THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 6, Number 1, 2000, pp. 31–35
Mary Ann Liebert, Inc.

# Commentary on Schoenthaler et al.: Vitamin and Mineral Supplements—Is the Methodology Sufficient to Support the Conclusions?

WENDY B. SMITH, Ph.D.

A number of articles on the effects of vitamin and mineral supplementation have appeared throughout the literature (Benton and Buts, 1990; Benton and Cook, 1991; Benton and Roberts, 1988; Crombie et al., 1990b; Schoenthaler et al., 1991a, 1991b). Recently, this journal published a number of articles focusing on the effects of supplements on a variety of outcome measures. In reviewing these, several issues have been raised that are not only relevant to these articles, but may also reflect methodologic issues common throughout the field.

Analysis of vitamin and mineral supplementation is different from many other areas within complementary and alternative medicine in that it lends itself naturally to study using conventional Western research methodologies. Conventional Western research methodologies are not necessarily the most appropriate ways to study a variety of medical and psychological phenomena, but appear to be well suited to this application. The authors of the preceding articles in this issue of the journal (Schoenthaler et al.; Schoenthaler and Bier) have based their investigation on a conventional biomedical Western approach and have incorporated some effective elements of these research methodologies. Although their design improves on earlier work in this topic, several issues and concerns remain and need to be addressed in order to advance our understanding of the effects of supplementation as well as to support the conclusions drawn by these authors.

First, these authors should be commended for their clear devotion to this topic and their efforts to increase knowledge in the field of nutrition. They continue to strive to improve their own work as well as that of others. These articles review the limited literature in this specific area, note strengths and weaknesses in design and analysis, and present an improved study designed to address these issues. The authors attempt to clarify the knowledge in an area in which diverse study designs have made definitive conclusions elusive. These two articles add to the literature by virtue of their research design and detail in reporting. They have used a sophisticated sampling procedure and analysis in an attempt to control for the effect of possible extraneous variables on their outcome measures. In particular, the application of a covariance analysis greatly improves on previous work in this area.

Their randomized control procedure is further enhanced by the addition of a blindedness assessment; that is, they evaluated subjects' ratings of whether they were given active supplements or placebos. This is especially important where strong beliefs and expectations, by both participants and researchers, exist. The authors have also attempted to consider the validity of their assessment tools: the use of one of the measurement instruments in a different language is addressed in detail. And finally, these articles demonstrate the importance of including methodologic detail. Evaluation, interpretation, and replication are difficult, if not impossible, without specific details of the in-

National Institutes of Health, Bethesda, Maryland.

tervention. Fortunately, these authors have provided complete descriptions of the components of the supplements used in their research, which will facilitate its future replication.

Although these articles include aspects that improve the quality of the research in this area, they also demonstrate some of the problems inherent in research on supplements as well as in research in general in complementary and alternative medicine. The absence of a firm theoretic foundation, additional unelucidated research design limitations, and possible overinterpretation of results are all serious concerns.

## FOUNDATIONS

One of the significant flaws throughout the literature about supplements is the lack of an underlying theory. Although the authors of these articles discuss some possible and plausible suggestions, there is little discussion about scientific support for these mechanisms. The specific literature in supplements is limited both in number of studies and number of investigators; however, the field would be greatly enhanced by a thorough review and analysis of related literature. For example, if any increases in nonverbal intelligence reported by children who were given supplements are purported to be related to increased blood flow to the brain, an analysis of the literature regarding other effects of blood flow to the brain should be included. Theory based on already documented science needs to drive the design of the research: outcome measures should be chosen based on scientifically based theory. Review of the literature in other areas may also drive the consideration of additional interpretations of the results of the research.

## RESEARCH DESIGN ISSUES

Interpretation of the literature on supplements is complicated by the varieties of designs used. Conflicting conclusions have been based on research using different outcome measures, different populations with a variety of diets, and with varying interventions: the supplements themselves. The authors of the accompanying articles have tried to address many of these issues in their present work and have been somewhat successful. However, several serious issues remain in the design of these investigations.

## SAMPLES

Many of the conclusions supporting the use of supplements have been based on a limited sample population. This issue is further complicated by the use of the same research sample for several analyses and resultant articles. There is a potential for misinterpretation when more than one study relies on the same data set. Furthermore, when the results from several outcome measures drawn from one data set are reported as different studies, there is an appearance of replication. This possibly illusory replication is clearly not the same as independent data sets from different samples confirming one another.

