**Department of Health and Human Services**

# PUBLIC HEALTH SERVICE

# NATIONAL INSTITUTES OF HEALTH

# NATIONAL INSTITUTE OF MENTAL HEALTH

## National Advisory Mental Health Council

## Minutes of the 213th Meeting

## September 14-15, 2006

# Minutes of the 213th Meeting of the National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 213th meeting in closed session to review grant applications at 10:30 a.m. on September 14, 2006, at the Neuroscience Center in Rockville, Maryland, and adjourned at approximately 3:30 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened for an open session at the same location from 4:00 p.m. to 5:25 p.m., and it continued the open session on the following day, September 15, 2006, in Building 31C, National Institutes of Health, Bethesda, Maryland, from 8:30 a.m. until adjournment at 12:45 p.m. In accordance with Public Law 92-463, the open policy session was open to the public. Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH) chaired the policy meeting.

**Council Members Present at the Grant Review and/or Open Policy Sessions**
(See Appendix B: Council Roster)

**Chairperson:** Thomas R. Insel, M.D.

**Executive Secretary:** Jane A. Steinberg, Ph.D.

**Council Members:**

Sergio A. Aguilar-Gaxiola, M.D., Ph.D.
Glorisa J. Canino, Ph.D.
Jonathan D. Cohen, M.D., Ph.D.
Susan M. Essock, Ph.D.
Raquel E. Gur, M.D., Ph.D.
Martha E. Hellander, J.D.
Renata J. Henry
Peter J. Hollenbeck, Ph.D.
Ned H. Kalin, M.D.
Jeffrey A. Kelly, Ph.D.
Norwood Knight-Richardson, M.D., M.B.A.
Helena C. Kraemer, Ph.D.
Pat R. Levitt, Ph.D.
Charles F. Reynolds, III, M.D.
Peter Salovey, Ph.D.
Suzanne E. Vogel-Scibilia, M.D.
Karen Dineen Wagner, M.D., Ph.D.
Stephen T. Warren, Ph.D.

**Ex-officio Members Present at the Grant Review and/or Open Policy Sessions:**
Robert Freedman, M.D., Department of Veterans Affairs
Douglas A. Waldrep, M.D., FAPA, COL, MC, USA, Department of Defense
Elias A. Zerhouni, M.D., Director, National Institutes of Health

**Liaison Representative Present at the Open Policy Session:**
A. Kathryn Power, Center for Mental Health Services (CMHS), Substance Abuse and Mental Health Services Administration (SAMHSA)

**Others Present:**
Reuven Ferziger, M.D., Johnson & Johnson
Andrea Fiero, NASMHPD Research Institute
Stephen Foote, (retired from NIMH)
E. Aracelis Francis, Council on Social Work Foundation
Junius Gonzales, ABT Associates, Inc.
Steven Hyman, Harvard University

Walter H. Kaye, University of Pittsburgh
Marion C. Kiley, National Foundation for Mental Health
Jeffrey Lieberman, New York State Psychiatric Institute
John March, Duke University Medical Center
Noel Mazade, NASMHPD Research Institute
Sheila McDonald, Child and Adolescent Bipolar Foundation
Anne Michaels, National Foundation for Mental Health
Amy Pollick, Association for Psychological Sciences
Beth Roy, Social and Scientific Systems, Inc.
A. John Rush, University of Texas Southwestern Medical Center
Gary Sachs, Massachusetts General Hospital
Karen Studwell, American Psychological Association
Barbara Wanchisen, Federation of Behavioral, Psychological & Cognitive Sciences
Joan Zlotnik, Institute for the Advancement of Social Work Research

## Open Policy Session: Call to Order and Opening Remarks

Thomas R. Insel, M.D., Director, NIMH, called the open policy session to order by acknowledging the contributions of Council members whose Council tenure ends on October 1: Dr. Susan Essock, Ms. Renata Henry, Dr. Charles Reynolds, III, Dr. Karen Wagner, and Dr. Douglas Waldrep.

Dr. Insel noted that Dr. Aguilar-Gaxiola had been elected Chairman of the National Mental Health Association Board of Directors, the first Latino to serve in that role.

## Council Workgroup on MRI Research Practices: Final Report

Dr. Jonathan Cohen began his presentation of the Workgroup's final report by noting that magnetic resonance imaging (MRI) has become a valuable tool for clinical and basic cognitive and affective neuroscience research. Such research often is conducted in facilities that are outside of traditional medical settings. In these non-clinical settings, physicians may not be involved in the research, and there may not be medical backup facilities readily available on site. Given the lack of comprehensive guidance on MRI research on human participants conducted outside of traditional medical settings, the Council Workgroup was established to consider safety, legal, and ethical concerns raised by the use of MRI across various settings. The Workgroup included researchers, clinicians, institutional representatives, and experts in MRI safety, MRI physicists, and a lawyer with neuroscience expertise. The Workgroup did not have regulatory authority and therefore could not issue guidelines, standards, or regulations about best practices. Rather, the group developed a list of "points to consider" that could serve as a template for investigators to use when addressing safety, legal, and ethical concerns associated with MRI research in non-clinical settings.

The "points to consider" were organized around six major topics: MRI screening processes; the facility's training, operating, and emergency procedures; physical facilities; participant health and safety considerations; practices in medical versus non-medical settings; and the need for additional data and updating as the technology develops.

The Workgroup noted that no one screening method is satisfactory to ensure the safety of participants. Rather, multiple complementary screening methods should be employed—e.g., multiple verbal interviews with participants, ensuring that participants are free of surface objects that may be unsafe for MRI (such as pens, coins, and other metals), and/or requiring participants to wear gowns.

