

The 2011 Oxford CEBM Levels of Evidence: Introductory Document

This must be read before using the Levels: no evidence ranking system or decision tool can be used without a healthy dose of judgment and thought.

What the 2011 OCEBM Levels of Evidence IS

1. A hierarchy of the *likely* best evidence.
2. Designed so that it can be used as a *short-cut for busy clinicians, researchers, or patients to find the likely best evidence*. To illustrate you may find the following analogy useful (Figure 1). Imagine making a decision about treatment benefits in 'real time' (a few minutes, or at most a few hours). There are five boxes each containing a different type of evidence: which box would you open first? For treatment benefits and harms, systematic reviews of randomized trials have been shown to provide the most reliable answers (1), suggesting we begin by searching for systematic reviews of randomized trials. If we didn't find any evidence in the systematic review box, you would go onto search for individual randomized trials, and so on across the OCEBM Levels of Evidence.

PICK A BOX!

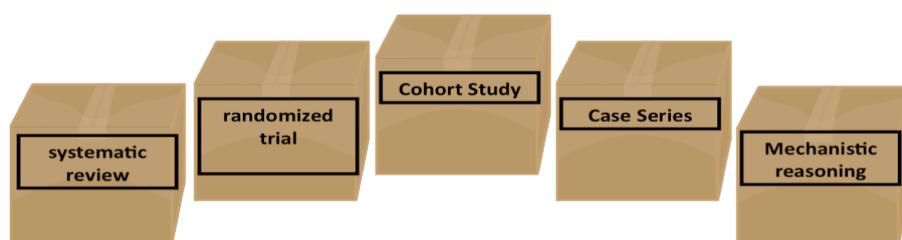


Figure 1. If you have limited time, where do you begin searching for evidence?

In an ideal world we would conduct our own systematic review of all the primary evidence if the systematic review box were empty. But we rarely have time for this. In searching for evidence about the benefits and harms of many ailments we often encounter thousands of articles. For example, a PubMed search of the words "atrial fibrillation AND warfarin" finds 2,175 hits, (see Table 1). You will not have time to filter all of these, let alone assess and review these, so it is rational to begin with the next best evidence – such as one of the seven randomized trials.

Table 1. Results of a PubMed search for "atrial fibrillation AND warfarin" plus some filters

Type	Term used	Number of articles
All articles	(no filter)	2175
RCT	"random allocation" [MeSH]	7
Cohort	"cohort studies" [MeSH]	366
Case-control	"Case-Control Studies"[Mesh]	234
Case report	Case Reports [Publication Type]	196

3. The OCEBM Levels assists clinicians to conduct their own rapid appraisal. Pre-appraised sources of evidence such as [Clinical Evidence](#), [NHS Clinical Knowledge Summaries](#), [Dynamed](#), [Physicians' Information and Education Resource \(PIER\)](#), and [UpToDate](#) may well be more comprehensive, but risk reliance on expert authority.



What the OCEBM Levels is NOT

1. The Levels are NOT dismissive of systematic reviews. On the contrary, systematic reviews are better at assessing strength of evidence than single studies(2, 3) and should be used if available. On the other hand clinicians or patients might have to resort to individual studies if systematic reviews are unavailable. The one exception is for questions of local prevalence, where current local surveys are ideal.
2. The Levels is NOT intended to provide you with a definitive judgment about the quality of evidence. There will inevitably be cases where 'lower level' evidence – say from an observational study with a dramatic effect – will provide stronger evidence than a 'higher level' study – say a systematic review of few studies leading to an inconclusive result (see Background Document).
3. The Levels will NOT PROVIDE YOU WITH A RECOMMENDATION(4). Even if a treatment's effects are supported by best evidence, you must consider at least the following questions before concluding that you *should* (5, 6) use the treatment:
 - a. **Do you have good reason to believe that your patient is sufficiently similar to the patients in the studies you have examined?** Information about the size of the variance of the treatment effects is often helpful here: the larger the variance the greater concern that the treatment might not be useful for an individual.
 - b. **Does the treatment have a clinically relevant benefit that outweighs the harms?** It is important to review which outcomes are improved, as a statistically significant difference (e.g. systolic blood pressure falling by 1mmHg) may be clinically irrelevant in a specific case. Moreover, any benefit must outweigh the harms. Such decisions will inevitably involve patients' value judgments, so discussion with the patient about their views and circumstances is vital (see (d) below)(7).
 - c. **Is another treatment better?** Another therapy could be 'better' with respect to both the desired beneficial and adverse events, or another therapy may simply have a different benefit/harm profile (but be perceived to be more favourable by some people) . A systematic review might suggest that surgery is the best treatment for back pain, but if exercise therapy is useful, this might be a more acceptable to the patient than risking surgery as a first option.
 - d. **Are the patient's values and circumstances compatible with the treatment?** (8, 9). If a patient's religious beliefs prevent them from agreeing to blood transfusions, knowledge about the benefits and harms of blood transfusions is of no interest to them. Such decisions pervade medical practice, including oncology, where sharing decision making in terms of the dose of radiation for men opting for radiotherapy for prostate cancer is routine (10).
4. The Levels will NOT tell you whether you are asking the right question. If you interpret meningitis as the common flu, then consulting the Table to find the best treatment for flu, will not help.

