Editorial

Combining Evidence From Clinical Trials

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The pooling of results from a series of clinical trials to evaluate the efficacy of a certain treatment for a specified medical condition is an attractive approach, one that is becoming increasingly popular in medical research. The approach is especially advantageous in clinical research where information on efficacy of a treatment is available from a number of different studies with similar protocols, each of which taken separately may either be too small or too limited in scope to come to generalizable conclusions about the effect of treatment. Combining the findings across such studies represents an attractive alternative for strengthening the evidence about the treatment efficacy. The report in this issue by Pace on "Prevention of Succinylcholine Myalgias: A Meta-Analysis" (1) underscores the attractiveness as well as the popularity of the approach in clinical research.

Meta-analysis is a general term to describe the statistical analysis of a collection of analytic results for the purpose of integrating the findings. Pace utilizes one such meta-analytic technique, a random-effects model, to pool the results from 45 clinical trials to evaluate the efficacy of several drug regimens for the prevention of myalgias after succinylcholine therapy. Considered separately, the individual trials yield inconsistent conclusions: some studies imply a positive treatment effect; others indicate no effect. Summarizing the evidence in a random-effects model, Pace concludes that all but one of the drug regimens are prophylactic for myalgias.

The use of a random-effects model to summarize the findings from a series of experiments is not new, and examples of the method's application are available from many areas of research including agriculture, education, and medicine (2–4). In clinical research, the basic idea of the random-effects approach is to parcel out some measure of the observed treatment effect into two independent and additive components, θ_i and e_i. θ_i is the "true" treatment effect, the quantity of interest attributable to treatment in the ith trial, and e_i is the sampling error. In the review of the trials for myalgias prevention, Pace considers the model where the treatment-effect measure is the risk difference. Other effect measures, such as the risk ratio or the relative odds, can be similarly considered.

The true treatment effect associated with the ith trial, θ_i, will be influenced by several factors, including patient characteristics and design and execution of the trial. To account explicitly for the variation in the true effects, the random-effects model assumes θ_i is the sum of μ and δ_i. Here, μ is the mean effect for a population of possible treatment evaluations (which we would like to make inferences about) and δ_i is the deviation of the ith study's true effect from the population mean. The population variance, $\text{var}(\delta) = \tau^2$, represents both the degree to which treatment effects vary across experiments and the degree to which individual trials give biased assessments of treatment effects. Regarding the trials at hand as a sample from this population of treatment evaluations, we can use the observed effects to estimate μ as well as τ^2. DerSimonian and Laird present simple noniterative estimators for the relevant parameters in this setting (5).

For the myalgias prevention study, the estimates of μ and τ^2 suggest generally positive treatment effects as well as large population variance (heterogeneity of effects). The phenomenon of treatment-effect heterogeneity (even across carefully controlled ran-

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domized studies) is not uncommon and has been previously noted (5). Unless it is negligible, this heterogeneity should be accounted for and incorporated into the analysis of the overall efficacy of the treatment. The random-effects model allows us to quantify the degree to which the treatment effects vary across the trials and to incorporate this variation, however small, into the analysis. The method is approximate, and, in reality, the model assumptions may not completely hold. Nevertheless, the random-effects approach to meta-analysis of clinical trials is useful both in summarizing the data and in characterizing the distribution of treatment effects in a series of studies.

To allow for more specific therapeutic recommendations, it is clearly preferable to reduce the heterogeneity of treatment effects. If the effect of treatment depends on patient characteristics, τ^2 will naturally be large if the studies included different types of patients. In principle, we can extend the simple random-effects model to include pertinent covariates, and the corresponding τ^2 will be reduced. This is often difficult in practice, however, because relevant covariate information may be missing for some trials (as it is in the myalgias prevention study). Improvement in standards for medical data gathering/reporting and further development of methods for handling missing covariate information are needed to strengthen our ability to combine results from clinical studies.

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