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Commentary

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DR. KRAMER COMMENTS ON PSYCHOACTIVITY OF CALCIUM CHANNEL BLOCKERS, CASE REPORTS, AND RESEARCH

Sir:

Price and Heil are riding the wave of curiosity about the role of calcium channel blockers in the treatment of psychiatric disorders. These authors, a senior resident and a medical student, have taken time to review literature and to organize their observations for publication. Dr. Price has previously reported, in late 1985, on a fairly careful, but nonparallel group design study on the antipsychotic effects of verapamil in eight schizophrenics. These efforts are to be commended. It is the appropriate beginning for more detailed and scholarly research. It would be encouraging to see more of this activity here and elsewhere.

The authors are aware of some of the limitations of their specific conclusions and those that, in general, accompany case reporting. While the following comments are somewhat specifically applicable to Price and Heil's present paper, they also serve to discuss the shortcomings of many of the case reports that are published these days.

Time alone, repeated "therapeutic" contacts, and fluctuations in the natural course of psychotic disorders are all factors which may influence outcome measures. For instance, we have recently completed a placebo-controlled double-blind study on the use of two different adjunctive antidepressants in 90 schizoaffective, mainly schizophrenic, patients. One minor and expected result was that the patients, irrespective of their experimental treatment group assignment, were rated as significantly improved after nine weeks of evaluation and treatment. This type of outcome should dissuade case reporters from drawing any but the most tentative conclusions from a sample of one. It is also risky to be decisive about the meaning of data collected from a large sample without parallel placebo or other parallel control groups.

Price and Heil could have instituted a few simple design and write-up techniques that may have allowed them and us to make some very tentative conclusions:

1. Diagnosis. It is assumed that their patient was schizophrenic. This should be specifically stated, and, if possible, the criteria method of diagnosis reported (*DSM-III*, Feighner, Research Diagnostic Criteria, etc.).

2. Quantification of Outcome. A simple rating instrument, like the Brief Psychiatric Rating Scale, could give us a better idea of the magnitude of the behavioral disturbances and improvement in the patient. In addition, an instrument like the Scale for the Assessment of Negative Symptoms (SANS, Dr. Nancy Andreason) could be employed in any future trials of verapamil in schizophrenia.

3. Repeated Crossovers. How would outcome measures be influenced if the authors switched the patient back to placebo, and then to verapamil or haloperidol again? A positive relationship between improved outcome ratings only during verapamil treat-

ment periods would lend credence to the possible efficacy of verapamil in this "schizophrenic" patient.

4. Unbias the Rater, Unbias the Patient. Patient and Rater expectations of treatment outcome may significantly influence results. I am impressed with the number of patients who "improve dramatically" simply because of their transfer to a friendly research unit, or upon receiving the new "magic medicine." While I may believe that this placebo effect represents a "real" biological change in the patient, I must not allow myself to conclude that the specific treatment, unless contrasted with placebo or other control, is the important factor. I remember that during one of my double-blind placebo-controlled studies, I tried to guess the identity of the encoded medications. My guesses were incorrect. Nevertheless, had I been an "unblind" rater, I would have unconsciously augmented the outcome measures of many of the placebo-treated patients, who I thought were being treated with active medications. If possible, it is worthwhile to consider encapsulating all medications within opaque capsules, and to utilize a blind rater.

5. Consider Alternative Reasons for an Apparent Treatment Effect. Why do the negative (and positive) symptoms of schizophrenia seem to improve in this verapamil-treated patient? Perhaps the improvement was due to the patient's previous response (improvement in positive symptoms) to haloperidol, time off neuroleptics, subsequent diminution of neuroleptic-induced akinesia and sedation (improvement in negative symptoms), and a further relapsing/remitting course, followed by relative remission. This is not an unusual direction for schizophrenia, and could be independent of verapamil treatment. We need to be free of the myth that schizophrenics need constant inpatient doses of neuroleptics. The emerging trend today is to treat these patients with very small doses of neuroleptics, until their target symptoms reemerge. This strategy seems to diminish the "negative" symptoms of schizophrenia. I think our "noncompliant" patients have practiced this all along.

