence-based' areas where studies could exists but have not been carried out because there is no commercial interest in running them, EBM is at high risk of being used a fashionable yet misleading key word [11].

The 'paternalism' inherent in the idea that experts 'know it better' and that they are thus entitled to make decisions on behalf of their patients is a third important enemy. Paternalism has many components all of which are dangerous and should be recognized. One component comes from the idea that the increasing complexity of modern medicine requires increasing specialization. More and more medicine is fragmented into sub-specialities where people have a very deep knowledge into an increasingly narrow spectrum of problems. This technical knowledge leads to an overemphasis of the yield of a particular intervention where benefits are much too overrated with respect to risks [12]. Linked to this is the inherent conflict of interest that unavoidably links the social and professional prestige of those that are experts in a given field to the success of the intervention/technology of which they are champions. Like for the bias of the research agenda there are signs of increasing awareness that conflicts of interest are a threat to an equitable and effective practice of medicine but still much less than it should be [13]. And, again, a narrow technical view of EBM could be insufficient and perhaps even misleading in this respect.

Lack of awareness of the above-mentioned problems is – we believe – a great danger to EBM. Assuming that all relevant 'information needs' can be derived from published studies, that all practice skills can be derived from being updated with the medical literature, that methodological rigor is the only dimension that matters – even divorced from clinical and epidemiological relevance – and that health policies should be dictated (rather than more humbly 'informed') by evidence of effectiveness alone, are all internal threats that should be seriously considered and challenged.

What have we learned from EBM?

Having discussed EBM's epistemological, structural and practical limitations it is also fair to reflect on what it has helped us to understand as of the major problems and limitations of today's clinical practice and health policies. Given the space constraints of this chapter we will summarize in short statements what we believe are issues that should inform an health care policy agenda that takes seriously some of the challenges that are ahead of us, if we care for effective and equitable systems of delivering health care. The list is tentative and incomplete and would hopefully be instrumental to stimulate a discussion on EBM's benefit/harm balance thus far.

Clinical practice

- There are not organized mechanisms and efforts to transfer and disseminate information on interventions that work from research to clinical practice; these efforts should become an integral part of the functioning of a good health care system.
- Medical practice is fraught with ineffective interventions and long delays before effective care enters clinical practice. Special attention should be given to in continuing medical education activities.
- Doctors and health professionals are not, by themselves alone, able to critically appraise the results of clinical research; consequently they can be (easily) misguided by unintentionally or intentionally wrong messages. Teaching critical appraisal skills should be an essential part of medical education.
- Clinical practice should (and can) be informed by results of systematic reviews of the best available information; knowledge of a given field based on just the few better known studies is dangerous because it ignores 'publication bias' and false negative results, etc. Medical education should stress the idea that knowledge is a 'cumulative' rather then a 'discrete' process and appropriate information tools should be made available to all health professionals [14].

Clinical research

- The quality of medical research is often poor and urgent improvements are needed. Poor quality has to do both with failure to apply appropriate designs and methodologies as well as paying attention to the search for relevant outcomes and for interventions that are generalizable outside the research settings.
- There are not explicit and transparent mechanisms for prioritizing research. Health care systems have almost exclusively delegated the responsibility to pharmaceutical companies and the commercial sector in general. Public and independent support to research is an urgent need [5].
- Conflicts of interest and lack of independence of investigators represent an increasing threat to the credibility of research [15,16].
- Patients' participation can be instrumental both in improving relevance and applicability of clinical research and in facilitating shared decision making. There is some evidence that, if properly involved, at the level of planning and identifying priorities, patients and consumers can provide valuable

inputs for research [17]. However, this is a process that requires a governance effort in order to avoid that increasing fragmentation is included in the prioritization process [18].