Further confusion may arise when independently reporting several outcome measures from the same sample: the reader is unlikely to be aware of possible confounding relationships among variables. It is possible that all the reported outcomes may correlate with each other and investigators may be measuring the same underlying characteristic with each outcome. Research based on a variety of samples and populations would serve to enhance the knowledge about supplements and strengthen the appropriate conclusions of the data.

The issue of statistical power is important for research in any topic, however, it is of particular importance in areas in which the literature reports conflicting results and interpretation is difficult. This is a serious concern throughout the literature on nutritional supplements. Without adequate sample sizes, conclusions are in question and the state of the knowledge is not adequately advanced.

## MEASUREMENT INSTRUMENTS

Consistency and use of valid, reliable measurement instruments are critical to the development of a consensus across the literature.

Throughout the literature on supplements, outcomes have typically been assessed with different instruments, making comparisons and interpretation across the research particularly difficult. It is also critically important that measurement tools be validated for whatever population is being sampled. For example in the accompanying article, the authors carefully discuss the issue of validation in their use of an outcome measurement tool in another language on a subpopulation. Efforts such as this should be commended and can serve as an example for addressing the use of appropriate measurement instruments.

Another issue related to the use of measurement instruments is the importance of theory-based choice of multiple outcomes. Measurement tools of divergent factors are particularly needed in this literature. For example, some forms of intelligence are more likely related to academic performance. Either using instruments designed to evaluate these independently or choosing the one tool that best evaluates the most likely underlying characteristic is preferable to measuring several related concepts within the same sample. It is conceivable that the majority of the literature on nutritional supplements is based on improvement on one or two underlying components that are related to several other outcome measures now being assessed and reported in the literature.

## STANDARDIZATION OF INTERVENTIONS

It is particularly difficult to draw conclusions from research literature based on a variety of designs and sample populations. However, this difficulty is further compounded by the limited knowledge about the primary intervention of interest: the supplements. Few studies list the actual ingredients and amounts, and standardized supplements are not used across studies. This not only affects interpretation of results and comparisons across studies, but compromises the development of the underlying theory. A related issue, not uncommon in other research areas, is the relationship between the provider of such supplements and the researchers. Although attempts to avoid bias are incorporated in the research design, affiliations of the researchers and the source of the supplements and funding should be disclosed in any research utilizing commercial products.

## APPROPRIATENESS OF CONCLUSIONS

These articles also demonstrate the need in the field for exploration of alternative interpretations and conclusions limited to the evidence in the data. Some conclusions may be based on clinically irrelevant differences or differences that are within the standard deviations for the measurement tools. Furthermore, conclusions should be guarded and alternative interpretations presented. Research that otherwise shows promising results may be dismissed due to exaggerated claims by investigators and lack of attention to alternative explanations.

In order to make a contribution to the literature, it is critical to discuss and interpret the implication of all the results. Specific focus on a limited number of results, often supporting the hypotheses of the researchers, without attention to other data serves to compromise the potential influence of the results. For example, research in supplements has reported both positive gains and negative decrements in performance by study samples given placebo. Discussion in these studies focuses on the gains in the treatment groups: those given active supplements. Although the reported gains in the treatment groups were greater than those given placebos, the changes due to placebo are still remarkable. Implications for underling theory are also relevant. For instance, while it is possible that nutritional supplements are responsible for an increase in positive outcome measures, it is also possible that they are responsible for limiting an otherwise occurring decrease in those measures. These alternative interpretations give rise to related issues: if one assumes that improved nutrition increases positive outcomes, what would the impact of fasting be on these outcome measures?

## RECOMMENDATIONS

Evaluations of complex issues and interventions often result in difficulty and confusion in the interpretation and application of research results (Crombie et al., 1990; Benton, 1990). The importance of nutrition and the possible effects of supplements on childhood development are clearly issues of importance. Utilizing methodology pioneered in other areas of research could possibly serve to enhance the knowledge and push the science forward. Based on the interpretation of the following articles, several possible research designs may be suggested. Stronger research methodologies are clearly needed to evaluate the impact of nutritional supplements on populations identified as both most at risk and most likely to benefit from intervention. In complex areas such as human development, it is especially important to control for as many factors as possible.