In terms of the practical and ethical issues involved in pregnancy screening, although there is no known risk to the developing fetus of MR brain scanning of a pregnant woman at 4 Tesla or less and no known mechanism of potential risk under normal operating procedures, the Workgroup noted that the possibility that risks may be discovered in the future cannot be ruled out. Thus, exposure of fetuses to MR scanning without any prospect of direct benefit may not be ethically justifiable, and it is thus appropriate for investigators to screen for pregnancy and exclude pregnant participants.

Regarding the training and certification of staff, Dr. Cohen pointed out that the Workgroup recognized the need for appropriate levels of training for all individuals who operate scanners and/or have routine access to an MR suite. In terms of the American College of Radiology guidelines, the Workgroup noted that personnel should be trained on all elements according to the guidelines insofar as they are relevant to their research practices. For many university settings, training in certain areas, such as in the use of contrast agents, may not be as exhaustive as would be required in a clinical setting, while other areas of training may require expansion. Dr. Cohen stressed the importance of standardizing and documenting safety procedures used at a research facility.

Dr. Cohen stressed the importance of having procedures in place for emergency situations and for communicating with emergency resources in the community so that personnel are made aware of any special safety concerns related to magnetic fields. Equally important, he said, is that investigators in non-medical settings inform participants that emergency medical services may not be available on site.

The Workgroup also gave considerable attention to the management of incidental findings or the possibility that an abnormality may be detected or suspected in the process of the research, the clinical significance of which may not be clear. Its members agreed on the importance of informing the participant of the policies and procedures in place concerning potential incidental findings. The Workgroup recommended that local IRBs be provided with relevant information about these issues when consent forms and practices are established at their facilities. Dr. Cohen also emphasized the need for facilities to have clearly defined procedures for documenting and reporting all incidents or near incidents that pertain to the safe operation of the facility. Such reports could become part of a database of circumstances that predispose to adverse events.

Dr. Cohen concluded by noting that the Workgroup's draft "points to consider" were reviewed by experts in MRI safety, including those involved in drafting the clinical (American College of Radiology) MRI guidelines, NIMH Council members, and relevant staff at NIMH and other NIH Institutes. Dr. Cohen concluded his presentation by thanking staff and Workgroup members who contributed to the report.

During the discussion that followed, Dr. Kalin asked for more specifics about recommendations for dealing with incidental findings. Dr. Cohen said that protocols should be in place for

managing incidental findings, including a consent form that clearly distinguishes research from clinical scans, that explicitly discusses the potential for incidental findings and associated risks, that informs the participant as to whether or not the scans will be reviewed by a clinician qualified to render a radiological interpretation, and that describes the path that will be taken in the event that an incidental finding occurs. Dr. Cohen said that a consensus is emerging that participants should be told about adverse incidental findings and then given a referral. How that will be handled should be specified, though the procedure may differ from one facility to another.

In answer to a question about how the recommendations would be rolled out to the community, Dr. Cohen said they would be published on the NIMH Web as a document.

Ms. Hellander suggested that consent forms may be improved by noting that a copy of the scan would be provided to the participant, the participant's family, or the physician to whom the participant is referred. Dr. Cohen agreed that the information should be made available to the participant or his/her physician.

Dr. Levitt asked whether IRB members had reviewed the report as the points to consider might be interpreted as binding when that was not the intention. Dr. Cohen replied that the Workgroup members had considerable experience in working with IRBs.

Dr. Insel pointed out that the report is not meant to be taken as NIH or Federal policy. Both he and Dr. Cohen emphasized that the report should be seen as a resource to investigators and facilities using MRI in research, and that it may require updating as technologies advance and additional information becomes available.

The Council then voted unanimously to accept the Workgroup's report.

## Concept Clearances

The Council then considered four concept clearance requests, three for initiatives in human genetics and one to build an AIDS mental health research component at NIH's Research Centers for Minority Institutions (RCMIs) (see http://grants.nih.gov/grants/guide/rfa-files/RFA-RR-99-005.html).

The genetics initiatives were described by Dr. Thomas Lehner, Acting Director of the NIMH Office of Human Genetics and Genomic Resources and Chief of the Genetic Basis of Mental Disorders Program in the Division of Neuroscience and Basic Behavioral Science (DNBBS). He noted that the genetics initiatives capitalize on conceptual advances in the field and on new and creative funding strategies.

The first project would support data analysis of whole genome association studies from the Genetic Association Information Network (GAIN) initiative, a public-private research partnership between the Foundation for the National Institutes of Health (FNIH), NIH, and the National Human Genome Research Institute (NHGRI). This initiative would be available to successful applicants to the GAIN initiative and will be for analyses of whole genome association data for clinical phenotypes of interest to NIMH. Of the seven top-ranking

applications submitted to GAIN, five are relevant to NIMH. At least one project is expected to be funded early next year.

The second genetics initiative would support the development of novel methods and statistical theory for analyzing large scale DNA sequence data in complex disorders with the ultimate goal of understanding both the genetic and environmental components of health and disease in complex disorders. Dr. Lehner noted that the field lacks a statistical theory for sequence analysis on a large scale. This initiative grew out of an NIH-wide project, the Genes and Environment Initiative (GEI), which has the goal of understanding the genetic and the environmental components of health and disease in complex disorders.