Eight months ago Drs. P. DeMaria, A. Mirow (both Jefferson residents) and myself completed a study and later submitted a paper for publication (under review), to the *Journal of Clinical Psychopharmacology,* on a double-blind, placebo-controlled double crossover study on the use of 60 mg (daily) of nifedipine (a calcium channel blocker) in five *DSM-III* diagnosed schizophrenics. In consideration of our small sample and lack of parallel group design, we cautiously concluded that nifedipine lacked an antipsychotic effect. The patients appeared to be clinically less amotivated, anergic, and/or asocial. Yet, this finding was not corroborated by specific BPRS item scores, nor confined to the nifedipine period. One patient did "improve dramatically" (clinically and with BPRS decreases of about 35 percent), but this also was not confined to the active treatment period. One patient had about a 25 percent increase in BPRS scores after neuroleptic withdrawal and placebo or nifedipine treatments. While it can be argued that nifedipine was effective in one patient, it is more likely that neuroleptic withdrawal was responsible for the apparent activation and other alterations in clinical state of most of the patients. There is the remote possibility that nifedipine may have potential efficacy for the negative symptoms of schizophrenia. However, we've decided to first investigate whether nifedipine is an antidepressant. Drs. K. Caputo, L. Maldonado, A. Mirow, and F. Sholevar, all Jefferson residents, have joined me in this investigation of nifedipine in ten endogenously depressed patients. We are more than half-way through this double-blind symmetrical placebo-controlled crossover trial.

I hope that these comments will not discourage case reporting, but rather will serve as some guidelines for enhanced clinical case reporting, and as an indication for the necessity of subsequent carefully designed, larger studies.

Mark Kramer, M.D., Ph.D.
Head of Division of Biological Psychiatry
Jefferson Medical College
Chief of Schizophrenia Research
Coatesville Veterans Administration Medical Center

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DR. SHORE COMMENTS ON "TREATMENT OF THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA WITH VERAPAMIL"

Sir:

It is encouraging to see papers on new treatment approaches to schizophrenia, especially those targeted on negative symptoms. While case reports may have limited scientific value, they are an excellent means by which one can progress from clinical observation to a research orientation. Reviewing the literature on a topic, synthesizing a variety of views and hypotheses, evaluating a therapeutic trial, and writing up the results in a research paper can all serve as important learning experiences. Many research scientists have begun with case reports and then gone on to learn blind assessment techniques, data analysis, and a host of methodological refinements. I believe that the authors of this article have gotten a promising start and I encourage them to consider further research on schizophrenia.

I was going to prepare a critique of the paper that would illustrate the utility and the potential pitfalls of case report studies, but after reading Dr. Kramer's excellent commentary, writing one myself seems unnecessary. His review of factors such as placebo effects in non-blind studies, related problems with subjective vs. more objective assessments, and variations in the natural course of psychiatric disorders such as schizophrenia, is very valuable. I, too, have gotten excited over treatment responses in patients who turned out to be on placebo. Since the patient, ward staff, and physician all want (and perhaps expect) the patient to get better, it is no surprise when that seems to occur. Crossover studies (such as the A/B/A design: placebo/active drug/placebo periods) can be very useful, but even with this design patients may seem to respond well to the active drug, but when later placed back on the drug (A/B/A/B design), blind assessment may fail to show the same positive response.

Another area that can be problematic for developing researchers is the literature review. It is a natural tendency to search for papers or other indications that a particular hypothesis, approach or drug is promising. Nevertheless, one must search at least as hard for evidence contrary to one's idea—sometimes we can avoid reinventing wheels, sometimes we can devise new speculations to explain contradictory results. Of course, unless one has firsthand experience with a given technique, assessment, or assay, it is hard to evaluate conflicting literature. Residents are at another disadvantage in that they may not know of recently completed or ongoing studies. Those who are able to read a large number of scientific journals, those who may learn of new studies from reviewing articles

for various journals or from reviewing grant applications, and those who personally know other scientists working in a given field obviously have an advantage. But none of these are insurmountable, and just as clinicians gradually grow in skills and knowledge, so researchers develop and learn with whom they should collaborate or consult, what meetings they should attend, and what journals they should read.

Because of the programs and priorities of the National Institute of Mental Health (NIMH), I am convinced that this is a particularly exciting time for psychiatry residents interested in schizophrenia research. There are a number of research, career development, and research training mechanisms available through NIMH grants and intramural programs, and I would encourage all those interested in schizophrenia research to learn about these opportunities. A summary of NIMH schizophrenia research programs of particular relevance for psychiatry residents follows.