One suggested study design is to conduct a large clinical study of a pre-post measurement crossover design with the sample sizes based on an appropriate power analysis. The study sample would be drawn from those who are identified as most at risk and most likely to demonstrate any effects of supplementation. In this case, as supported by the accompanying papers, it is assumed that a subpopulation of children, those who are nutritionally compromised, would be the target population. Although the present articles conclude that the minor benefits from supplementation are actually due to large increases in this subpopulation, this suggested design would provide more compelling evidence of an effect on nutritionally compromised children. This sample of children should be evaluated prior to administration of the supplements on a variety of measures, including outcomes of immediate interest such as academic performance and behavioral problems, as well as those that relate to the constructs underlying performance such intelligence, attention, mood (Benton and Cook, 1990, 1991) and memory. Because research has demonstrated conflicting results regarding gender differences in response to supplementation (Benton and Roberts, 1988; Benton and Buts, 1990), it is also essential to include enough subjects of each gender to make analyses meaningful. Although there are documented difficulties with such an approach (Crombie et al., 1990a), attempts to measure associated activities such as diet diaries through the study are also recommended. After randomization to either supplement or placebo, the measures would then be assessed again.

Given an adequate number of subjects, it would be ideal to include a crossover component to such a study: those receiving placebo then receive active supplements and vice versa so that every subject receives both interventions. The use of a crossover design is well known in pharmaceutical trials and could appropriately be applied to the study of nutritional supplements. The increased power of adding a within-subject design component to a between-subject design study is especially important when conducting research to clarify contradictory conclusions in the present literature.

Considering the potential results of such a study and the results already demonstrated in the literature, several new directions for research on nutritional supplements arise. For example, if supplements are shown to be effective in increasing several positive outcome measures, are there individual elements responsible for these changes? Perhaps there is a minimum number and combination of elements that are essential for certain changes. Also, there is limited knowledge about the length of time any positive responses last or any interaction between the length of time supplements are taken and their effects. And finally, investigations into any possible negative effects of the use of supplements should also be conducted. Although unlikely, it is possible that supplementation could lead to negative effects such as parents paying less attention to ensuring their children eat proper diets if supplements are given. As in other areas of medicine, assumptions about safety should be explicitly thought through and based on documentation.

## REFERENCES

Benton D. Response to Crombie et al, Vitamin/mineral supplementation and intelligence. Lancet 1990;336: 175–176.

Benton D, Buts J-P. Vitamin/mineral supplementation and intelligence. Lancet 1990;335:1158–1160.

Benton D, Cook R. Vitamin and mineral supplements improve the intelligence scores and concentration of six-year old children. Pers Individual Differences 1991;12: 1151–1158.

Benton D, Cook R. Selenium supplementation improves mood in a double-blind crossover trial. Psychopharmacology 1990;95:99–102.

Benton D, Cook R. The impact of selenium supplementation on mood. Biol Psychiatry 1991;29:1092–1098.

Benton D, Roberts G. Effect of vitamin and mineral supplementation on intelligence of a sample of schoolchildren, Lancet 1988;i:140–143.

Crombie IK, Todman J, McNeill G, du V. Florey C. Vitamin/mineral supplementation and intelligence. Lancet 1990a;336:175–176.

Crombie IK, Todman J, McNeill G, du V. Florey C, Menzies I, Kennedy RA. Effect of vitamin and mineral supplementation on verbal and non-verbal reasoning of schoolchildren. Lancet 1990b;335:744–747.

Schoenthaler SJ, Amos SP, Doraz WE, Kelly MA, Wakefield J. Controlled trial of vitamin-mineral supplementation: Effects on intelligence and performance. Pers Individual Differences 1991a;12:343–350.

Schoenthaler SJ, Amos SP, Eysenck HJ, Peritz E, Yudkin J. Controlled trial of vitamin-mineral supplementation: Effects on intelligence and performance. Pers Individual Differences 1991b;12:351–362.

Address reprint requests to:
*Wendy B. Smith, Ph.D.*
*DCPR-NIAAA*
*National Institutes of Health*
*6000 Executive Boulevard*
*Suite #505*
*Bethesda, MD 20892-7003*

*E-mail:* wsmith@willco.niaaa.nih.gov