The third initiative is a center for genomic and phenomic studies in autism, which would capitalize on the findings that will result from initiatives such as GEI, GAIN, and NIMH's autism portfolio. Several promising candidate genes have been found in the last few years, but the relationship of the genotype to the phenotype is unclear because the phenotypes are highly complex. The proposed center would provide access to large clinical populations to do in-depth phenotyping, including potential endophenotypes and subphenotypes. Its major function would be to establish, maintain, and distribute resources. Families having one or multiple members with autism would be included. All data and samples would become part of the NIMH genetic repository.

During the discussion period, Dr. Levitt sought assurances that the autism center would not overlap or conflict with existing databanks supported through private means. Dr. Lehner said that entities receiving current support through foundations, etc., would be primary candidates for the new center.

Dr. Hollenbeck stressed the importance of having a robust database structure to allow rich multidimensional data sets to be entered and available for study once genetic "hot spots" for autism are identified.

The fourth project was described by Dr. David Stoff, Program Chief of HIV Neuropsychiatry, AIDS Research Training, and Health Disparities in the Division of AIDS and Health and Behavior Research (DAHBR). He began his presentation by informing the Council that although minorities make up about 30 percent of the U.S. population, they account for about 70 percent of AIDS cases. The RCMIs were mandated by Congress in 1985 to examine the causes of disparities in several diseases, including AIDS. The Centers are geographically diverse and have an established infrastructure, and more than three-fourths of them have biomedical AIDS interests. This initiative will add the mental health dimension of HIV/AIDS research (behavioral, clinical and biological studies) to this Center program. The proposed initiative would supplement the cooperative agreement between the RCMIs and the National Center for Research Resources (NCRR), which has supported the RCMIs over the years. During the first phase of the new project, linkages and collaborations would be organized, and during the second phase, exploratory studies would be conducted. The programs are expected to lead to better research strategies for studying the mental health aspects of HIV, as well as improved collaborations and career development. In the long term, Dr. Stoff said, it is hoped that clinical research capacity will be improved and the pool of racial and ethnic minority investigators to conduct this kind of research will grow. The ultimate goal is improved health among minority groups.

In answer to a question from Ms. Henry, Dr. Stoff said that as far as he knew there are no Native American RCMIs.

The Council unanimously voted to approve all four concepts.

## Data-Sharing Proposal

Council member Dr. Helena Kraemer introduced the importance of sharing data in clinical research studies that have the potential to impact clinical practice, including randomized clinical trials, risk research, studies on disease prevention, health services research, and medical test evaluation. She provided as examples two well-designed and well-executed clinical trials where erroneous conclusions led to widespread use of treatment later found to have adverse effects. The first, the Cardiac Arrhythmia Suppression Trial (CAST), evaluated the efficacy and safety of arrhythmia suppression therapy in patients with asymptomatic or mildly symptomatic ventricular arrhythmia after myocardial infarction. After less than 1 year of followup, the trial was stopped as the treatments thought to prevent heart disease were later found to increase it (see http://www.nhlbi.nih.gov/resources/deca/descriptions/cast.htm).

In the mid-1980s, hormone replacement therapy (HRT) was thought to prevent cardiac disease. By the 1990s, HRT was routinely offered in clinical care. However, in 2002 the Women's Health Initiative reported findings from a multisite randomized clinical trial that was stopped early because of convincing evidence that HRT is a risk factor (rather than protective factor) for heart disease, cancer, cognitive impairment, and other conditions (see http://www.whi.org/newsletter/update_ht2002.pdf ).

The issue of errors in medical research has been addressed in the literature [see Ioannidis, J.P. "Why Most Published Research Findings are False." *Public Library of Science* 2(8):e124, 2005]. A 1979 review of the *British Journal of Psychiatry* showed that about 45 percent of the papers that used statistical methods had statistical errors, which often were sufficient to raise doubts about the inferences (see White S.J. "Statistical Errors in Papers in the British Journal of Psychiatry." *The British Journal of Psychiatry* 135:336-342, 1979*).* Similar results have been found in other medical journals. Inadequate reporting of data is one problem; inadequate statistical analysis another, she said. What is missing is a check on the quality of data analysis, interpretation, and presentation. In her own experience in reviewing papers, Dr. Kraemer said that it is sometimes impossible to detect statistical errors because to do so would require access to the data and assumptions not presented in the paper.

Dr. Kraemer proposed that every clinical research study funded by NIMH and NIH be required to archive its data, the documentation for the data, and the analyses underlying each published paper. The archive data would be included in progress reports to NIMH and NIH. That data would not necessarily include the whole dataset, only the data on which a paper is based. The data would be made available immediately upon publication to other qualified researchers for a second independent opinion on the research conclusions. Dr. Kraemer also recommended that the entire dataset and documentation be archived for use by other qualified researchers 5 years after the study completion.

Dr. Kraemer next discussed some potential objections to her proposal and her reply to those concerns:

- Isn't this already being done: In many cases, the data are never made available. In other cases, the delay is 5 years by which time any resulting damage is done.
- Problem of confidentiality: Ensuring confidentiality is already required and therefore will not add to the researcher's burden.
- Too much time and effort: If the request for data is made while a study is underway or already completed, additional time and effort may be needed. However, if it were understood to be a condition for funding, it would add very little time and effort.
- Increased costs: Increases would be trivial when compared with the potential harm to patients.
- Investigators' rights to the data: Only the data on which published conclusions are based would be available to other investigators, at least for the first 5 years after the study was completed.
- Opening the door to poor research done on good data: Contractual agreements should be in place that spell out the limits of the secondary analysis and acknowledge the source of the data. Also, dissemination of a second opinion should be submitted to the original investigators to guard against erroneous interpretations of the data and provide them the opportunity to respond.

