

Editorial: Where have all the clinical trials gone?

Like many forums in the clinical sciences, the *JCPP* typically presents more results from observational than experimental-therapeutic studies. Indeed, the current edition of the *Journal* contains nary a single clinical trial. A similar trend in many mental health journals reflects the general dearth of research on therapeutics. Results from observational studies, no matter how rigorously executed, generate more definitive conclusions concerning mechanisms of disease when the results are extended in experimental studies. Experimental studies often are better suited than observational studies for demonstrating causal relationships among variables and disorders. Thus, scientists, policy-makers, clinicians, and families all must explicitly foster research on experimental therapeutics if advances are to occur at a reasonable pace.

Because research on experimental therapeutics is extremely difficult and costly, one can reasonably ask if the effort required is too great. Might we learn just as much from observational studies that assess changes in symptoms longitudinally following potentially harmful or therapeutic events? Clearly, observational studies provide crucial insights concerning mechanisms that produce mental illness. Yet, such studies should not be conducted in isolation. Rather, they should lay the groundwork for randomized controlled trials that can be used to provide more definitive tests of mechanistic hypotheses.

Results from three articles in this edition of *JCPP* illustrate the manner in which high-quality observational studies generate hypotheses that can be definitively tested through experimental designs. Each article uses novel, state-of-the-art methodology, including careful observation, to demonstrate an association between a modifiable risk factor and an adverse psychiatric outcome in youth. Each article could generate potentially provocative conclusions, moving the field towards specific treatment recommendations targeting potentially modifiable risk factors. However, because the studies are observational rather than experimental in nature, any such recommendations must be tempered. Experimental work provides a particularly sound means for gauging risk/benefit ratios of specific recommendations and for drawing strong conclusions about causal mechanisms. All three papers are appropriately cautious about the limitations of observational methods for drawing conclusions about causality. Nevertheless, the point is worth emphasizing: interventions delivered in the community before data accrue from clinical trials could carry potential unintended consequences. As discussed below, such consequences could result if the relationship between a risk factor and disorder is not causal or involves an unanticipated mechanism. Not only does a randomized controlled design allow valid inferences to be drawn concerning mechanisms, but this design also provides information directly relevant to families about the risk-benefit ratios of particular interventions. Two specific areas are relevant to this month's edition.

In the first area, as the latest part of an elegant series of observational studies, Endresen and Olweus suggest that participation in 'power' sports enhances antisocial behavior in adolescent boys, while also surmising that quitting power sports actually may lead to a lowering of antisocial

involvement. As with prior papers from Olweus, this report provides a carefully crafted argument, based on a reasonably large, longitudinally followed, community-based cohort. The authors argue persuasively for a causal relationship between sports participation and antisocial behavior, though they appropriately fall short of providing practical recommendations. For example, the association could be driven by third factors that influence both a predilection to participate in particular sports and a tendency to behave violently. A premature recommendation to limit participation in some forms of athletics could have significant negative effects, if aspects of participation in power sports also served beneficial purposes. Offord and colleagues (1998) have in fact suggested that at least some forms of physical contact sports may actually provide specific mental health benefits to children. Clearly, a randomized control trial could provide useful information about changes in specific aspects of sports participation that might yield a favorable risk-benefit profile. For example, one might consider a study that randomly assigns children to an active intervention condition, which encourages participation in specific non-power sports while discouraging participation in power sports. In the absence of data from such studies, caution is needed when making inferences concerning causality or making recommendations concerning youth sporting activities.

It should be noted that not all clinical scientists agree about the value of the clinical trial in these and related circumstances of common potentially risky exposures, such as 'power' sports in this instance. Beyond the difficulty and cost of completing such work, randomized clinical trials have their own set of methodological limitations. For example, one can only generate data for subjects who are willing to be randomized to one or another experimental condition. Since some suitable subjects surely will be unwilling to undergo treatment or remain in a clinical trial, biases are likely to emerge concerning the populations to which the results will generalize. Moreover, in other areas of medicine, appropriate conclusions concerning causality have been drawn in the absence of data from randomized controlled trials. This typically has occurred when a series of independently performed observational studies demonstrates large, dose-response associations using longitudinal designs, sometimes conducted in an area where a randomized design either would be unethical or infeasible. The association between cigarette smoking and lung cancer may represent a particularly cogent example. The association between social adversity and behavior problems may be emerging as another relevant example from the field of developmental psychopathology (Costello, Compton, Keeler, & Angold, 2003). Nevertheless, these important observations should not be used as a justification for eschewing the randomized controlled trial in circumstance where it is feasible to implement such studies. Clinical recommendations in developmental psychopathology clearly would benefit from a more extensive basis of support in carefully conducted randomized controlled trials.