Differences between the 2011 Levels and other evidence-ranking schemes

Different evidence ranking schemes (11-14) are geared to answer different questions(5). The current OCEBM Levels is an improvement over the older Table in that the structure reflects clinical decision-making; moreover it is simpler (fewer footnotes) and is accompanied by an extensive glossary. Then, unlike GRADE, it explicitly refrains from making definitive recommendations, and it can be used even if there are no systematic reviews available.



How to cite the Introductory Document

Jeremy Howick, Iain Chalmers, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton. "The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document)". Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

References

1. Lacchetti C, Ioannidis JP, Guyatt G. Surprising results of randomized, controlled trials. In: Guyatt G, Rennie D, editors. *The Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. Chicago, IL: AMA Publications; 2002.
2. Chalmers I. The lethal consequences of failing to make full use of all relevant evidence about the effects of medical treatments: the importance of systematic reviews. In: Rothwell PM, editor. *Treating individuals: from randomised trials to personalized medicine*. London: The Lancet; 2007.
3. Lane S, Deeks J, Chalmers I, Higgins JP, Ross N, Thornton H. Systematic Reviews. In: Science SA, editor. London 2001.
4. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. *BMJ*. 2008 May 10;336(7652):1049-51.
5. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924-6.
6. Hume D, Norton DF, Norton MJ. *A treatise of human nature*. Oxford: Oxford University Press; 2000.
7. Hewlett SA. Patients and clinicians have different perspectives on outcomes in arthritis. *J Rheumatol*. 2003 Apr;30(4):877-9.
8. Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice. *ACP J Club*. 2002 Mar-Apr;136(2):A11-4.
9. Howick J. *The Philosophy of Evidence-Based Medicine*. Oxford: Wiley-Blackwell; 2011.
10. van Tol-Geerdink JJ, Stalmeier PF, van Lin EN, Schimmel EC, Huizenga H, van Daal WA, et al. Do patients with localized prostate cancer treatment really want more aggressive treatment? *J Clin Oncol*. 2006 Oct 1;24(28):4581-6.
11. Canadian Task Force on the Periodic Health Examination. The periodic health examination. *Can Med Assoc J*. 1979;121:1193-254.
12. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1986 Feb;89(2 Suppl):2S-3S.
13. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1989 Feb;95(2 Suppl):2S-4S.
14. Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1992 Oct;102(4 Suppl):305S-11S.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson



Background document

Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence

Introduction

The OCEBM Levels of Evidence was designed so that in addition to traditional critical appraisal, it can be used as a heuristic that clinicians and patients can use to answer clinical questions quickly and without resorting to pre-appraised sources. Heuristics are essentially rules of thumb that helps us make a decision in real environments, and are often as accurate as a more complicated decision process.

A distinguishing feature is that the Levels cover the entire range of clinical questions, in the order (from top row to bottom row) that the clinician requires. While most ranking schemes consider strength of evidence for therapeutic effects and harms, the OCEBM system allows clinicians and patients to appraise evidence for prevalence, accuracy of diagnostic tests, prognosis, therapeutic effects, rare harms, common harms, and usefulness of (early) screening.

Pre-appraised sources such as the Trip Database (1), (2), or REHAB+ (3) are useful because people who have the time and expertise to conduct systematic reviews of all the evidence design them. At the same time, clinicians, patients, and others may wish to keep some of the power over critical appraisal in their own hands.

