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Evidence-based practice: performing and using systematic reviews

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This lecture covers the basic principles of systematic reviews and meta-analyses and their role in the process of evidence-based decision making. The problems associated with traditional narrative reviews are discussed, as is the role of systematic reviews in limiting bias associated with the assembly, critical appraisal, and synthesis of studies addressing specific clinical questions. The relevant steps in writing a systematic review from the formulation of an initial research question to sensitivity analyses in conjunction with the combined analysis of the pooled data are described. Important issues that need to be considered when appraising a systematic review or meta-analysis are outlined, and some of the terms used in the reporting of systematic reviews and meta-analyses, such as relative risk, confidence intervals, the Forest plot or the L'Abbé plot, are introduced.

Introduction

Shortage of resources is a given constant in almost every industry. In the healthcare industry it affects the macro-, meso- and micro-level and, thus, each anaesthesia department and individual anaesthetist. Therefore, evidence-based medicine, with its claim to apply the 'current best evidence in making decisions about the care of individual patients' [1], has gained widespread acceptance as the basis for clinical decision-making. The challenging goal for every health professional is to guarantee not only that good things are done, but to do more good than anything else that could be done with the same resources; this is true for both publicly financed as well as private financed healthcare insurance systems.

One of the key drivers of the 'success' of evidence-based practice is the rapidly increasing amount of clinical evidence that demands quality assessment and the correct tools to summarise the findings as well as to produce a clinical 'bottom-line'. When aiming to base clinical decision-making on the current best evidence, systematic reviews, especially when performed in an adequate way, are considered of paramount importance. The 'hierarchy' of evidence is mainly determined by various suggestions of levels of evidence and the description by the Oxford Centre of Evidence Based Medicine has gained widespread acceptance (<http://www.cebm.net/index.aspx?o=1025>). If transferred to a clinically oriented search algorithm, the recommendations mean that one should first search for systematic reviews and if these or other higher ranked resources of evidence are not available, to try and locate case series, expert opinion without formal quality-assessed recommendations or even case reports (which can help a lot, if there is no information as far as anaesthetic management is concerned for uncommon diseases). Furthermore, well-informed patients have increasing access to the same evidence that functions as the basis for clinical decision-making. This influences the decision-making process and forces us to 'keep up with them' so as to prevent us being taught by patient what the 'state of the art' is in distinct clinical situations.

Critical clinical thinking demands we re-assess our practice and to question the added-value and potential harm of so-called 'routine interventions'. On a departmental level, new devices or pharmacological interventions are thoroughly assessed before widespread use is encouraged. Aspects of patient safety as well as budget restraints foster these developments.

Systematic reviews are one way of dealing with uncertainty and over-information with respect to new as well as traditional interventions in the healthcare system. Although most practicing anaesthesiologists will probably not write systematic reviews, the need for knowledge in this field is clear since quality assessment is an important step before the results of systematic reviews are transferred to clinical pathways and impact on the care of individual patients.

Systematic reviews versus narrative reviews - and why we need both of them

Owing to the fact that textbooks usually transfer scientific medical information with a considerable time lag, published traditional review articles represent an ideal way of keeping 'up-to-date' if original data are difficult to retrieve or – which is more often the case – exist in such a multitude that under a given constraint of time, nobody can quickly extract the relevant information. In these descriptive overviews usually an expert describes and explains the findings regarding a rather broader topic.

Whether a narrative review article has a broader (such as 'labour analgesia' or 'anaesthetic implications of pregnancy') or narrower (such as 'epidural analgesia for labour pain' or 'coagulation disorders during pregnancy') scope is not predetermined and it's up to the author to provide background information, epidemiologic data or some other kind of preclinical information. This freedom is both friend and foe. On one hand it provides an easy to read message in conjunction with useful background information. On the other hand, and this is the case if the scope of the article as well as the existing information is too extensive, the fact that it is up to the 'expert author' as to which references he quotes introduces a bias that is difficult to control. The suggested main causative factors for discrepancies between knowledge and the described opinion in a narrative review are as follows:

- experts are out of touch with everyday experience and thus do not represent current 'best practice';
- if they are experts in the field and have a research history in a specific field they may be inclined not to acknowledge the work done by others, while neglecting the weaknesses and limitations of their own research.

