A Word From Our Moderator

To the Editor: In their Commentary, Dr Kraemer and colleagues[1] draw attention to the importance of moderators of treatment outcomes, the often unsatisfactory way these are dealt with (if at all) in randomized clinical trials (RCTs), and the potentially serious consequences of this neglect on patient care. They propose that every RCT should include a search for putative moderators of treatment outcome. Although acknowledging that positive results of such analyses rarely provide proof of the existence of these moderators, they stress that the importance resides in the hypotheses that the analyses generate. These hypotheses can then be tested in subsequent adequately powered and populated RCTs. However, it may take years to design, acquire adequate funding for, and execute such an RCT.

As an alternative, conducting N-of-1 trials[2] can be valuable to further investigate information on moderators of treatment outcome. As a hypothetical example, suppose an RCT had been conducted to test the efficacy of drug treatment of primary Raynaud phenomenon, that no overall benefit of the drug had been found, but analysis of putative moderators of treatment outcome had suggested that women might respond favorably, although this result was not statistically significant. Women with Raynaud phenomenon could then be included in N-of-1 trials, in which they would be treated in a double-blind crossover design with multiple treatment pairs with either the drug or a placebo in random order.[2] The presence or absence of differences in symptom scores during treatment would then prove or disprove the effectiveness of this drug for the patient.

Pooling the results of all of these N-of-1 trials may substantiate that sex is a moderator of treatment outcome.[3] Moreover, comparison of responders and nonresponders in these N-of-1 trials may be used to identify additional moderators of treatment outcome. This approach may obviate the need for RCTs, which would be a great boon in the case of rare chronic diseases. It has an additional advantage in that daily patient care can be integrated with clinical research.

N-of-1 trials have their own limitations. They are not applicable to surgical or acute medical conditions. However, for chronic medical conditions, they may be invaluable in the quest for "tailored therapy," one of the holy grails of clinical medicine.

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To the Editor: In their Commentary, Dr Kraemer and colleagues[1] raise the important issue of exploring moderators of treatment outcome in randomized trials. I agree that reliance on the *P* value for hypothesis testing has limited value for clinicians who need to decide if a treatment is appropriate for a particular patient. There are also 2 other points to consider.

First, the hypothesis-generating exercise that the authors promote may be valuable. However, I believe it must be accompanied by a rational discussion of possible mechanisms based on known or potential mechanisms from observational and basic science studies. If the hypotheses are supported by these data, there is a greater probability that the hypotheses will be supported by future research. In addition, the process may help future researchers design the most appropriate studies by avoiding confounding and by examining the appropriate interactions through restricted inclusion/exclusion criteria or stratification.

Second, although the focus of the Commentary is the patient-centered question, "Would this treatment elicit a better response than the control for me in particular?" the clinician and patient actually have a more difficult task. They must choose the most appropriate treatment for a particular patient from a variety of options, and simply knowing that one treatment is effective has limited value. Because of resource and time limitations, it is unreasonable to expect that each new treatment be compared with every other treatment for a condition. A traditional meta-analysis is not much of an improvement because it requires a single comparison group across all studies.

Although it is possible to qualitatively compare across different comparison groups in a systematic review, meta-analytic methods have been developed whereby different studies use different comparison groups (mixed-treatment or multitreatment meta-analysis).[2-5] With these methods, an investigator combines information from studies comparing treatment A with treatment B with studies that compare treatment B with treatment C (and so on) to obtain estimates of relative effectiveness across all the different treatments. I believe these types of meta-analyses will become more prevalent in the near future.

A mixed-treatment meta-analysis alone does not resolve the issues raised by Kraemer et al; therefore, both methods are required to provide the best treatment for individual patients.

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In Reply: The comments by Drs Deinum and van der Wilt and by Dr Shrier focus on the important question: Once a moderator is found in exploration, what comes next? Both letters propose interesting and potentially viable strategies.

Drs Deinum and van der Wilt propose N-of-1 trials followed up by pooling of the results. Every clinician making treatment decisions for a patient is, in effect, doing an N-of-1 trial, first formulating a hypothesis of what is wrong and what might make it right, testing it, and if the evidence does not support the original hypothesis, reformulating the hypothesis and starting over again. Unfortunately, we cannot generalize results from any such trial or pool multiple N-of-1 trials unless there is consistency in the design.

The research version is a crossover design, in which each patient in a sample is assigned to the 2 treatment groups to be compared in random or counterbalanced order. In theory, this design should yield more power to detect treatment effects and be more clinically informative. However, the basic assumption underlying this design is absence of carryover effects (ie, the response to whatever treatment is given second is not affected by whatever treatment is given first).[1-3] Even with washout periods much longer than the half-life of drugs, there are often carryover effects of drugs, and psychotherapeutic or educational interventions cannot be "washed out." Where there are no carryover effects, we agree that such designs are preferable to the parallel-groups design on which we focused.

Dr Shrier proposes a mixed-treatment meta analysis, in which studies comparing treatment A vs treatment B, and treatment B vs treatment C, and so on are combined to estimate the indirect effect size of A vs C. The difficulty here is that even with multiple studies, all of which compare A vs B, the sampled populations rarely have exactly the same characteristics, treatment delivery, duration of treatment, length of follow-up, or (most important) reported outcome measure. This has caused problems in traditional meta-analyses[4,5] and is likely to be even more problematic with indirect effect size estimation.

However, we agree with Dr Shrier on the importance of such pooled analyses of independent studies and would like to push his suggestion a bit further. Many of the problems of meta-analysis could be overcome if it were mandated that when the report of an RCT is published, the data on which that report is based be made available to other qualified researchers for reanalysis. The person performing the meta-analysis could then subsample to generate comparable samples if necessary, verify any assumptions made, compute whatever effect size is most appropriate along with its confidence interval, and optimally combine results over studies. Because RCT studies typically include descriptors of age, sex, ethnicity, and other pertinent baseline characteristics, moderator analyses could then be performed for studies in which they had not been performed, and such moderator analyses could be combined across multiple independent studies.

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Psychosocial Aspects of HIV Treatment

To the Editor: In their Special Communication on the treatment of adult human immunodeficiency virus (HIV) infection, Dr Hammer and colleagues[1] did not mention the significant psychosocial aspects of this disease. Evaluation and management of psychiatric, neuropsychiatric, and substance abuse problems is essential in the successful treatment of HIV/AIDS. Recognizing the mental health-related manifestations of HIV is often complicated by the complex interaction of psychosocial and biological factors. A wide spectrum of psychiatric disorders has been associated with HIV: mood, anxiety, cognitive, psychotic, personality, sleep, sexual, and substance use disorders.[2] Estimates of lifetime and past-year prevalence of psychiatric disorders in individuals with HIV/AIDS are as high as 68% to 89%.[3] The percentage of HIV-positive patients with any cognitive impairment during the course of their illness is 38.8% to 54.4% overall, and for those meeting full criteria for dementia is 10.4% to 25.2%.[4]

It is arguable whether the high prevalence of psychiatric disorders among HIV-positive persons is due to high rates of preexisting illness or increased risk for HIV infection among those with mental illness. Some propose that anxiety, depression, and suicidal ideation may be a response to patients learning their seropositive status