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What is a systematic review?

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- **Systematic reviews are superseding narrative reviews** as a way of summarising research evidence.
- Systematic reviews attempt to bring the **same level of rigour to reviewing research evidence** as should be used in **producing that research evidence** in the first place.
- High-quality systematic reviews take great care to **find all relevant studies** published and unpublished, **assess each study, synthesise the findings from individual studies in an unbiased way** and **present a balanced and impartial summary** of the findings with due consideration of any flaws in the evidence.
- **Many high-quality reviews are available** both in journals and from electronic sources such as the Cochrane Library.
- Not all published systematic reviews have been produced with meticulous care – therefore the **findings may sometimes mislead**. Interrogating published reports by asking **a series of questions can uncover deficiencies**.

Abbreviated prescribing information is on page 6

What are systematic reviews?

The need for reviews

The explosion in biomedical publishing in the latter half of the 20th century (perhaps 20,000 journals and upwards of 2 million articles a year) makes keeping up with primary research an impossible feat.

Moreover, clinicians, therapists and healthcare managers have wide-ranging information needs – that is, they need good information on the effectiveness of a large number of therapeutic interventions; not just one or two.

In even a single area it is not unusual for the number of published trials to run into dozens or even hundreds. Further, many of these studies will give unclear, confusing or downright contradictory results. Looked at individually, each trial may offer little insight into effectiveness; the hope is that, when taken together, a clearer (and more consistent) picture will emerge.

Failings in traditional reviews

Reviews have always been a part of the medical literature. Respected peer leaders, experts in their field, have sought to collate existing knowledge and publicise these summaries. Frequently such reviews have been about assessing the effectiveness (or otherwise) of therapeutic interventions.

Unfortunately, such attempts at synthesis have not always been as rigorous as might have been hoped. One obvious problem is that, traditionally, reviewers rarely began with an open mind as to the likely recommendations. Indeed, those involved in developing a review may well have started a review (or have been commissioned to write one) precisely because of their accumulated experience and professional opinions.

However, if strong prior beliefs are held then a dispassionate review of evidence will be difficult to achieve. At worst, a reviewer may simply build a case in support of their personal beliefs, selectively citing appropriate studies along the way. Even if the reviewer does begin with an open mind, traditional narrative reviews are rarely explicit about how studies are selected, assessed and integrated. Thus the reader is generally unable to assess the likelihood of prior beliefs or other biases clouding the review process.

For all this, such narrative reviews were and are widespread and influential.

The lack of rigour in the creation of reviews went largely unremarked until the late 1980s when several commentators exposed the inadequacies of the process and the consequent bias in recommendations.[1,2] Not least of the problems was that small but important effects were being missed, different reviewers were reaching different conclusions from the same research base and the findings reported often had more to do with the specialty of the reviewer than with the underlying evidence.[3]

The inadequacy of traditional reviews and the need for a rigorous systematic approach were emphasised in 1992 with the publication of two landmark papers.[4,5] In these Elliot Antman, Joseph Lau and colleagues reported two devastating findings:

- **First, that if original studies of the effects of clot busters after heart attacks had been systematically reviewed the benefits of therapy would have been apparent as early as the mid-1970s.**
- Second, Antman and Lau showed that **text books and narrative reviews were woefully inadequate in summarising the current state of knowledge**. These reviews either omitted mention of effective therapies or suggested that the treatments should be used only as part of an ongoing investigation – when in fact the evidence (if it had been collated) was near incontrovertible.

These papers showed that there was much knowledge to be gained from collating existing research, but that traditional approaches had largely failed to extract this knowledge. What was needed was the same rigour in secondary research (research where the objects of study

A review of only leading journals is likely to give an over-optimistic view of therapy effectiveness

are other research studies) as is expected from primary research (original trials).

When systematic reviews are needed

Systematic reviews are needed whenever there is a substantive therapeutic question, several primary studies – perhaps with disparate findings – and substantial uncertainty.

For example, the growing literature comparing the antithrombotic action of low molecular-weight heparins with unfractionated heparin[6,7] suggests that there may be some benefits in using the newer drugs. However, a recent narrative review[8] enumerated a number of unanswered therapeutic questions and sounded an important caveat: not all low molecular-weight heparins are the same. Here, then, is an area where a systematic review may help clarify matters; preparing one, however, is not a trivial exercise.

The process of systematic review

The need for rigour in the production of systematic reviews has led to the development of a formal process for their conduct. Understanding the approach taken and the attempts to minimise bias can help in the appraisal of published reviews.

Briefly, developing a systematic review requires the following steps:

1. Defining an appropriate therapeutic question. This requires a clear statement of the intervention of interest, relevant patient groups (and sometimes the settings where the intervention is administered), as well as appropriate outcomes. These details are used to select studies for inclusion in the review.