Depending on the opinion of the author, she or he will neglect papers that are equally important but do not support the message that is intended to be transferred. The popular saying: "ask three different experts and you will get three different answers" nicely describes this inherent threat of narrative reviews. But even if an author aims to provide unbiased and objective data, if the number of available trials exceeds three or four, it is difficult to 'digest' the figures and pool the results to provide a new insight without doing this by means of formal summary statistics in a meta-analysis. Some of these fundamental differences of narrative versus systematic reviews are depicted in Table 1.

Table 1

Key features associated with narrative and systematic reviews. Please note that none of the given criteria is exclusively valid for one or other category.

Narrative review	Systematic review
Broad scope	Focused clinical question
Broad coverage of the topic, i.e. including epidemiology, pathophysiology and all available treatment options	Focused either on epidemiologic questions, risk factors, prevention or treatment. Sometimes focused exclusively on one treatment option.
Single author	Team of authors
Author is usually has some expert knowledge in the field	Team of authors with different background knowledge (e.g. of the methodology or topic discussed). Sometimes multi-disciplinary.
Subjective decisions about which sources and references to include in the review.	Hopefully unbiased research to identify and retrieve all relevant literature.
Sometimes biased results	Transparent and traceable results
No objective quality criteria regarding the assessment of the included primary studies or resources used to back up statements	Overt quality criteria regarding the assessment of the included primary studies
No statistical synthesis of trial results	For a 'meta-analysis' (which is not always reasonable to perform) results are pooled to end up with a new, and hopefully more robust, result.
Conclusions reflects subjective view and assessment of the available literature by the author	Conclusion reflects 'study results', i.e. results of the meta-analysis or the systematic review.
Difficult to re-enact	All parts (search of the primary studies as well as pooled analysis) can be easily replicated

The special need for systematic reviews

In an age, where only a few clinical trials are published each year, it would be quite easy to keep up-to-date by reading these original research articles and frame one's own view regarding the available evidence. This is impossible in a time when 'information explosion' is a common buzzword in medicine and anaesthesiology alike. A 'quick look in MEDLINE' would also be of little help if the retrieved results are too confusing. Consider, for example, the question whether a background infusion in association with an opioid PCA pump is beneficial or not. Using the search terms 'intravenous PCA morphine background infusion' and the restriction to 'randomised controlled trial' in MEDLINE (<http://www.pubmed.org>, last accessed 10/12/2008) would reveal 34 results. Among others, two trials (No. 10 and No. 14) would be especially relevant at first sight for the interested reader. However, the results are conflicting, since although the country and setting – both trials were performed in cardiac surgery – were almost identical, in the conclusion section of the trial published in 2003 it was stated that: 'PCA with morphine effectively controlled postoperative pain after cardiac surgery. The addition of a background infusion of morphine did not enhance analgesia and increased morphine consumption' [2], while the second trial published one year later concluded: 'Morphine PCA effectively controlled postoperative pain after cardiac surgery. The addition of a background infusion of morphine enhanced analgesia and increased morphine consumption' [3]. Interestingly, both trials were published in the same journal and under the auspices of the same subsection, namely 'Cardiothoracic anesthesia, respiration and airway'.

There is, therefore, a need for so-called 'secondary research', which does not mean 'inferior', but instead refers to research based on previously acquired results from primary research. Like all research, systematic reviews can be good or bad and may even lead to misleading conclusions, which has led to collateral damage for the reputation of systematic reviews. However, it does not make sense to discredit systematic reviews as it does not make sense to denigrate clinical trials just because a few are not performed according to well-established standards [4, 5]. These standards also exist for systematic reviews and meta-analyses [5] and may be useful for 'consumers' – the people who use the results of these types of research for clinical decision-making.

The content of a systematic review and how it produced

What should be the scope of the review and which questions should be answered?

Usually a systematic review starts with a clinician or researcher wanting to answer a specific research question. Such a question – in contrast to writing a narrative review – should be clear and specific. Sometimes it is argued that the answer to such a question should not be self-evident. However, it is sometimes surprising how a research question evolves, including those that were previously considered fully answered. Creating an up-to-date compilation of relevant trials may reveal unexpected insights.