History

Evidence ranking schemes have been used, and criticised, for decades (4-7), and each scheme is geared to answer different questions(8). Early evidence hierarchies(5, 6, 9) were introduced primarily to help clinicians and other researchers appraise the quality of evidence for therapeutic effects, while more recent attempts to assign levels to evidence have been designed to help systematic reviewers(8), or guideline developers(10).

While they are simple and easy to use, early hierarchies that placed randomized trials categorically above observational studies were criticized(11) for being simplistic(12). In some cases, observational studies give us the 'best' evidence(11). For example, there is a growing recognition that observational studies – even case-series (13) *and anecdotes* can sometimes provide definitive evidence(14).

More recent evidence-ranking schemes such as GRADE avoid this common objection by allowing observational studies with dramatic effects to be 'upgraded' (12), and trials may be 'downgraded' for quality and other reasons. Another advantage of the GRADE approach is that it takes other important factors such as directness, precision, and consistency when appraising quality of evidence. However, what GRADE has gained in accuracy, it may have lost in simplicity and efficiency. The GRADE system takes time to master and moreover is intended for appraising systematic reviews used in the production of guidelines.



Meanwhile, busy clinicians, who have only have a few minutes to answer a clinical question, will need a “fast and frugal” heuristic search tool to find and use the likely best evidence (15, 16).

The original CEBM Levels was first released in September 2000 for [Evidence-Based On Call](#) to make the process of finding evidence feasible and its results explicit. Busy clinicians sometimes need to make decisions quickly, sometimes in the middle of the night. One problem with many of the evidence ranking schemes at the time was that they ranked evidence for therapy and prevention, but not evidence for diagnostic tests, prognostic markers, or harm. A team led by Bob Phillips and Chris Ball, which included Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, and Martin Dawes therefore produced a Levels that included levels of evidence for therapy/prevention/aetiology/harm, prognosis, diagnosis, differential diagnosis, and economic and decision analyses.

While still useful as they are, in 2009 the Levels was over a decade old, and feedback over the years about the Levels led members of the OCEBM to believe it was time to review them. An international team led by Jeremy Howick (with considerable help from Olive Goddard and Mary Hodgkinson) that included Iain Chalmers, Paul Glasziou (chair), Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton met for 2 days in Oxford in December 2009 to discuss potential changes to the OCEBM Levels.

After brainstorming for a few hours, the group voted on what they thought required revision. The following emerged as essential to developing a revised Evidence Levels:

1. That the Levels should be designed in a way that they could be used as a *search heuristic* for busy clinicians and patients to use in real time in addition to serving as a hierarchy of evidence. With that in mind, they simplified the Levels in several ways. For example, levels ‘1a’, ‘1b’, and ‘1c’, in the original Levels was replaced with simply ‘1’. It was also modified to represent the natural flow of a clinical encounter (diagnosis, prognosis, treatment, benefits, harms).
2. ALL the relevant terms should be defined in an extensive glossary, and the definitions should be both technically accurate and easily understood. The glossary was compiled by Jeremy Howick with help from Hazel Thornton, Ian Chalmers, and two research assistants (Morwenna James, and Katherine Law).
3. That screening tests were sufficiently important to merit a separate entry, and that the importance of systematic reviews should be emphasized. That we should consider all relevant evidence is a fundamental tenet of the scientific method (reproducibility).

After the meeting, Jeremy Howick, Paul Glasziou, and Carl Heneghan drafted a Levels and in January Jeremy Howick sent it to the Working Group for feedback. In March and May 2011 Jeremy Howick posted it on the [OCEBM website](#), and invited subscribers to the CEBM mailing list to comment before September 1st. Jeremy Howick also sent the documents to Gordon Guyatt, Brian Haynes, and Dave Sackett. Brian Haynes made some useful suggestions. On September 1st, Jeremy Howick collated the feedback, made some changes to the Levels, and circulated both the feedback and the revised Levels to the OCEBM Evidence



Working Group.

Major Changes to the 2011 OCEBM Levels

What is the same (the good things we didn't change)

The Levels allows interested parties to answer a range of clinical questions, including diagnosis, prognosis, therapy, and harms.