In describing the potential benefits of her proposal, Dr. Kraemer noted that having the data available would facilitate data audits and likely would promote increased attention and training in research methodology and increased emphases on the quality of measurement and choice of analyses. Dr. Kraemer concluded by noting that the benefits of her proposal would be to increase the likelihood that original publications are correctly reported and interpreted. Should errors occur, they could be quickly detected and corrected before patient care is harmed and the directions of future clinical research compromised.

Dr. Levitt commented that statisticians may disagree about methodology, and an investigator may intend to disprove original results by using statistical approaches or applications that are under debate. Dr. Kraemer said that to guard against such eventualities, the data should be available only to qualified investigators and the original team should review the reanalysis before publication.

Dr. Cohen pointed out that archiving neuroimaging data involves technical hurdles because of the size of the datasets and the lack of standard formats.

Dr. Insel noted that the trend toward more sharing of data represents a cultural change in science. He cited the example of the GAIN Initiative that aims to release genotyping and phenotyping data as rapidly as possible to qualified investigators. Principal investigators have 9 months of exclusive rights to publish, after which the data are open to others. The broad data sharing in genomics will probably occur for epidemiological studies, he said. However, a policy for data sharing for clinical studies is not yet in place. That is where the implications could be the greatest, Dr. Insel said. He did question whether 5 years following the completion of a study is too long to wait before others can use the same database. He asked the Council to consider, at a future meeting, whether some large-scale clinical studies, particularly those done on contract,

should require more data sharing. With that comment, Dr. Insel closed the initial session of the Council meeting.

## Call to Order and Opening Remarks

The Council reconvened to continue the session the following morning on the main campus of NIH in Bethesda, Maryland. Dr. Insel opened the session by noting that the meeting would include reports on the initial results of the large practical trials that NIMH began in 1999.

Before proceeding, Dr. Insel took note of the death of Dr. Wayne Fenton, who had served as the Director of the Division of Adult Translational Research and Treatment Development and as the Clinical Affairs Associate Director at NIMH. Dr. Insel recalled some of Dr. Fenton's contributions, notably his leadership in implementing research initiatives in the pathophysiology and treatment of schizophrenia and other major mental illnesses. In his private practice, Dr. Fenton treated individuals with the most serious mental illnesses. He also supported local and national advocacy efforts. Dr. Fenton's death is a huge loss for the Institute and for people with serious mental illness everywhere, Dr. Insel said.

Dr. Insel then introduced three new NIMH division directors: Dr. Linda Brady in the Division of Neuroscience and Basic Behavioral Science, Dr. Phillip Wang in the Division of Services and Intervention Research, and Dr. Alcino Silva, Scientific Director of the Institute's Intramural Research Program.

## NIH at the Crossroads: Strategies for the Future

Dr. Insel introduced Dr. Elias Zerhouni, the 15th Director of NIH who began his tenure in May 2002. Dr. Insel said that Dr. Zerhouni has had a critical leadership role in reshaping and restructuring NIH.

Dr. Zerhouni began his talk by acknowledging that NIMH faces some of the most difficult scientific, social, and translational issues in medical science. Diagnosing mental illnesses earlier so that interventions can begin earlier is necessary, he said. Even more important is ensuring that fundamental scientific discoveries are translated into the practice of medicine and health gains for the Nation.

A fundamental change in the landscape of diseases has taken place, Dr. Zerhouni said. Given the successes of treating many acute conditions, the burden of illness is shifting from acute to chronic conditions, whether it is diabetes, high blood pressure, or depression. The challenge of transforming medicine and health through a series of discoveries, he continued, can only be effective with the participation of communities, patients, and the entire health care structure. Tackling issues related to the health care delivery system, including the cost of health care and disparities in access to care, will require strong leadership from NIH.

He then pointed out the policy and scientific issues that have arisen as a result of the leveling off of the NIH budget following the 5-year doubling period. The national research capacity was built up as a result of the doubling budget, and that in turn has led to a marked increase in demand for research funding. Along with the growth in the number of research facilities is a corresponding growth in the number of scientists seeking grant funds. In 1998, NIH received 24,000 grant applications, whereas this year that number will exceed 48,000. Half of the growth in demand occurred after the end of the doubling. That is, there was more growth in the 2 years following the doubling than during the entire 5 years of the doubling. Also, each funded application is more expensive today than it was 5-6 years ago by about 40 percent. As a result of more research capacity and flat budgets, the success rate for grant applications has dropped and now is about 20 percent.

Dr. Zerhouni described five principles for maintaining research enterprise vitality in light of reduced purchasing power:

- Protect core values and mission. As the primary Federal agency for conducting and supporting medical research, NIH promotes the discovery and generation of new knowledge relevant to multiple areas of health. Despite pressures to the contrary, NIH must maintain a balance between basic translational and clinical research. NIH invests about $28 billion annually in medical research, of which about 55 to 60 percent supports basic research, 25 percent supports translational research, and 15 percent supports clinical research. In the private sector, which spends about twice as much on research, the pattern is reversed with most support dedicated to clinical research. Furthermore, NIH must continue to promote high-risk, high-impact research and new scientists with new ideas. The NIH Director's Pioneer Award supports individual scientists of exceptional creativity who propose pioneering approaches to major challenges in biomedical and behavioral research.