As far as the focus of the research question is concerned the general 'PICO-rule' of questions for evidence-based decision-making is applicable also to research questions in the context of systematic reviews:

- Patient (for example: 'In nulliparous women at term, presenting in spontaneous labour...')
- Intervention (for example: '... patient-controlled analgesia with intravenous remifentamil...')
- Comparator (for example: '...compared with intramuscular pethidine...')
- Outcome (for example: 'more effectively controls labour pain with fewer side-effects').

Such a question is obviously much more specific and focused than the question 'Is remifentanil suitable for labour analgesia?' or 'Is remifentanil a useful opioid in anaesthesia practice?'. On the other hand, even with such a narrow scope there will be considerable variation in the trials that are included in the review (lockout-intervals, bolus-doses, time of institution of the intervention, assessment scales and outcome definitions, etc.). It is self-evident that without such a focused question, a search for the relevant primary studies based on objective inclusion and exclusion criteria will not be possible.

Which studies are included and why?

Primary studies are included based on predefined inclusion and exclusion criteria. These are primarily set by the relevance to the research question and the methodological quality of the studies that should be considered. Relevance to the research question is the key feature for a review to be a 'systematic review'. The methodological quality that needs to be defined as a 'threshold' for primary studies to be included in the review depends on the research question and also on the availability of a sufficient number of trials focusing on that question. The goal to only include 'randomised, controlled double-blinded and placebo-controlled trials' may not be appropriate if a 'gold-standard' already exists. Given such a scenario, clinicians would be more interested to know how the investi

gated intervention (active intervention 'B') compares with the existing gold-standard (active intervention 'A'), because they want to know whether it makes sense to introduce a new treatment rather than to stay with the established one. Blinding is a worthwhile goal in clinical trials to prevent subjective assessment and minimise bias. However, this principle is not feasible for all treatments and even pharmacological interventions, which can be blinded easily, may un-blind themselves due to some characteristic effects. Randomisation is considered of utmost importance if a treatment effect should be ascribed to a specific intervention. The underlying rationale is that it is impossible to balance relevant but yet unknown confounding factors between two groups. Thus, even if researchers aim to balance risk factors (which eventually increase the event rate in one group), it is impossible to do this for unknown factors which might lead to a bias in the observed results (that is that results are due to the underlying risk distribution rather than the investigated intervention). Again, there is no dogma that dictates that only randomised trials should be included in a systematic review (even in a systematic review on treatment options). An interested reader may even benefit from a systematic review on case series, especially if other types of evidence are not (yet) available. In the latter case, of course, potential biases should be discussed and considered when implementing the results of such a review. For formal quality-assessment of included trials the Oxford Scale may help to provide an overview of trial features [6]. This popular five-point scoring system uses three criteria and asks the following questions:

- Is the trial randomised (1 point). Additional point if the method is given and appropriate?
- Is the trial double-blind (1 point). Additional point if the method is given and appropriate?
- Were withdrawals and dropouts described and assigned to different treatments (1 point)?

Trials that score three points or more are usually considered relatively free of bias and could be trusted. Lower scores in some therapeutic areas were shown to be associated with increased treatment effects - they were biased [7, 8]. More comprehensive scoring systems exist but is questionable if these provide any value to the overall results of a systematic review.

To avoid a conclusion that there are no trials available (Typical conclusion: 'There is not enough evidence to say whether treatment A works to treat disease B or whether it is harmful'), it is reasonable to perform some pilot searches before inclusion and exclusion criteria are defined.