Health care policies

- Evidence should 'inform' but may be often inadequate to 'guide' decision making at the policy level. The sort of evidence that is usually produced by traditional clinical research is too narrow and lacks important elements that are otherwise crucial in policy making [19].
- Resources are often wasted by not acting against the use of ineffective interventions or by implementing effective interventions with ineffective strategies. A better link between efforts to improve quality at the micro level is needed.
- Health care system should assume more responsibility in knowledge production and should themselves promote research into areas that are likely not to attract resources due to limited commercial return [5].

Conclusions

There is no doubt that EBM does not, and cannot, answer all the epistemological and practical questions surrounding the practice of medicine. On the contrary, it is important that expectations from EBM are appropriate in order to prevent conceptual and practical mistakes. EBM provides methodological tools and a cultural framework. Methodologically it is useful to understand how we can produce valid and relevant information about the effectiveness of medical care. Culturally, its anti-authoritarian spirit is important to increase the participation of different stakeholders and to increase the opportunity for a multidisciplinary approach to health care problems.

It is clear that, thus far, the potential of EBM has not been fully exploited and that too narrow views of it have created avoidable confrontations with those that may be concerned that an 'EBM-dominated view' can do more harm than good. As efforts by methodologists have chiefly focused on how to design, conduct and interpret studies aimed at assessing efficacy/effectiveness of drugs, EBM is today mostly 'evidence-based therapy' with robust tools (i.e. RCTs) especially for assessing the worth of relatively simple interventions. The fact that we currently have limited ability to reliably assess complex interventions, preventative care in general as well as diagnosis or prognosis, should be seen not only as the results of the greater intrinsic complexity of these areas, but also as the consequence of the lower intellectual investments. A reflection, in turn, of the more limited commercial interests is at stake here.

It is our view that – despite the many limitations we have highlighted in this chapter – EBM has, at least in some areas of medicine, resulted in better clinical research and greater awareness of health professionals, health administrators and policy makers. A lot remains to be done in order to create a better understanding of the nature of proof, evidence and uncertainty; a more balanced research agenda; more coherent mechanisms to improve quality of care; more substantial cultural efforts to empower patients and consumers. But we should be ready to recognize that most of this goes beyond what EBM can do alone and depends, more broadly, on health policy and politics with capital 'P'.

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Appendix

The Appendix shows summaries from the Cochrane Library [14]. We have chosen four examples that can be considered typical of a few categories that have been mentioned above. In the first example, the evidence is rather sparse (only 453 patients) and results are conflicting, with a non-statistically significant trial showing protection and one significant trial showing an excess of deaths in the corticosteroid arm. The second example is more complex, since the information available was not enough to evaluate the efficacy of treatment. If all missing data (drop-outs) are attributed to disease progression (worst-case scenario) then treatment is associated with a slight adverse effect. Lack of data of good quality is the main problem in this example.

The third example shows how useful a systematic review and meta-analysis can be. Individual trials were equivocal, but the overall consideration of their results showed and that anticoagulants do more harm than benefit in acute ischaemic stroke. On the opposite, the fourth example (Warfarin in atrial fibrillation, AF) is paradigmatic of a situation in which a systematic review and meta-analysis clearly reveals – more than single trials – that the benefits are considerable and the treatment should be transferred into practice.

1 *Corticosteroids in ischaemic stroke*: Seven trials involving 453 people were included. Details of trial quality that may relate to bias were not available from most trials. No difference was shown in the odds of death within 1 year (odds ratio (OR) 1.08, 95% confidence interval (CI) 0.68–1.72). Treatment did not appear to improve functional outcome in survivors. Six trials reported neurological impairment but pooling the data was impossible because no common scale or time interval was used. The results were inconsistent among individual trials. The only adverse effects reported were small numbers of gastrointestinal bleeds, infections and deterioration of hyperglycaemia across both groups.