2. Searching the literature. The published and unpublished literature are carefully searched for all reports of controlled trials of this intervention (on the right patients, reporting the right outcomes and so on). For an ***unbiased*** assessment, this search must cover all the literature (not just Medline, where typically less than half of all trials will be found), including non-English sources. Further, studies reported only at conferences, in company reports or unreported and buried in filing cabinets must also be sought.

The concern is over ***publication bias***[9,10] – the notion that studies which report a positive effect of therapies are more likely to be reported in good English language journals than studies that report no effect. Thus a review of only leading journals is likely to give an overoptimistic view of therapy effectiveness.

3. Assessing the studies. Once all possible study reports have been identified, each study needs to be assessed for **eligibility** for inclusion, **study quality** and **reported findings**. Ideally, such assessment should involve two independent reviewers.

4. Combining the results. The findings from the individual studies must then be aggregated to produce a 'bottom line' on the clinical effectiveness of the intervention. Sometimes this aggregation is qualitative, but more usually it is a quantitative assessment using a technique known as meta-analysis (see ***What is meta-analysis?*** in this series).

5. Placing the findings in context. The findings from this aggregation of an unbiased selection of studies then need to be discussed to put them in context. This will address such issues as the quality and heterogeneity of the included studies, the likely impact of bias and chance and the applicability of the findings. Thus judgement and balance are not obviated by the rigour of systematic reviews – they are just reduced in impact and made more explicit.

Useful websites for systematic reviews

Systematic Reviews Training Unit
http://www.ich.ucl.ac.uk/srtu

Cochrane Collaboration
http://hiru.mcmaster.ca/cochrane/default.htm

NHS Centre for Reviews & Dissemination
http://www.york.ac.uk/inst/crd/welcome.htm

Centre for Evidence-Based Medicine at Oxford
http://cebm.jr2.ox.ac.uk/

Bandolier
http://www.jr2.ox.ac.uk/bandolier/index.html

A word of caution, however. Performing a rigorous systematic review is far from easy. It requires meticulous and laborious searching and considerable attention to methodological detail before it truly deserves the badge 'systematic'. Clear guidance on the process of developing systematic reviews is available[11,12] as are courses run at Oxford and other centres of excellence.

Finding existing reviews

High-quality systematic reviews are published in many of the leading journals. In addition, electronic publication by the Cochrane Collaboration, the NHS Centre for Reviews and Dissemination and others offers speedy access to regularly updated summaries (see Box, page 3).

Drawbacks of systematic reviews

Systematic reviews appear at the top of the 'hierarchy of evidence' (see Box, below). This reflects the fact that, when well conducted, they should give us the best possible estimate of any true effect. As noted previously, such confidence can sometimes be unwarranted, however, and caution must be exercised before accepting the veracity of any systematic review. A number of problems may arise:

- First, like any piece of research, **a systematic review may be done badly**. Attention to the questions listed in the section 'Appraising a systematic review' can help separate the rigorous research from the quick and slapdash.
- **Inappropriate aggregation of studies** that differ in terms of intervention used or patients included can lead to the **drowning of important effects.** For example, the effects seen in some subgroups may be concealed by a lack of effect (or even reverse effects) in other subgroups.
- The **findings from systematic reviews are not always in harmony with** the findings from **large-scale high-quality single trials**.[13,14] Thus findings from systematic reviews need to be weighed against perhaps conflicting evidence from other sources. Ideally, an updated review would deal with such anomalies.

Appraising a systematic review

Not all systematic reviews are rigorous and unbiased. The reader will want to interrogate any review that purports to be systematic to assess its limitations. The following questions provide a framework. Further guidance on appraising a systematic review can be found in several useful publications.[15–17]

- **Is the topic well defined** in terms of the intervention under scrutiny, the patients receiving the intervention (plus the settings in which it was received) and the outcome that was assessed?
- **Was the search for papers thorough?** Was the search strategy described? Was manual searching used as well as electronic databases? Were non-English sources searched? Was the 'grey literature' covered – for example, non-refereed journals, conference proceedings or unpublished company reports? What conclusions were

Hierarchies of evidence

I–1 Systematic review of several double-blind randomised control trials.

I–2 One or more large double-blind randomised control trials.

II–1 One or more well-conducted cohort studies.

II–2 One or more well-conducted case-control studies.

II–3 A dramatic uncontrolled experiment.

III Expert committee sitting in review; peer leader opinion.

IV Personal experience.

drawn about the possible impact of publication bias?