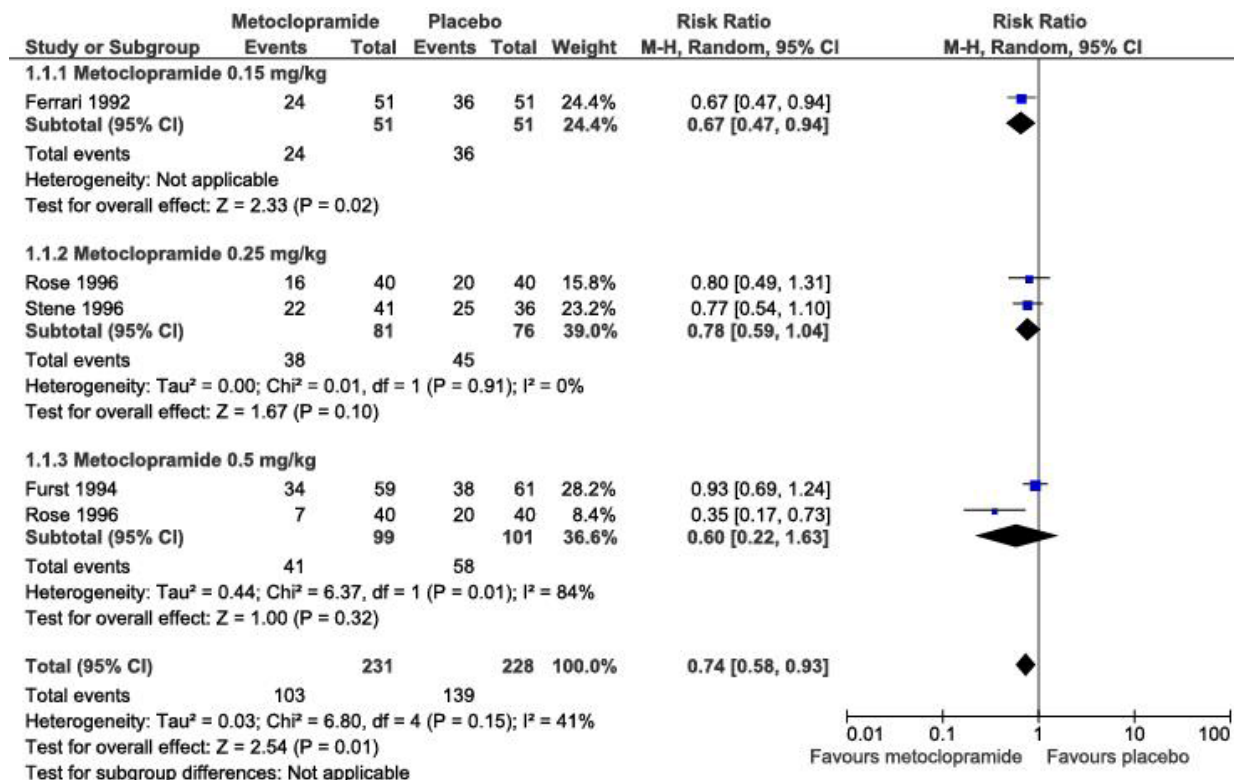
Which data are extracted and which analyses are performed and displayed?

Based on the inclusion and exclusion criteria, a search strategy will be created that hopefully finds all relevant literature. Obviously the more sensitive such a search algorithm is, the more time is required to manually search through retrieved articles in order to decide which ones should be included. If the pilot search reveals that the literature is limited, then it doesn't make sense to be too restrictive regarding the search algorithm. Thus, potential relevant articles are not missed and by screening the hits of the search the reviewers gain insight regarding the background of the research question and possible links to other topics relevant to the question to be answered. While screening the abstracts obviously irrelevant articles should be excluded and all articles that are likely to be relevant (or those that don't present enough information to decide whether they are relevant or not) should be obtained as full-text articles. This selection, as well as the data extraction, is usually done by at least two independent researchers who are familiar with the procedure. In case of a disagreement, a third reviewer is sometimes necessary to resolve the discrepancy. It may be worthwhile to blind reviewers to the origin of the article and its authors so that assessment is truly unbiased. If reviewers possess a prior in-depth knowledge of the existing literature and are experts in the field, such a procedure is nearly impossible. A flow-chart usually highlights this selection process and informs the reader of a systematic review which primary studies are excluded at which stage.