David Shore, M.D.
Chief, Biological and Clinical Factors Research Program
Schizophrenia Research Branch
Division of Clinical Research
National Institute of Mental Health

SCHIZOPHRENIA RESEARCH CAREER OPPORTUNITIES

Schizophrenia affects at least 1 percent of the population and has been estimated to cost the U.S. over 20 billion dollars per year in treatment costs and lost income. Psychiatric residents are well aware of the severe disability caused by schizophrenia and the limits of currently available treatments. Nevertheless, with the many career options open to them, schizophrenia research is too often overlooked.

The climate for schizophrenia research has been changing recently, so that an academic career in this field could be particularly exciting. The convergence of several factors, especially the many recent advances in the neurosciences, makes those of us on the staff of the National Institute of Mental Health (NIMH) very enthusiastic about new opportunities. With the introduction of non-invasive scanners such as the CT, MRI, CBF, and PET, researchers have been able to examine the structure and function of the brains of schizophrenic patients. These studies have demonstrated subtle atrophy in schizophrenic patients' brains and shown differences in metabolism and receptor density compared to controls. Along with the emergence of these sophisticated scanning methods, the biological theories of schizophrenia have also gained momentum. Examples of this trend include the increase in studies of neurotransmitters and their metabolites, pharmacological trials with "state of the science" antipsychotic medications, measurement of peptides that function as neuromodulators, physiological measures such as eye tracking, and molecular genetics.

These advances in clinical applications of basic science advances are, however, only part of the reason there is increased enthusiasm in schizophrenia research. In the late 1970s, family groups began to organize to decrease their

isolation and advocate for better mental health care. These family groups have become a political force, pressing legislators to do more in the areas of treatment and research on major mental illnesses, and they have lobbied successfully in Congress for increased funding of schizophrenia research and research training.

Residents should be informed that research on major mental illnesses such as schizophrenia has become a leading priority of NIMH. The Institute is especially concerned about schizophrenia research manpower needs, and has been exploring incentives to develop a new generation of research scientists. Given the shift toward a more biological approach to schizophrenia, psychiatry residents and others with biomedical training have special potential for making contributions to schizophrenia research progress in the coming years. Rapidly developing areas such as molecular genetics, neurovirology, neurochemistry, structural and functional imaging, and psychopharmacology all hold the potential for breakthroughs in schizophrenia research.

Of course, research is not for everyone, and there have been numerous disincentives to schizophrenia research careers as noted in the Spring 1986 issue of *Schizophrenia Bulletin* (1). One of the problems is that, unless a person has been involved in research, there is no sure way to determine whether he or she would be happy in such a role. Medical students and residents interested in research should seek out opportunities for such experience with successful investigators. Many psychiatry departments have ongoing research projects, and NIMH can provide lists of schizophrenia research grants funded in recent years at institutions all around the country. These are summarized in the upcoming issues of the *Schizophrenia Bulletin,* Volume 13, Numbers 1 and 2. If a given institution does not have a researcher or program in one's area of interest, a fellowship to study with a mentor elsewhere may be worth considering. In addition to helping a potential research trainee decide about the desirability of this career option, experience in research (and publication) is important in the review of research training applications.

NIMH now offers three research support mechanisms, two research scientist development mechanisms, and two research training mechanisms for support of developing investigators. As a result of this wide variety of opportunities, it is often unclear to the potential applicant which opportunity is best suited to his or her needs. As a first step, a potential applicant needs to be knowledgeable about what these different mechanisms were developed to accomplish, as well as the details of their administrative requirements.

I. Research Support Mechanisms: All three of these mechanisms mainly provide support for research costs, but the applicant can assign a part of the budget for his or her own salary or for the salary of research personnel.

   A. Small Grant: The small grants mechanism was developed to provide funds for pilot work or start up funds for new investigators. Funds

are available to a maximum of $25,000 for a period limited to one year (extensions without additional funds are routinely available). This mechanism is best suited for discretely defined studies that can be completed in about a year within this funding limitation. It has been used successfully in the past by beginning investigators.

