Have You Ever Meta-Analysis You Didn't Like?

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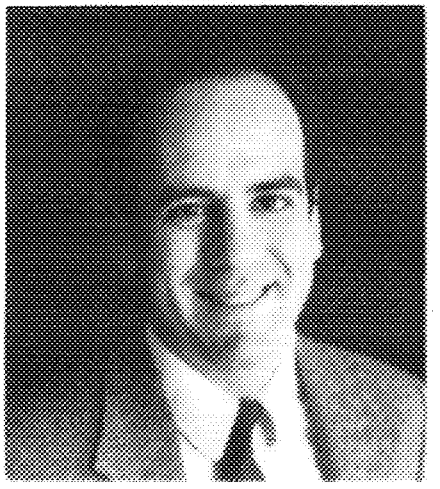
ABSTRACT

Meta-analyses and their proper place in medical literature are explained along with how they differ from traditional literature reviews. Both the qualitative and quantitative aspects of meta-analysis are considered in relation to studying the results of clinical trials.

This issue [1 February 1991] includes a meta-analysis of the use of steroids in treating chronic obstructive pulmonary disease.[1] Meta-analyses such as this one command our attention, both because they purport to provide a "definitive" answer to a clinical question that has eluded other researchers and because the work of those researchers, the grist for the meta-analytic mill, is often subject to embarrassingly intense scrutiny. They represent a new class of article, one that straddles the traditional boundaries between original research and review articles. Because meta-analysis is a relatively new and partially technical method, many physicians find themselves unable to appreciate the nuances or limitations of meta-analyses in the same way that they can appreciate those of a traditional review or original research article. Meta-analyses therefore are sometimes distrusted by physicians who do not understand the statistical techniques and resented by researchers who do not like seeing their years of effort rapidly reduced to an "effect size," with the consequent elevation of the meta-analyst to an expert in the field. These tensions have provoked controversy[2-4] as well as attention from the lay press.[5]

The term "meta-analysis" was coined in 1976 by Glass[6] in the psychology literature,



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and texts on the subject appeared in the 1980s.[7,8] The field is rapidly evolving, with the annual number of such analyses in the general medical literature increasing exponentially; the *meta*-meta-analysis, evaluating the quality of meta-analyses themselves, also has been developed.[9-11]

What are meta-analyses, and what is their proper place in medical research? This question is best answered by examining the ways

in which they differ from traditional reviews. First, meta-analyses tend to be more narrowly focused than reviews—they usually examine a single clinical question, which may relate to treatment, causation, or the accuracy of a diagnostic test. Second, they have a strong quantitative component—they attempt to pool the quantitative results of several studies to give a more precise estimate of effect than would the results of any of the component studies, while still remaining clinically meaningful and statistically valid. Meta-analyses are done when there seems to be a disparity among several studies' results or when there may be an important main or subgroup effect that is too small to be measured accurately in individual trials.

The initial phase of a meta-analysis is qualitative, with an eye toward minimizing the bias arising from study design. In the report of a meta-analysis, the research question first must be posed, with no less thorough a biologic discussion than would appear in a traditional review. Meta-analysts then must comb the scientific literature comprehensively and systematically to find studies that address the question; choose an outcome variable that can be assessed from each study; pare the list to those studies that use comparable interventions and outcomes; examine the differences in patients, protocols, and confounding variables within that list; assess the "quality of information" provided by each study; and decide how to adjust for and summarize each of these many differences. Why the combination of studies with possibly different patients, interventions, and even outcomes would have clinical or biologic meaning must be clearly explained. This qualitative component of meta-analysis, usually its most useful contribution, is also the component that is most likely to be inadequate.

The quantitative part of a meta-analysis starts with an effort to ensure that the trials are similar enough so their results can be combined; that is, a statistical "test of homogeneity." The oft-repeated notion that meta-analysis can resolve "conflicting" trial results is not really true; if, with a test of homogeneity, the disparity among trial results is judged to be too great to have arisen by chance, the trial results should not be pooled. Instead, why they differ should be explained. Only fairly dramatic differences among trial outcomes, however, will result in a statistical verdict of heterogeneity if just a few trials are tested, regardless of their size. The failure to find such heterogeneity thus does not absolve the researcher from justifying biologically, by carefully examining individual trials, why the trials are combinable. As Greenland[12] noted, "...causal explanation of similarities and differences among study results is...outside the realm of statistical meta-analysis...the statistics serve as no more than a fallible pattern-recognition device, and explanation of the origin of observed patterns is beyond the scope of the device."

The next step in reporting a meta-analysis is giving a sense of what is being combined. The individual study results (with their variability) must be displayed—preferably graphically—so that even a technically unsophisticated reader can understand the essence of the studies at a glance. Callahan and associates[1] accomplish this goal by displaying effect size as a function of study sample size. Graphs showing confidence intervals for each study, perhaps with studies organized into important subgroups (for example, by study design or patient characteristics), convey this information best.

The stage is now set to do the statistical pooling, which involves not only summarizing all of the information in the studies into one number, but also examining the sensitivity of the summary result to various biologic and methodologic assumptions. Such examining is done to explore the possibility that there are identifiable subgroups of patients or studies with different responses. Callahan and colleagues[1] looked for subgroups by plotting outcome against various study characteristics. They provided one of these graphs in their report, that of treatment effect, plotted against initial forced expiratory volume in 1 second, grouped by study eligibility criteria.

Unfortunately, the ease with which pooled estimates can be calculated has resulted in a torrent of meta-analyses in which the purely quantitative components dominate. Some observers are concerned, "that the study of

previous studies is being reduced to a routinized task of coding relegated to a research assistant, upping output per author-month by suppressing any role for wisdom."[2] The expectation that meta-analyses should provide "definitive results," instead of a synthesis of existing knowledge, exacerbates this problem.

A meta-analytic summary may not always be the most useful number for clinicians. When treating Ms. Jones, the clinician may want to focus on the single trial or subset of trials conducted in patients most like Ms. Jones. The initial qualitative component of a meta-analysis should present enough information about the patients and interventions in each study so that the clinician can examine the most relevant trial or trials. For example, Callahan and colleagues[1] provide such information in their Table 3. Less commonly used meta-analytic techniques focus not on pooling trial results, but on modifying individual trial estimates on the basis of the spectrum of results.[13,14] These techniques should be used more frequently.

Regardless of the summary number, meta-analysis should shed light on why trial results differ; raise research and editorial standards by calling attention to the strengths and weaknesses of the body of research in an area; and give the practitioner an objective view of the research literature, unaffected by the sometimes distorting lens of individual experience and personal preference that can affect a less structured review. The best meta-analyses knit clinical insight with quantitative results in a way that enhances both. They should combine the careful thought and synthesis of a good review with the scientific rigor of a good experiment. When a sufficient number of similar studies address a topic, a meta-analysis can move us closer to a quantitative "truth"; however, the computing of weighted averages is a comparatively small part of the process and should not be seen as its most important contribution.

With these caveats, *Annals* welcomes meta-analyses as quantitative reviews. We look for those that address important clinical questions, integrate biology and numbers in plausible and creative ways, and use statistics to clarify, not to obfuscate. These are standards that do not reside in equations and that few meta-analyses meet. We trust that our contributors will rise to the challenge.

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