Apart from methodological features of the included trials, some descriptive data are usually extracted for presentation of the included trials. This information is usually given in the first table of the systematic review. Efficacy data which are obtained from primary studies can be either dichotomous (how many patients die, for example) or continuous (the mean pain level was 7 on a scale from 0 to 10, with some estimate of variance). The weighted mean could be calculated for groups before and after an intervention (such as blood pressure lowering), and the weighted mean difference (WMD) would be the difference between start and finish values. For this, though, the difference would usually be calculated not as the difference between the overall start value and the overall final value, but rather as the sum of the differences in the individual studies, weighted by the individual variances for each study. Dichotomous efficacy data in treatment studies are usually combined and presented as relative risk (RR) or odds ratio (OR) and, like the WMD, are provided with a (95%) confidence interval (the range of values within which we can be 95% sure that the true value for the whole population lies). Forest plots (Figure 1) and L'Abbé plots (Figure 2) help to provide a visual impression of the included data from the primary studies. While the relative risks with associated confidence intervals and the attributed weight of each study in the Forest provides information on the magnitude of effect of each trial and its influence on the pooled statistics, the L'Abbé plot allows insight

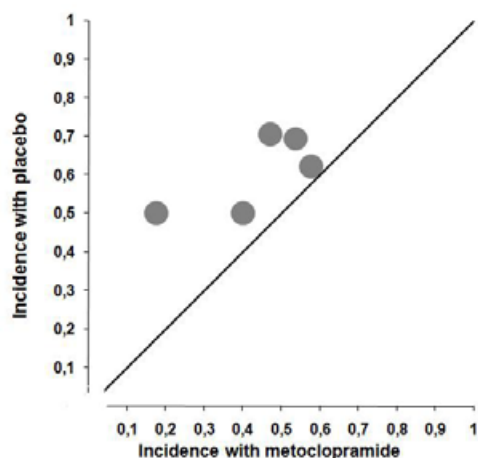
as to what extent the investigated population, with its underlying risk, resembles the population of interest (relevant question: Is the control event rate nearly the same?).

Figure 1



Forest plot of trials investigating metoclopramide in the prevention of postoperative nausea and vomiting in children undergoing tonsillectomy. Relative risk (risk ratio) with the corresponding 95% confidence interval (95% CI) is represented by the squares with connected lines. While the summarized results (subtotals - distinct dose groups, as well as totals - all results irrespective of the doses used) are displayed by diamonds. The sample is a subset of a previous systematic review investigating interventions to prevent postoperative vomiting in children undergoing tonsillectomy [16].