- Protect the future. Protecting the future of science requires fostering young scientists. Toward that end, NIH has created the Pathway to Independence Award, which is open to postdoctoral fellows and provides up to 5 years of support consisting of two phases: Phase I provides 1-2 years of mentored support for advanced postdoctoral fellows; Phase II provides up to 3 years of independent R01-equivalent research support. In the first two rounds of submissions, 700 applications were received, and NIH is anticipating 150-200 awards per year.
- Focus on balancing supply/demand. In the present economic environment, there is an imbalance between demand for grants—demand for new ideas to be supported—and the supply of resources to fund them. Advisory councils will have an active role in priority setting and adjusting programs as needed to maintain reasonable investigator-initiated success rates, with the goal of exceeding the present 20 percent success rate. Research and development costs should have priority over other ancillary costs if possible. The peer review process must be as efficient as possible to minimize unnecessary burdens on the scientific community. Among the steps NIH is taking is speeding up the review process, particularly for the receipt of summary statements for new investigators with the goal of all investigators receiving them within 1 month of review. Other mechanisms are being explored to lessen the disparity between the low approval rates for the first submission and subsequent resubmissions.
- Proactively communicate about investment in NIH. It is important to show that the research portfolio is balanced and relevant. The practical clinical trials undertaken by NIMH are an example. NIH is engaged in an important strategy to transform health care from a curative paradigm to a more predictive, more personalized, and more preemptive paradigm. The NIH has become more proactive in informing the public of the benefits from public investment in biomedical research. Changes have been made to the NIH home page, and easily understood fact sheets are issued by every Institute. States and localities are targeted, and more effort is going into other means of communicating directly with the public. A new magazine, *NIH MedlinePlus*, funded by the Friends of the National Library of Medicine, will be distributed in seven million doctors' offices around the country.
- Promote NIH's vision for the future. Dr. Zerhouni proposed that the vision of how medicine and health will evolve should encompass the four Ps of medicine: predictive, personalized, pre-emptive, and participatory medicine.

Dr. Zerhouni concluded his comments by commending NIMH for its support of the practical clinical trials because they illustrate more participatory, more community-based, more reality-based, more personalized, and more predictive medical science.

In answer to a question from Dr. Aguilar-Gaxiola about initiatives to merge research supported by the Federal Government with that supported in the private sector, Dr. Zerhouni replied that partnerships between universities, industry, and the Government are very important. Ways of facilitating these public-private partnerships are needed, he said, and he cited as an example the GAIN Initiative. An initiative on biomarkers will soon be announced, as will an osteoarthritis initiative. More public-private initiatives have begun in the past 3 years than had been undertaken in any of the previous years, he said. New ground also was broken with the global health initiative for underserved populations, a partnership between the NIH and the Gates Foundation.

A question from Ms. Hellander elicited Dr. Zerhouni's enthusiastic endorsement of early identification and intervention for psychiatric illnesses. He said that it is important to align reimbursement policies with that goal. Also needed is the ability to identify early those at risk for illness.

Dr. Levitt asked how NIH is taking a lead in translating findings in brain science into policies, particularly in the area of child development where the science could inform effective policies for increasing preventive steps and reducing vulnerability for illness in the child population. Dr. Zerhouni replied that the NIH is dedicated to supporting a robust program of scientific discovery that will enable a more predictive, personalized, and preemptive health care environment. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, he continued, is an example of research with profound implications for public policy.

Dr. Knight-Richardson asked whether NIH has been making inroads into increasing the diversity of scientists in all areas of science, from management to the conduct of science, to be more reflective of groups that disproportionately bear the greatest disease burden. Dr. Zerhouni replied that the ability to do research relies on trust and the ability to understand a culturally sensitive environment. The diversity of those who do research should mirror the diversity of those for whom research is intended. That is the NIH policy, he said. Increasing diversity is not advancing as fast as one would like, however. The reason many young minority college students do not enter biomedical research is socioeconomic and systemic. He said that efforts will be required to address this situation.

## The NIMH Clinical Trials Program: Major Findings and Implications for Everyday Practice

Turning to the next agenda item, Dr. Insel noted that the concept of supporting large-scale practical clinical trials was one of the recommendations contained in the NIMH Council report, "Bridging Science and Services," that was issued about 10 years ago (see http://www.nimh.nih.gov/publicat/nimhbridge.pdf ). Initial results from four of five large NIMH-supported trials have been published, at least in part. Findings from the fifth trial, the use of antipsychotic medication in people with Alzheimer's disease, will be published in the fall and will not be presented at this meeting. Dr. Insel explained that these trials are qualitatively different from most NIH and industry-supported clinical trials in that they examine a wider range of outcomes, including long-term changes in patient functioning. The goal in supporting these studies was to examine a range of illnesses and provide important and useful information to consumers, providers, payers, and policymakers. Dr. Insel asked the Council to consider strategies to facilitate the greatest use of the public investment in these trials.

*Background and Context for the Program*

An overview of the program was given by Dr. Steven Hyman, NIMH Director from 1996 to 2001, who is now Harvard University Provost and Professor of Neurobiology at the Harvard Medical School. Dr. Hyman said that the program was begun because available medications and psychotherapies had limitations, including problematic side effects. Furthermore, novel mechanisms of action for psychotropic drugs, the lack of new types of medications, and the complexity of using the drugs on the market presented a pressing public health problem—how best to use available treatments.

In response to these pressing issues, the NAMHC established the Clinical Treatment and Services Research Workgroup to propose a series of recommendations to better enable people with mental illnesses to access optimal care in community settings. The Workgroup's key recommendations included expanding treatment research from small select populations to multisite community-relevant populations, investigating the impact of illness and treatment on function as well as symptoms, exploring the impact of system, provider, and consumer behavior on treatment, and involving stakeholders in priority setting.