What has changed (improvements over the previous OCEBM 'Levels')

1. The rows and columns are switched.
 - a. Each **row** represents a series of steps to should follow when searching for likely best evidence. The likely strongest evidence is likely to be found furthest to the left of the Levels, and each column to the right represents likely weaker evidence.
 - b. Each **column** represents the types of questions the clinician is likely to encounter *in the order the clinician will encounter them*. For example, the first question a clinician might want to ask is the prevalence (How common is it?). Then, they might like to know whether the diagnostic test was accurate. Next, they should wonder what would happen if they did not prescribe a therapy, and whether the likely benefits of the treatment they propose outweigh the likely harms.
2. Although busy clinicians might have to resort to individual studies, the OCEBM Levels is NOT dismissive of systematic reviews. On the contrary, systematic reviews are better at assessing strength of evidence than single studies(17, 18) and should be used if available. On the other hand clinicians or patients might have to resort to individual studies if a systematic review is unavailable. GRADE, for example, assumes that there is a systematic review and is of limited use when systematic reviews have not been conducted. The one exception to using a systematic review first is for questions of local prevalence, where a current local survey is ideal.
3. We added questions about common and rare harms, and the value of (early) screening because we felt that these were important and clinically relevant questions.
4. We omitted questions about economic and decision analysis. Although analyses are essential, we felt that further research, perhaps together with economists and policy makers, was required before pronouncing on what counts as good evidence in these areas.
5. We omitted most of the footnotes from the original Levels.
6. A new OCEBM Glossary will accompany the Levels. The new Glossary is more extensive and friendly.
7. We divided harms into 'common' and 'rare'. A rule of thumb is that a common harm involves more than 20% of participants.



Justification for the 2011 OCEBM Levels

Although the 2011 OCEBM Levels is based on what type of evidence is *likely* to provide strongest support from both empirical (19-21) and theoretical (11, 22, 23) work. In a word, the lower the risk of confounding (bias), the further to the left the type of evidence will lie.

Empirical investigation of OCEBM Levels

While it is difficult to assess the number of citations to the OCEBM Levels because the original document did not provide instructions for how to cite the Levels, a Google search of "Oxford CEBM Levels" yields over 10 000 results, a Google search of "OCEBM Levels" yields over 300 results, and a PubMed search of "Oxford Levels of Evidence" yields 794 results. Systematic reviewers (24-28), clinicians, and policy makers (29) have all used the OCEBM Levels to judge the strength of evidence. Instruction for citing the revised OCEBM Levels is clearer which should make tracking its use more straightforward.

Potential limitations of the 2011 OCEBM Levels

While relatively simple rules of evidence can be more reliable than more complex strategies (15, 16, 30), they are not foolproof. Certainly one can always imagine scenarios where evidence from a column further to the right – say observational studies with dramatic effects – will provide stronger evidence than something currently ranked further to the left – say a systematic review of randomized trials. For example, imagine a systematic review with that didn't include all the relevant studies and was conducted by a potentially biased organization (31) suggested that a treatment had a positive benefit. We might stop our search in the belief that we had found sufficiently strong evidence to make a decision. However, if we continued, we might have found a recent, large, well-conducted randomized trial indicating that the same treatment had no benefit or perhaps was harmful. Which evidence do we accept?

There are two potential answers to this question. One would be to make the Levels more complex by introducing more columns. Instead of having 5 columns, we could have 10, 20, or more. In the different columns we could differentiate all the different 'qualities' of, say, systematic reviews of treatment benefits. For example, we might place systematic reviews of low quality randomized trials in a column to the right (likely worse evidence) than a large, high-quality randomized trial. The problem with introducing more columns is that the Levels would no longer be simple, and clinicians would not be able to use in real time. Moreover exceptions would never altogether disappear and empirical investigations might reveal that the simpler hierarchies lead to better average decisions than more complex alternatives.

The other solution is to insist that the Levels be interpreted with a healthy dose of common sense and good judgment (13, 14, 32, 33), which brings us to the next section.



The role of expertise in using the OCEBM Levels

A problem with all hierarchies of evidence is that, psychologically and sociologically speaking, they encourage people to stop using judgment. No hierarchy or levels of evidence can be used without careful thought (34).