Figure 2

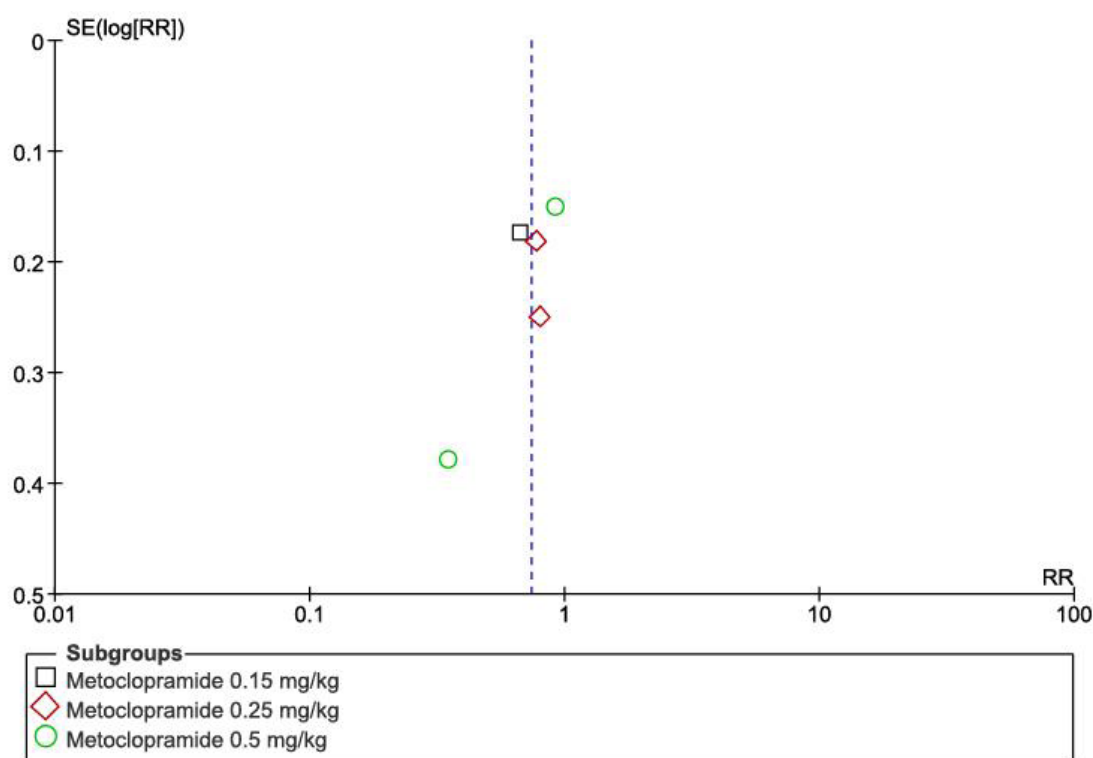


L'Abbé plots of trials investigating overall efficacy of metoclopramide of postoperative nausea and vomiting in children undergoing tonsillectomy. Symbols are comparisons between metoclopramide arms and placebo arms. Line with 45° slope indicates equality. The sample is a subset of a previous systematic review investigating interventions to prevent postoperative vomiting in children undergoing tonsillectomy [16].

Sometimes publications that include meta-analyses also present sensitivity analyses testing the robustness of the results under the condition that certain studies (poor quality, small sample size) are excluded. Restricting the pooled analysis to a defined intervention or patient population may also be termed sensitivity analysis and may provide insight into association between the observed effect and the causative conditions. However, the results should usually be viewed as hypothesis framing and at best as a weak hint for a real causative condition, since all such analyses are post-hoc analyses.

In order to elucidate whether the results of the meta-analysis are influenced by sources of bias or other reasons for having doubts about the veracity of results of clinical trials, funnel plots are sometimes included in publications. A funnel plot is where some trial specific effect (odds ratio, relative risk) is plotted against some measure of its precision. Precision may be defined in different ways. Commonly used are the numbers of subjects in a trial, or some function of the standard error (Figure 3). If the plot is symmetric, like an inverted V ('funnel'), this is interpreted as demonstrating that there is probably no publication bias. If the plot is asymmetric, the interpretation is that publication bias is likely (Figure 3). The interpretation of asymmetrical plots is often that there must be unpublished negative trials that would serve to negate the positive findings of a meta-analysis if only they could be found. However, there is great scepticism whether such tools make sense and there is some empirical evidence that funnel plots may be misleading [10, 11].

Figure 3



Funnel plot of trials investigating metoclopramide in the prevention of postoperative nausea and vomiting in children undergoing tonsillectomy. The sample is a subset of a previous systematic review investigating interventions to prevent postoperative vomiting in children undergoing tonsillectomy [16].

Clinicians should not decline to transfer results of meta-analyses to the treatment of patients simply because there is some asymmetry in the funnel plot. Rather they should ask the following questions in order to get an impression whether the results of a meta-analysis matter to their patients:

- Are the patients in the trials like mine?
- Are the inclusion criteria sensible?
- Do the outcomes make sense?
- Are they useful and do they matter to my patients?

What to do with the result of systematic reviews

Systematic reviews encompass the first three principles of evidence-based practice:

- ask (a clinical relevant question)
- search (for external evidence)
- and appraise (the retrieved evidence).

The fourth and fifth principle, 'Apply' (the evidence) and 'Evaluate' (the obtained results) are the logical next steps. This can only be done by the practicing clinician or by managerial decision making in the healthcare industry (for example, hospitals or anaesthesia departments). Researchers of the systematic reviews can only choose the right format to disseminate their results in the most effective way.

As described previously, a quality assessment may help clinicians to decide whether the results of a systematic review should be trusted (which may depend on the availability of primary studies rather than the methodology applied for the systematic review). The following questions may help to get a more precise picture of a systematic review:

- Did the review address a clearly focused question that is also my own clinical question?
- Did the review include the type of studies that are most likely to deliver unbiased results?
- Did the reviewers make efforts to identify all relevant primary studies?
- Did the reviewers assess the quality of the included studies and was the quality acceptable to guarantee valid results?
- In case of a pooled analysis: was it reasonable to combine study results or does it look like comparing apples with oranges?
- What are the main results (direction)?
- How precise are the results (width of the confidence intervals and heterogeneity)?
- Were all important outcomes (favourable outcomes as well as adverse outcomes) considered and is the outcome that was mentioned in my clinical question (PICO-principle) among the outcomes discussed in the review?