There were key challenges in moving beyond the classical randomized clinical trial to support for the large clinical trials: many confounding variables (e.g., populations are heterogeneous, patients have comorbid conditions, and community treatment settings are diverse with staffs that focus on clinical concerns rather than research requirements); the loss of statistical power given assessment of multiple outcomes; the requirement to recruit a diverse population that would permit generalizability of findings; the risks of extending the duration of the trials given anticipated patient dropout rates; and the costs associated with conducting the trials. However, with the support of the Council and staff, NIMH made the decision to move forward with the trials.

Dr. Hyman concluded his comments by noting that he looked forward to hearing from the investigators for the trials.

*Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)*

Dr. Jeffrey Lieberman, Chairman of the Department of Psychiatry at Columbia University and Director of the New York State Psychiatric Institute, began his presentation by explaining the rationale for the CATIE schizophrenia trial. He reminded the Council that prior to the introduction of clozapine in 1990 when it was approved for use in the United States, conventional antipsychotic drugs were the standard medications used for the treatment of schizophrenia. Given its side effect profile, clozapine has typically been prescribed for treatment-resistant patients. Other currently available second-generation antipsychotic drugs include risperidal, which was introduced in 1994, zyprexa in 1996, and seroquel in 1997; thereafter geodon and abilify came on the market. These drugs account for more than $10 billion annually in sales in this country or about 95 percent of the market share for antipsychotic drugs. In addition to being used as treatments for schizophrenia, they are prescribed for other conditions, including Alzheimer's disease, bipolar disorder, and depression. The benefits of the second-generation drugs are that they are believed to lessen negative symptoms, cognitive deficits, and functional disabilities associated with the illness and do not appear to produce the neurologic side effects associated with first-generation antipsychotic drugs. Although more

costly initially, in the long run it is believed that the second-generation drugs are cost-effective because they reduce the need for mental health services and increase the ability of people to be gainfully employed, productive, and independent.

The CATIE schizophrenia trial was designed to examine the long-term effects and usefulness of the newer second-generation (atypical) antipsychotic medications and a first-generation (typical) antipsychotic for the treatment of persons with chronic schizophrenia. The trial also examined cost-effectiveness factors. Initial results were reported in September 2005 [see Lieberman J.A., Stroup T.S., McEvoy J.P., Swartz M.S., Rosenheck R.A., Perkins D.O., Keefe R.S., Davis S.M., Davis C.E., Lebowitz B.D., Severe J., Hsiao J.K.; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. "Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia." *New England Journal of Medicine* 353(12):1209-23, 2005]. The cost analyses will be published in December (see Rosenheck, R.A., Leslie, D.L., Sindelar, J., Miller, E.A., Lin, H., Stroup, T.S., McEvoy, J., Davis, S.M., Keefe, R.S.E., Swartz, M., Perkins, D.O., Hsiao, J.K., and Lieberman, J., for the CATIE Study Investigators. "Cost-Effectiveness of Second-Generation Antipsychotics and Perphenazine in a Randomized Trial of Treatment for Chronic Schizophrenia. *American Journal of Psychiatry* 163:2080-2089, 2006). The results of the CATIE Alzheimer's trial will be published in the fall (see Schneider, L.S., Tariot, P.N., Dagerman, K.S., Davis, S.M., Hsiao, J.K., Ismail, M.S., Lebowitz, B.D., Lyketsos, C.G., Ryan, J.M., Stroup, T.S., Sultzer, D.L.., Weintraub, D., and Lieberman, J.A., for the CATIE-AD Study Group. "Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease." *New England Journal of Medicine* 355:1525-1538, 2006).

Dr. Lieberman said that 57 clinical sites in 24 states in different geographic regions of the United States participated in the schizophrenia trial. The diverse settings reflect the different systems of care available to patients in the community. About fifteen hundred outpatients who were diagnosed with schizophrenia and required antipsychotic medication were recruited and enrolled. Patients were excluded if they were in their first episode of schizophrenia or had proven to be treatment refractory. Individuals with comorbid medical and psychiatric conditions were eligible to participate. Patients were initially randomized under double-blind conditions to one of five treatments (Phase 1)—olanzapine, risperidone, ziprasidone, or quetiapine (all second-generation antipsychotic medications) or perphenazine (a first-generation antipsychotic)—for up to 18 months. Concomitant medications were permitted throughout the trial, except for additional antipsychotic medications. Recognizing that the initially assigned medication may not be effective, patients could be re-randomized to the Phase 2 trial. If the Phase 2 medication was discontinued, patients could enter Phase 3 (an open-label treatment). The CATIE treatment protocol was designed to retain patient involvement for the entire 18 months of the study.

The primary outcome measure was the time that passed before a participant discontinued treatment for any reason. That measure was selected because it represented an important clinical endpoint that reflected both clinical and patient judgments about efficacy and tolerability. Dr. Lieberman said that he and his colleagues predicted that over the 1½ years of the study, about 60 percent of study patients or their doctors would want to switch the assigned study medication because it either did not control symptoms or produced undesirable side effects. The discontinuation rate of study medication before 18 months for the overall sample during Phase 1 turned out to be higher than predicted, 74 percent. The treatment that did the best of the five in the initial phase of treatment was olanzapine as 64 percent of patients originally assigned

discontinued treatment, followed by risperidone at 74 percent, perphenazine at 75 percent, ziprasidone at 79 percent, and quetiapine at 82 percent.

