

Update 32

Questions Concerning Evidence-based Health Care's Hierarchy of Evidence

The widely accepted hierarchy of evidence, that underlies Evidence-based Health Care (EBHC), looks like this -

- Meta-analyses of RCTs
- RCTs
- Cohort studies
- Case-control studies
- Case series
- Expert opinion
- In vitro and animal studies

However, some studies published in the last few years (1,2), which identified non-significant differences in results between randomized, controlled trials, and observational studies, have challenged the veracity of the notion that observational studies find stronger treatment effects than RCTs.

Benson and Hartz (1) examined 136 reports about 19 diverse treatments, such as calcium-channel-blocker therapy for coronary artery disease, appendectomy, and interventions for subfertility. In most cases they found that the estimates of the treatment effects from observational studies and randomized, controlled trials were similar. In only 2 of the 19 analyses of treatment effects did the combined magnitude of the effect in observational studies lie outside the 95 percent confidence interval for the combined magnitude in the randomized, controlled trials. Similarly, Concato et al. (2) found, for five clinical topics and 99 reports evaluated, that the average results of the observational studies were remarkably similar to those of the randomized, controlled trials. Those authors concluded that, "The results of well-designed observational studies (with either a cohort or a case-control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic."

As a result there has been substantial debate about whether the results of non-randomized studies are consistent with the results of randomized controlled trials on the same topic. Both the above studies (1,2) have been criticized for their limited selection of articles, methods, and conclusions (3). Furthermore, it has been suggested that neither report contains sufficient detail for readers to analyse the data and draw one's own conclusions.

Others have found support for the present hierarchy. The objective of one study (4) was to compare the results of randomized trials and observational studies of interventions to prevent adolescent pregnancy. Those authors identified 13 randomized trials and 17 observational studies that were relevant to the topic at hand. They generated estimates of the impact of the interventions separately for males and females for all four outcomes for both observational studies and randomized trials. For six of the eight outcomes the summary odds ratios for the observational studies showed a significant intervention benefit ($P < 0.05$) while the randomized trials did not show a benefit for any outcome in either females or males. The difference between the results of the observational studies and randomized trials was statistically significant in two of the eight outcomes ($P < 0.05$ for initiation of intercourse and pregnancy in females). The authors concluded that, "Observational studies yield systematically greater estimates of treatment effects than randomized trials of adolescent pregnancy prevention interventions."

More recently, researchers from the Division of Clinical Care Research, New England Medical Center, published a review (5) in which they identified 45 diverse topics for which both randomized trials ($n = 240$) and nonrandomized studies ($n = 168$) had been performed and had been considered in meta-analyses of binary outcomes. Very good correlation was observed between the summary odds ratios of randomized and nonrandomized studies ($r = 0.75$; $P < .001$); however, nonrandomized

studies tended to show larger treatment effects (28 vs 11; $P = .009$). The authors state, "Despite good correlation between randomized trials and nonrandomized studies-in particular, prospective studies-discrepancies beyond chance do occur and differences in estimated magnitude of treatment effect are very common."

Adding to the confusion is the fact that Gordon Guyatt, a leading proponent of EBHC, and others recently proposed a hierarchy of strength of evidence of treatment decisions with the N of 1 randomized trial at its pinnacle. Three weeks ago I attended lectures and workshops lead by Gordon Guyatt at the 11th Cochrane Colloquium here in Europe, and Guyatt justified his beliefs regarding the importance of N of 1 RCTs with comments like the following which are taken from one of his textbooks (6) -

The philosophy of EBHC suggests that clinicians should use the results of RCTs of groups of patients to guide their clinical care. When deciding which management approach will be best for an individual patient, however, clinicians cannot always rely on the results of RCTs. An RCT addressing a particular issue may not be available. Furthermore, even when a relevant RCT generates a clear answer, its results may not apply to an individual patient. In short, just because a treatment showed a positive effect in a group of other patients does not mean that the patient before us will benefit. Under these circumstances, clinicians typically conduct the time- honoured trial of therapy, in which the patient receives a treatment and the subsequent clinical course determines whether the treatment is judged effective. However, many factors may mislead us in conducting conventional therapeutic trials. To maintain the methodologic safeguards provided by RCTs and to determine the best care for an individual patient, RCT's in individual patients (N of 1 RCTs) build on the work of experimental psychologists with single-case or single-subject research.

The clinical usefulness of N of 1 RCTs is born out of the fact the conventional EBHC is concerned with what happens on average, whilst clinicians and their patients want to know what is going to happen in a particular case.

References:

1. Benson K, Hartz AJ. A comparison of observational studies and randomised, controlled trials. *N Eng J Med.* 2000; 342:1878-86.
2. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research design. *N Eng J Med.* 2000; 342:1887-92.
3. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Eng J Med.* 2000; 342:1907-09.
4. Guyatt GH, DiCenso A, Farewell V, Willan A, Griffith L. Randomized trials versus observational studies in adolescent pregnancy prevention. *J Clin Epidemiol.* 2000; 53:167-74.
5. Ioannidis JP, Haidich AB, Pappa M, Pantazis N, Kokori SI, Tektonidou MG, Contopoulos-Ioannidis DG, Lau J. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA.* 2001; 286:821-30.
6. Guyatt G, Rennie D. *Users' guides to the medical literature - a manual for evidence-based clinical practice.* Chicago, IL: American Medical Association, 2002. pp. 275-90.