However, the most important questions as far as the implementation process is concerned are:

- Can the results be applied to my local population? Or, to be more precise: is the patient I want to treat similar enough to the studied population so that the results apply to him?
- Should practice or policy change as a consequence of the clinical bottom line of the review?

These are typical questions in the daily practice of evidence-based medicine. Since they are context sensitive, there is no general valid 'yes' or 'no' answer that apply to all patients and populations even if there is a clear bottom-line in a systematic review that supports one intervention. Economic considerations as well as skills and availability of resources (equipment, time, and so forth) may play an important role in this decision process.

As a general simple rule, policy changes are most likely to affect costs and outcome of healthcare if a rare condition associated with great costs / severe clinical outcome is concerned or if a frequent condition with small costs / minor clinical outcome is in the focus.

How to find systematic reviews

There are numerous ways to find high-quality systematic reviews and a good start is to consult the Cochrane Library (<http://cochrane.org/>). However, full-text versions of reviews published in the Cochrane Library are not available to all individual and institutions. Furthermore, other systematic reviews published in a journal format may be more suitable regarding the scope and patient population. Therefore, a simple and universally applicable approach is to use the clinical queries link on PubMed in order to identify systematic reviews. Starting with <http://www.pubmed.org>, the Clinical Queries are one 'mouse-click' away and the interested clinician is able to insert the relevant search terms in the section 'Find Systematic Reviews' and then press 'go' in order to automatically add the search filter to locate these types of research (http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html).

How to implement the results of systematic reviews

Creating standard operating procedures (SOP) to guide and streamline clinical decision-making has become very popular in recent years. In order to provide the manuals that complement clinical pathways, they usually represent a kind of 'how-to-do' manual for the busy clinician who cannot keep up-to-date in every area of expertise. Furthermore, these guidelines represent some sort of documentation of the process quality, which represents a vital part of quality assurance and quality management. However, usually these guidelines are 'expert guidelines', which means that the department head or some other expert defines what is the current 'state-of-the-art' regarding diagnosis or treatment in a hospital. There would be minimal additional effort if such guidelines or SOP were to be 'backed-up' by some scientific evidence. In such circumstances systematic reviews provide an excellent way of doing this. Authors of the guidelines are not forced to quote numerous references but are able to link a statement to the current available evidence. If new evidence emerges (for example, an updated systematic review) this can be easily inserted and, in case of changed conclusions, the resulting recommendations can be modified accordingly.

Summary

Systematic reviews apply scientific strategies to provide a transparent summary of all studies addressing a specific question, thereby allowing account to be taken of the whole range of relevant findings on a particular topic. Meta-analysis, which may or may not accompany a systematic review, can increase power and precision of estimates of treatment effects by pooling the results of primary studies. People working in the field of anaesthesiology and critical care should understand the fundamental principles of systematic reviews and meta-analyses, including the ability to apply critical appraisal not only to the methodologies of review articles, but also to the applicability of the results to their own patients, for clinical decision-making and to base policy changes on the best available and most appropriate resources.

Further Reading

This refresher course lecture provides a concise overview of the value, components and critical appraisal of systematic reviews and the question of when and how the results of systematic reviews should be implemented in daily clinical decision making. A more comprehensive review of this topic can be found in books [12] and detailed review articles [13-15].

Key Learning Points

- Systematic reviews are considered of paramount importance in the aim to base clinical decision-making on the current best evidence.
- Systematic reviews are usually more focused than narrative reviews and typically address one distinct research question.
- In contrast to systematic reviews, which represent a research paper, narrative reviews usually provide a better overview on a broader topic including epidemiological findings and some relevant background information. Thus, they are usually more "reader-friendly".
- Questions which are addressed in systematic reviews should typically contain the following components (PICO-principle): 1. Patient, 2. Intervention, 3. Comparator and 4. Outcome.
- Like every research methodology, inherent weaknesses associated with systematic reviews and especially poor execution may render misleading results.
- Therefore, before implementing the results of systematic reviews clinicians should check whether the methodology applied was appropriate and whether the investigated population in the included clinical trials resembles the patient population they care for.

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