This does not imply, of course, that experts should ignore evidence. Indeed both in the original (35) and revised 'Bradford Hill Guidelines' (33), researchers are asked to consider various factors when making clinical decisions. At the same time we believe that a healthy dose of scepticism and judgement will always be required to appraise evidence and apply it to individuals in routine practice (11, 36, 37).

Future directions

The strength of evidence is related to what the evidence is *for*(11), and good evidence for clinical decisions should answer clinically relevant questions. What the clinician, patient, or policy maker wants to know (amongst other things) is, 'Which treatment, from among all the available alternatives, has the most favourable benefit/harm balance?' For example, surgery may well be effective for back pain, but so may other, less risky treatments (38-40). Or consider depression. There are several selective serotonin reuptake inhibitors (SSRIs) and numerous other pharmacological antidepressants (tricyclics, monoamine oxidase inhibitors (MAOis), serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NASSAs), norepinephrine (noradrenaline) reuptake inhibitors (NRIs), and Norepinephrine-dopamine reuptake inhibitors). Then, there are many non-pharmaceutical treatments used to treat depression, including St. John's wort, Cognitive Behaviour Therapy (CBT), exercise, and self-help. None of these treatments has demonstrated consistent superiority to others in trials (41). In order to rationally choose which therapy to use we must understand the relative benefits and harms of these different options.

With this in mind, the row in the Levels about therapeutic benefits should, ideally, be 'Which treatment, from among all available alternatives, has the most favourable benefit/harm balance?' The evidence to answer such a question would most probably come in Levels that included the various treatment options, together with the quality of evidence for benefits and harms. We chose not to include such a row because such evidence is, at the time of writing, rare. Fortunately, evidence comparing all available alternatives is becoming more common in the form of 'umbrella reviews' (42) and 'comparative effectiveness research' (43). We expect that the next version of the OCEBM Levels will ask clinicians to consider the relative benefits and harms of all available alternatives.

Conclusion

The 2011 OCEBM Levels was developed by an international group and took into account feedback from clinicians, patients, and all those on the OCEBM mailing list. It retains the spirit of the original 1998 OCEBM Levels in that it covers a range of clinical questions, it can be used to find the likely best evidence quickly, and it encourages clinicians and patients to assess evidence autonomously. The



main changes include reversal of the rows and columns, additional Levels for harms and screening tests, increased simplicity and an extensive glossary.

How to cite the Background Document

Jeremy Howick, Iain Chalmers, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton.

"Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document)". Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

References

1. TRIP. The Trip Database. Newport, UK2009 [cited 2009 12 November 2009]; Available from: www.tripdatabase.com.
2. NIH. PubMed. Bethesda: U.S. National Library of Medicine; 2009 [cited 2009 12 November 2009]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/>.
3. REHAB+. REHAB+. Hamilton: McMaster University; 2009 [cited 2009 12 November 2009]; Available from: <http://plus.mcmaster.ca/Rehab/Default.aspx>.
4. Canadian Task Force on the Periodic Health Examination. The periodic health examination. *Can Med Assoc J.* 1979;121:1193-254.
5. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest.* 1986 Feb;89(2 Suppl):2S-3S.
6. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest.* 1989 Feb;95(2 Suppl):2S-4S.
7. Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest.* 1992 Oct;102(4 Suppl):305S-11S.
8. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008 Apr 26;336(7650):924-6.
9. The periodic health examination. Canadian Task Force on the Periodic Health Examination. *Can Med Assoc J.* 1979 Nov 3;121(9):1193-254.
10. Harbour RT, editor. SIGN 50: A guideline developer's handbook. Edinburgh: NHS Quality Improvement Scotland; 2008.
11. Howick J. *The Philosophy of Evidence-Based Medicine.* Oxford: Wiley-Blackwell; 2011.
12. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ.* 2003 Dec 20;327(7429):1459-61.
13. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. *BMJ.* 2007 Feb 17;334(7589):349-51.
14. Aronson JK, Hauben M. Anecdotes that provide definitive evidence. *BMJ.* 2006 Dec 16;333(7581):1267-9.