2 *Interferon and MS*: Although 1215 patients from seven trials were included in this review, only 919 (76%) contributed to the results concerning exacerbations and progression of the disease at 2 years. Specifically, interferon significantly reduced the occurrence of exacerbations (relative risk (RR) = 0.80, 95% CI 0.73, 0.88, $P < 0.001$) and progression of the disease (RR = 0.69, 95% CI 0.55, 0.87, $P = 0.002$) 2 years after randomization. However, the correct assignment of drop-outs was essential to the demonstration of efficacy, most conspicuously concerning the effect of the drug on disease progression. If interferon-treated patients who dropped out were deemed to have progressed (worst-case scenario) the significance of these effects was lost (RR = 1.31, CI 0.60, 2.89, $P = 0.5$). The evolution in magnetic resonance imaging (MRI) technology in the decade in which these trials were performed and different reporting of data among trials made it impossible to perform a quantitative analysis of the MRI results. Both clinical and laboratory side effects reported in the trials were more frequent in treated patients than in controls. No information was available regarding side effects and adverse events after 2 years of follow-up. The impact of interferon treatment (and its side effects) on the quality of life of patients was not reported in any trial included in this review. Reviewers' conclusions: The efficacy of interferon on exacerbations and disease progression in patients with relapsing–remitting MS was modest after 1 and 2 years of treatment. It was not possible to conduct a quantitative analysis beyond 2 years. Longer follow-up and more uniform reporting of clinical and MRI outcomes among these trials might have allowed for a more convincing conclusion.

3 *Anticoagulants in ischaemic stroke*: Twenty-one trials involving 23,427 patients were included. The quality of the trials varied considerably. The anticoagulants tested were standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants and thrombin inhibitors. Based on eight trials (22,450 patients) there was no evidence that anticoagulant therapy reduced the odds of death from all causes (OR 1.05, 95% CI 0.98–1.12). Similarly, based on five trials (21,846 patients), there was no evidence that anticoagulants reduced the odds of being dead or dependent at the end of follow-up (OR 0.99, 95% CI 0.94–1.05). Although anticoagulant therapy was associated with about 9 fewer recurrent ischaemic strokes per 1000 patients treated, it was also associated with a similar sized 9 per 1000 increase in symptomatic intracranial haemorrhages. Similarly, anticoagulants avoided about 4 pulmonary emboli per 1000, but this benefit was offset by an extra 9 major extracranial haemorrhages per 1000.

Sensitivity analyses did not identify a particular type of anticoagulant regimen or patient characteristic associated with net benefit.

4 *Warfarin in patients with AF*: Fourteen articles were included in this review. Warfarin was more efficacious than placebo for primary stroke prevention (aggregate OR of stroke = 0.30 (95% CI 0.19, 0.48)), with moderate evidence of more major bleeding (OR = 1.90 (95% CI 0.89, 4.04)). Aspirin was inconclusively more efficacious than placebo for stroke prevention (OR = 0.68 (95% CI 0.29, 1.57)), with inconclusive evidence regarding more major bleeds (OR = 0.81 (95% CI 0.37, 1.78)). For primary prevention, assuming a baseline risk of 45 strokes per 1000 patient-years, warfarin could prevent 30 strokes at the expense of only six additional major bleeds. Aspirin could prevent 17 strokes, without increasing major haemorrhage. In direct comparison, there was moderate evidence for fewer strokes among patients on warfarin than on aspirin (aggregate OR = 0.64 (95% CI 0.43, 0.96)), with only suggestive evidence for more major haemorrhage (OR = 1.58 (95% CI 0.76, 3.27)). However, in younger patients, with a mean age of 65 years, the absolute reduction in stroke rate with warfarin compared to aspirin was low (5.5 per 1000 person-years) compared to an older group (15 per 1000 person-years). Low-dose warfarin or

low-dose warfarin with aspirin was less efficacious for stroke prevention than adjusted-dose warfarin. Reviewers' conclusions: The evidence strongly supports warfarin in AF for patients at average or greater risk of stroke, although clearly there is a risk of haemorrhage. Although not definitively supported by the evidence, aspirin may prove to be useful for stroke prevention in subgroups with a low risk of stroke, with less risk of haemorrhage than with warfarin. Further studies are needed of low-molecular-weight heparin and aspirin in lower-risk patients.