In terms of medication side effects, the overall rates of parkinsonism and tardive dyskinesia were under 10 percent. Even the use of perphenazine at study dosages appeared to result in rates that were no higher than the other study medications. Elevations in prolactin were associated only with risperidone. About 12-15 percent of the patients gained weight. Olanzapine was the most effective medication in terms of the rates of discontinuation, but it also was associated with greater weight gain and increases in measures of glucose and lipid metabolism than any of the other study medications. The second-generation medications did not appear to offer advantages over perphenazine in terms of the alleviation of negative and cognitive symptoms.

In Phase 2 of the study, patients who discontinued their assigned study medication in Phase 1 could enter one of two Phase 2 treatment options. Patients who discontinued Phase 1 study medication due to lack of efficacy were offered the clozapine treatment arm where they were randomly assigned to receive clozapine or one of the other second-generation drugs that they did not receive in Phase 1. Time to treatment discontinuation was significantly lower in patients who switched to clozapine. For patients who were re-randomized in Phase 2 because of intolerable side effects of the treatment provided in Phase 1, they could receive either ziprasidone or another second-generation drug that they did receive in Phase 1. For patients who entered this treatment arm, those who received olanzapine and risperidone did best, whereas those on ziprasidone and quetiapine had the poorest outcome.

The clinical implications of the findings can be summarized as follows: All five study medications were effective but have substantial limitations reflected by high discontinuation rates. Particularly noteworthy is that perphenazine offered a viable treatment option for patients with schizophrenia. Olanzapine should be considered for patients where efficacy but not weight gain is the primary concern. For patients where weight gain is a major consideration, ziprasidone should be considered. Quetiapine should be considered for patients who fail to respond to conventional medications. Risperidone provides an intermediate choice in terms of treatment options. For patients with persistent symptoms, clozapine is a good treatment option. Dr. Lieberman said that the high rates of non-adherence suggest greater use of long-acting medications. Also clear from the CATIE results showing high rates of discontinuation is the need for better treatment options—not just new treatments but mechanistically novel treatments.

Dr. Lieberman concluded by noting that treatment can be individualized to the specific needs of patients with schizophrenia. However, doctors and patients must carefully evaluate the tradeoffs between efficacy and side effects and past treatment history in determining the best course of treatment. Clearly, the clinician can turn to the next choice on the clinical algorithm when an initial treatment proves ineffective or produces intolerable side effects.

*Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)*

Dr. Gary Sachs, Director of the Bipolar Clinical and Research Program at Massachusetts General Hospital, said that when planning the study of bipolar disorder, the challenge was: (1) to develop a common disease management model that could be used across diverse settings with patients in

every phase of the illness, all across the United States; (2) to develop clinically meaningful outcome measures for patients with bipolar disorder in every phase of illness; and (3) to determine the effectiveness of treatment for bipolar depression.

In STEP-BD, clinicians initially received 20 to 40 hours of training on nine major clinical pathways for the management of bipolar illness, each referred to as a Standard Care Pathway (SCP). STEP-BD best-practice treatment options included the use of mood-stabilizing medications, both newer and older classes of antidepressants, atypical antipsychotic medications, and psychosocial interventions. The psychosocial interventions included cognitive behavioral therapy, family-focused therapy, interpersonal and social rhythm therapy, and collaborative care. Dr. Sachs commented that involving patients in their own care contributed considerably to the success of the project. Patients in the SCP could receive any intervention felt to be clinically indicated by their clinician and participate in one of the STEP-BD Randomized Care Pathways (RCPs) and receive one of several psychotropic medication regimens considered to be first-line treatment options.

The researchers judged success of the treatments by the proportion of patients who achieved recovery, defined as having no more than two symptoms of the disorder for a period of at least 8 weeks. The majority (70 percent) of recurrences were characterized by a return to a depressive state. Several studies, including STEP-BD, have shown that by and large, patients with bipolar disorder spend the greatest proportion of their time dealing with depression. Thus, the treatment of depression in bipolar patients became a major priority for the study.

The study enrolled more than 4,300 outpatients, age 15 and above, at 26 sites—the largest sample of patients with bipolar disorder that has ever been assembled. Among the findings from the naturalistic study data enumerated by Dr. Sachs were the following:

- The average age of onset for the study patients was early—about 16 years of age.
- Depression was three times more common than mood elevation.
- Patients had high rates of comorbid conditions, including anxiety and substance abuse.
- About 60 percent of patients who were symptomatic when they entered STEP-BD had at least a 2-month interval of being completely well within the first year of the study, almost all within the first 6 months. Among those who got well, 51 percent stayed well for 2 years or longer. For those patients who did not remain well, relapse was associated with the presence of residual mood symptoms at initial recovery. This finding suggests that treatment should be aggressive and residual symptoms of depression, mania, and anxiety should be treated [see Perlis R.H., Ostacher M.J., Patel J.K., Marangell L.B., Zhang H., Wisniewski S.R., Ketter T.A., Miklowitz D.J., Otto M.W., Gyulai L., Reilly-Harrington N.A., Nierenberg A.A., Sachs G.S., and Thase M.E. "Predictors of Recurrence in Bipolar Disorder: Primary Outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)." *American Journal of Psychiatry* 163(2):217-24, 2004].
- There was no demonstrated evidence that standard antidepressant medications were more beneficial than mood stabilizers alone, that they worsened the course of bipolar disorder, or that they exacerbated suicidality.
- Prior to study entry, a low percentage of patients received an adequate treatment for comorbid anxiety disorders, the most common comorbidity in the study. The combination of a mood and anxiety disorder was found to be associated with a 2-3 fold

increase in the history of suicide attempts, a first episode onset on average 4 years earlier, and shortened durations of well intervals.