B. RO1: The investigator-initiated research grant is the bread and butter research funding mechanism of NIMH. It provides research funds for qualified applicants at qualified institutions; up to five years of funding can be requested with a funding limit determined by the fiscal needs of the supported research. This mechanism is best suited for support of relatively complex studies that require multiple years of support and may be part of a long-range program of research. It has often been used in the past by beginning investigators whose work does not fit within the confines of the small grant.

C. FIRST: A new research funding mechanism at NIMH designed to provide salary and research support to the investigator who has never before been the principal investigator on a Public Health service funded grant. This mechanism provides up to $100,000 per year for up to five years of support, with a total funding limit of $350,000; the funds can be used for both salary and the support of research expenses. Because of its five year duration and relatively large funding limit, the applicants must have a well thought out program of research to support these limits. This is a new program and there is no track record regarding the review groups' reaction to these applications. The Institute hopes that the reviewers will look upon these as opportunities to allow bright, capable young investigators to begin a research career.

II. Research Scientist Development Award (RSDA) Mechanisms: These are designed primarily to provide salary support and research training opportunities for developing scientists. Limited funds can be requested for research support.

A. Physician Scientist Award (PSA): This award is designed to enhance the development of physicians in research careers. Five years of support for salary, as well as up to $10,000 per year for research and training costs for the first three years and up to $20,000 per year for the final two years of support can be requested. Physicians with little research experience have found this mechanism to be quite helpful as they develop into research scientists. A minimum of two years of post-doctoral experience is required before support can be granted.

B. Research Scientist Development Award (RSDA) Level I: This award is designed to support individuals with outstanding research

potential who need further supervised research experience. Applicants are usually scientists or clinicians with some research experience or scientists prepared in one discipline who need supervised experience in another. Five years of salary, research, and research training costs can be requested. This mechanism has been remarkably successful in helping young investigators develop into independent scientists. A minimum of three years of post-doctoral experience is required before support can be granted.

III. Research Training Mechanisms: In these programs, the primary goal is to provide support during a research training interval. Both are for a maximum of three years of post-doctoral training.

A. National Research Scientist Award (NRSA) Individual Fellowship: This award is designed to provide stipend support during research training. Prior to formal submission, the applicant must arrange acceptance by a sponsor who will supervise the research training experience in a facility that has an appropriate environment to provide the proposed research training. Post-doctoral stipends range from $16,000 to $30,000 per year depending on years of experience. In addition, $3,000 may be requested for institutional allowances.

B. Public Health Service (PHS) Epidemiology Fellowship: This award is somewhat different from the other awards described above in that the first year of support is for training leading to an MPH and the second and third years of support are for research experience in epidemiology at the NIMH. Recipients of these awards receive NIMH appointments equivalent to the intramural Clinical Associates. Salary support begins at $30,000 for the first year with $2,000 increments for each year of support. The purpose of this program is to increase the number of medical professionals in mental health epidemiology.

IV. NIMH Intramural Research Programs (IRP): Medical Staff (Clinical Associate) Fellowships at NIMH in Bethesda or at St. Elizabeth's Hospital in Washington, DC, are available for those who are completing or have completed residency training. Unlike the extramural grant programs described in I–III above, the IRP conducts research on its own campuses, rather than providing grants to other institutions. There are active research programs in schizophrenia, affective and anxiety disorders, basic neuroscience, imaging, etc. Medical staff fellowships are for two years, with a starting annual salary of $32,000.

The events described earlier have provided the impetus for increased support for careers in schizophrenia research, but money and research tools are not in themselves a reason to make a career decision. The most compelling

reason for more residents and medical students to look at a career in schizophrenia research is that these seriously ill patients need the help of dedicated and energetic physicians. Developing research psychiatrists now have increased opportunities to contribute to advances in finding the etiology or better treatments for this severe and chronic mental disorder.

David Shore, M.D.
Chief, Biological and Clinical
Factors Research Program
Schizophrenia Research Branch
Division of Clinical Research
National Institute of Mental Health

Leonard Lash, Ph.D.
Associate Director for Research Training and
Research Resources
Division of Clinical Research
National Institute of Mental Health

S. Charles Schulz, M.D.
Chief, Pharmacologic and Somatic
Treatments Research Program
Schizophrenia Research Branch
Division of Clinical Research
National Institute of Mental Health

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