In the second area, both Cummings et al. and Burt et al. describe associations among parental depressive

symptoms, aspects of the home environment, and developmental psychopathology. These reports extend many prior studies emphasizing a role for both genetic and environmental factors in the link between parental depression and childhood mood or anxiety disorders. Results from the current studies suggest that marital conflict and other aspects of parental behavior at least partially mediate the relationship between parental depression and child psychopathology. Moreover, both articles suggest the possibility of causal relationships between such potentially modifiable parental behaviors and childhood symptoms. Nevertheless, like the prior study linking sports participation to antisocial behavior, these observational studies do not demonstrate causality: third factors could account for the observed association among the environment, parent-, and child-psychopathology. Thus, caution is urged before recommending that parents with depression adopt specific, alternative child-rearing practices. Not only is it time consuming and difficult for parents with depression to actively alter their behavior, but implicating parenting behavior in the causes of childhood depression or other psychopathology sends the message to parents that they are responsible for their children's suffering. We have seen the toll that such messages can take. Parents in the past endured needless guilt and pain due to inappropriate attributions of autism and schizophrenia to parental rearing practices. One must not draw these inferences lightly. Of course, this is not to minimize the clear benefits of working with parents therapeutically to change their behaviors so that their children might benefit. Rather, clinicians should remember that they stand on the firmest scientific grounds when they work with parents to change their behavior in ways that accord with data from randomized controlled trials demonstrating the specific benefits of changing specific parenting behaviors.

Future randomized controlled trials could provide crucial guidance for clinicians and parents with depression so that they might most effectively work to build a health-promoting environment for children. Such a trial might attempt to alter specific, relatively narrow aspects of parenting behavior presumed to mediate the link between parental depression and childhood psychopathology. For example, findings in Burt et al. might encourage a study that randomly assigns families with male children at high risk for depression to interventions that foster stimulation, social involvement, and positive emotional factors in the home environment. This would facilitate attempts to properly weigh the advantages and disadvantages of encouraging specific parenting behaviors directed towards at-risk children. If such a study could demonstrate a desirable risk-benefit ratio, both clinicians and parents could approach the difficult task of changing parenting behavior with a clear sense of the payoffs for children.

Given the obvious importance of this research, one could reasonably ask why so few randomized controlled trials appear in the very best mental health journals, including the *JCPP*. First and foremost, this is because very few randomized controlled trials are submitted for review. The *Journal* places research on novel therapeutics at the highest level of priority, and the editors look forward to the day when more randomized controlled trials might be submitted. While the *Journal* is eager to publish reports on experimental therapeutics, such research is difficult and

presents truly unique conundrums. The financial cost of research is tremendous. Moreover, due at least partially to the stigma of mental illness, families are hesitant to participate in clinical trials. Even when families are willing to participate in such research, they often view the possibility of randomization to placebo or an undesired treatment with considerable trepidation. While these factors complicate studies in adults as well as children, families appear particularly uneasy with the potential for stigma and adverse treatment reactions in children, given their vulnerable status as minors. Yet, randomization remains an essential feature of rigorous treatment studies, since randomized controlled trials provide a particularly sound means for drawing definitive conclusions concerning causal relationships in the clinical sciences. Finally, such a call for randomized controlled trials is not meant to imply that observational studies are unnecessary. Research on novel treatment benefits greatly from observational data. By documenting the range of relationships among the many potential intervention targets and disorder outcomes, observational studies facilitate the implementation of particularly sound experimental therapeutic research. Rather, a call for more research on therapeutics is meant to encourage a more balanced mix of research than extant currently in the field. The hope is that we might reach understandings of mental illnesses that reflect an equally strong grounding in observational and experimental therapeutic research.

Considerable effort will be required before advances accrue in research on experimental therapeutics. My hope would be that the interest generated from observational reports such as those by Endresen and Olweus, by Cummings et al., and by Burt et al. will be channeled into research on therapeutics. Given the difficulty of implementing such research in the most rigorous fashion, I fear that the work will require concerted, focused efforts by scientists, clinicians, and advocates alike. Perhaps an important first step involves an explicit 'taking-stock' of this need. This might allow research that translates results from observational studies into clinical trials to assume its rightful place as the major driving force that informs clinical practice.

The opinions and assertions contained in this paper are the private views of the author and are not construed as official or as reflecting the views of the NIMH or the Department of Health and Human Services.

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References

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