15. Gigerenzer G. Gut feelings : short cuts to better decision making. London: Penguin, 2008; 2007.
16. Gigerenzer G, Todd PM. Simple heuristics that make us smart. New York: Oxford University Press; 1999.
17. Chalmers I. The lethal consequences of failing to make full use of all relevant evidence about the effects of medical treatments: the importance of systematic reviews. In: Rothwell PM, editor. Treating individuals: from randomised trials to personalized medicine. London: The Lancet; 2007.
18. Lane S, Deeks J, Chalmers I, Higgins JP, Ross N, Thornton H. Systematic Reviews. In: Science SA, editor. London 2001.
19. Khan KS, Daya S, Collins JA, Walter SD. Empirical evidence of bias in infertility research: overestimation of treatment effect in crossover trials using pregnancy as the outcome measure. Fertil Steril. 1996 May;65(5):939-45.
20. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995 Feb 1;273(5):408-12.
21. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ. 2008 Mar 15;336(7644):601-5.
22. La Caze A. Evidence-Based Medicine Must Be. J Med Philos. 2009 Aug 18.
23. Worrall J. *What Evidence in Evidence-Based Medicine?* Philosophy of Science. 2002;69(Supplement):S316-S30.
24. Beaton R, Pagdin-Friesen W, Robertson C, Vigar C, Watson H, Harris SR. Effects of exercise intervention on persons with metastatic cancer: a systematic review. Physiother Can. 2009 Summer;61(3):141-53.
25. Moreno L, Bautista F, Ashley S, Duncan C, Zacharoulis S. Does chemotherapy affect the visual outcome in children with optic pathway glioma? A systematic review of the evidence. Eur J Cancer. Aug;46(12):2253-9.
26. Galderisi S, Mucci A, Volpe U, Boutros N. Evidence-based medicine and electrophysiology in schizophrenia. Clin EEG Neurosci. 2009 Apr;40(2):62-77.
27. Cooper C, Balamurali TB, Livingston G. A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. Int Psychogeriatr. 2007 Apr;19(2):175-95.
28. Freeman BJ. IDET: a critical appraisal of the evidence. Eur Spine J. 2006 Aug;15 Suppl 3:S448-57.
29. Naver L, Bohlin AB, Albert J, Flamholc L, Gisslen M, Gyllensten K, et al. Prophylaxis and treatment of HIV-1 infection in pregnancy: Swedish Recommendations 2007. Scand J Infect Dis. 2008;40(6-7):451-61.
30. Gigerenzer G. Reckoning with risk : learning to live with uncertainty. London: Penguin, 2003; 2002.
31. Jorgensen AW, Hilden J, Gotzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. BMJ. 2006 Oct 14;333(7572):782.



32. Glasziou P, Vandenbroucke JP, Chalmers I. Assessing the quality of research. *BMJ*. 2004 Jan 3;328(7430):39-41.
33. Howick J, Glasziou P, Aronson JK. The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute? *J R Soc Med*. 2009 May;102(5):186-94.
34. Hill ABS, Hill ID. Bradford Hill's principles of medical statistics. 12th ed. ed: Edward Arnold; 1991.
35. Hill AB. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*. 1965;58:295-300.
36. Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice. *ACP J Club*. 2002 Mar-Apr;136(2):A11-4.
37. Straus SE, Richardson WS, Glasziou P, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*. 3rd ed. London: Elsevier: Churchill Livingstone; 2005.
38. Mirza SK, Deyo RA. Systematic review of randomized trials comparing lumbar fusion surgery to nonoperative care for treatment of chronic back pain. *Spine (Phila Pa 1976)*. 2007 Apr 1;32(7):816-23.
39. Brox JI, Reikeras O, Nygaard O, Sorensen R, Indahl A, Holm I, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. *Pain*. 2006 May;122(1-2):145-55.
40. Fritzell P, Hagg O, Nordwall A. Complications in lumbar fusion surgery for chronic low back pain: comparison of three surgical techniques used in a prospective randomized study. A report from the Swedish Lumbar Spine Study Group. *Eur Spine J*. 2003 Apr;12(2):178-89.
41. Howick J. Questioning the Methodologic Superiority of 'Placebo' Over 'Active' Controlled Trials *American Journal of Bioethics*. 2009;9(9):34-48.
42. Becker L. The Cochrane Colloquium: Umbrella Reviews: What are they, and do we need them? : The Cochrane Collaboration; 2010 [cited 2010 10 September 2010]; Available from: <http://www.slideshare.net/Cochrane.Collaboration/umbrella-reviews-what-are-they-and-do-we-need-them-160605>.
43. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med*. 2009 Aug 4;151(3):203-5.