- **Were the criteria for inclusion of studies clearly described and fairly applied?** For example, were blinded or independent reviewers used?
- **Was study quality assessed by blinded or independent reviewers?** Were the findings related to study quality?
- **Was missing information sought from the original study investigators?** Was the impact of missing information assessed for its possible impact on the findings?
- **Do the included studies seem to indicate similar effects?** If not, was the heterogeneity of effect investigated, assessed and discussed?
- **Were the overall findings assessed for their robustness** in terms of the selective inclusion or exclusion of doubtful studies and the possibility of publication bias?
- **Was the play of chance assessed?** In particular, was the range of likely effect sizes presented and were null findings interpreted carefully? That is, a review that finds no evidence of effect may simply be an expression of our lack of knowledge rather than an assertion that the intervention is worthless.
- **Are the recommendations based firmly on the quality of the evidence presented?**

In their enthusiasm, reviewers can sometimes go beyond the evidence in drawing conclusions and making their recommendations.

Conclusion

All studies have flaws. It is not the mere presence of flaws that vitiates the findings. Even flawed studies may carry important information. The reader must exercise judgement in assessing whether individual flaws undermine the findings to such an extent that the conclusions are no longer adequately supported.

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What is a systematic review?

Abbreviated prescribing information: Clexane®

Presentation: Clear, colourless to pale yellow solution of 100mg enoxaparin sodium per 1mL (anti-factor Xa activity of 10,000IU/mL with reference to the WHO First International LMW Heparin Reference Standard). **Cartridges:** single dose prefilled syringes fitted into a cartridge containing either: 20mg enoxaparin sodium in 0.2mL (2,000IU) or 40mg enoxaparin sodium in 0.4mL (4,000IU) The cartridge is to be fitted into the Clexane® Auto-Injector. 100 mg/mL prefilled syringes: single dose prefilled syringes containing either: 20mg enoxaparin in 0.2mL (2,000IU) or 40mg enoxaparin in 0.4mL (4,000IU). **Indications:** Prophylaxis of thromboembolic disorders of venous origin, in particular those associated with orthopaedic or general surgery and in medical patients bedridden due to acute illness. **Dosage & Administration:** Patients with low to moderate risk of thromboembolism, eg general surgery, recommended dose of Clexane® is 20mg (2,000IU) once daily subcutaneously, the initial dose being given approximately 2 hours preoperatively. Patients with high risk of venous thromboembolism, eg orthopaedic surgery, the recommended dose is 40mg (4,000IU) once daily subcutaneously, the initial dose being given approximately 12 hours preoperatively. Clexane® should be continued for 7 to 10 days or until risk of thromboembolism has diminished. Medical patients bedridden due to acute illness, the recommended dose is 40mg (4,000IU) once daily for a minimum of 6 days until return to full ambulation, for a maximum of 14 days. ***Elderly:*** No dosage adjustment necessary. ***Children:*** Not recommended. Contraindications: Acute bacterial endocarditis, major bleeding disorders, thrombocytopenia in patients with positive *in-vitro* aggregation test in presence of Clexane®, active gastric/duodenal ulcer, hypersensitivity to enoxaparin, stroke (unless due to systemic emboli) and other patients with increased risk of haemorrhage. **Warning:** Clexane® must not be administered by the intramuscular route. **Precautions:** Clexane® should be used with care in hepatic insufficiency, history of thrombocytopenia, and conditions with increased bleeding potential. Different low molecular weight heparins may not be equivalent; alternative products should not be substituted during therapy. Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia. **Pregnancy:** Clexane® should not be used during pregnancy unless no safer alternative is found. **Lactation:** Advise avoidance of breast-feeding. **Interactions:** Care in patients receiving agents affecting haemostasis, eg oral anticoagulants, thrombolytics, systemic glucocorticoids, NSAIDs, aspirin. **Adverse Reactions:** Bleeding in the presence of associated risk factors, rarely retroperitoneal and intracranial bleeding. Rarely thrombocytopenia, liver abnormalities (eg transaminases and alkaline phosphatase changes), allergic reactions. At site of injection: pain, haematoma, irritation, rarely hard inflammatory nodules and skin necrosis. Osteoporosis has not been reported with Clexane® but the risk cannot be excluded. Heparins can cause increase in plasma potassium, and rarely, clinically significant hyperkalaemia. Rare reports of intra-spinal haematoma when using spinal/epidural anaesthesia and post-operative indwelling catheter. **Pharmaceutical Precautions:** Do not mix with other injections or infusions. Clexane® cartridges: store at or below 25°C. Do not freeze cartridges. Prefilled syringes: do not store above 25oC. Do not refrigerate or freeze.

Legal Category: POM; Clexane® cartridges PL 0012/0336, Clexane® 100 mg/mL prefilled syringes PL 0012/0196. **Basic NHS cost for 10 cartridges:** 20mg – £47.90, 40mg – £60.79. **Basic NHS cost for 10 prefilled syringes:** 20mg – £33.89, 40mg – £45.16.

Full Prescribing Information and further information is available on request from Aventis Pharma, 50 Kings Hill Avenue, West Malling, Kent. ME19 4AH. **Date of preparation:** June 2000. ® denotes a Registered Trade Mark

This publication, along with the others in the series, is available on the internet at www.evidence-based-medicine.co.uk

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