- The randomized double-blind trials embedded in STEP-BD that examined the role of standard antidepressants are under embargo, but one published randomized study provided evidence that lamotrigine may be superior to inositol and risperidone in improving treatment-resistant bipolar depression. That is, using a rigorous definition of sustained response or recovery for 8 weeks in the randomized open-label medication augmentation trial, patients taking risperidone were well 5 percent of the time; those taking inositol were well 17 percent of the time, and those taking lamotrigine 24 percent of the time [see Nierenberg A.A., Ostacher M.J., Calabrese J.R., Ketter T.A., Marangell L.B., Miklowitz D.J., Miyahara S., Bauer M.S., Thase M.E., Wisniewski S.R., Sachs G.S. "Treatment-Resistant Bipolar Depression: A STEP-BD Equipoise Randomized Effectiveness Trial of Antidepressant Augmentation with Lamotrigine, Inositol, or Risperidone." *American Journal of Psychiatry* 163(2):210-6, 2006].
- Studies of women's health, most of them pilot studies, were also done. The largest of the randomized women's studies examined whether valproate was associated with polycystic ovarian syndrome, a condition associated with infertility, masculinization, and irregular menses. Using a sensitive rigorous design to assess for these conditions, the results showed that treatment with valproate resulted in a 10.5 percent rate of treatment-emergent polycystic ovary syndrome, compared to a 1.4 percent rate for other treatments. That finding is important for women with bipolar disorder who must be told about the risk before they start treatment (see Joffe H., Cohen L.S., Suppes T., Hwang C.H., Molay F., Adams J.M., Sachs G.S., and Hall J.E. "Longitudinal Follow-up of Reproductive and Metabolic Features of Valproate-Associated Polycystic Ovarian Syndrome Features: A Preliminary Report." *Biological Psychiatry*, August 31, 2006).

Dr. Sachs said that as the findings from STEP-BP are published, they will have broad implications for how bipolar depression is managed in everyday practice. The large database, which is available for collaborative use, will provide important new information. In addition, the large genetics repository amassed during the study includes whole genome scans and an unprecedented level of associated clinical data that may shed new light on the genetics and treatment of bipolar illness.

*Treatment for Adolescents with Depression Study (TADS)*

Dr. John March, Professor of Psychiatry and Chief of Child and Adolescent Psychiatry at Duke University Medical Center, said that TADS was conducted at 13 academic and community sites around the country. The objective was to examine the effectiveness of four treatments acutely and over the long term for teenagers with DSM-IV major depression: (1) medication management with fluoxetine (FLX), the only antidepressant at the time the study started that had shown benefit in the pediatric population; (2) cognitive behavioral psychotherapy (CBT); (3) the combination of FLX and CBT, a combined treatment untested in pediatric populations; and (4) a placebo control medication condition. The study was done in three stages across 36 weeks: 12 weeks of acute randomized treatment (Stage I), followed by consolidation treatment where full medication responders at the end of stage I were moved to maintenance treatment and partial responders were given 6 weeks of additional high-intensity treatment (Stage II). Stage III consisted of 18 weeks of maintenance treatment, for a total of 9 months of randomized treatment for TADS participants. Placebo patients were unblinded at 12 weeks for ethical reasons and

given open treatment. Assessments were done by independent evaluators blind to treatment status. The 439 participants recruited averaged 15 years of age; half were males, half females. Seventy-five percent of patients were Caucasian, 13 percent African American, and 9 percent Hispanic. The average family income was $75,000, slightly tilted towards middle and upper middle class, but incomes ranged from the poverty level up to higher socioeconomic levels.

Prior to study entry, the participants were diagnosed with moderate to severe depression and had a mean duration of illness of approximately 1 year. The teenagers were chronically and stably depressed. Fifty percent were comorbid for another mental illness: 40 percent had a mood or anxiety disorder, 25 percent had a disruptive behavior disorder that was not attention deficit/hyperactivity disorder (ADHD), and 15 percent had ADHD, about a third of whom were taking a psychostimulant at the start of the trial.

Dr. March summarized some of the major findings:

- In terms of improvement in depression as measured by the Children's Depression Rating Scale, at week 12 of acute treatment, the two medication-containing conditions, combination treatment and medication management with FLX, were clearly superior to CBT and placebo, which did not differ. Statistically, there was no difference between the combination treatment and FLX. Dr. March noted that these findings suggest that to accelerate recovery from depression early in treatment, medication must be included in the treatment algorithm.
- Across the course of the trial, every group continued to improve beyond 12 weeks. At week 18, the combination of FLX and CBT or FLX alone was still significantly better than CBT alone, and the combination group was near threshold for remission. At 9 months, the benefits of CBT alone were similar to those for the combined treatment. The take-home message, Dr. March said, is that over the 36 weeks of treatment, all of the treatments have come together with a significant level of improvement, but treatment with CBT requires more time to achieve the same level of improvement.
- At week 12, the response rates were significantly better in the combination and FLX groups than in the CBT or placebo groups. About 70 percent of patients achieved a response with combination treatment, 60 percent with FLX alone, around 44 percent with CBT, and 34 percent with placebo. At week 18, CBT had caught up with fluoxetine, while the combination treatment was still much better than either CBT or the drug alone. By week 26, all the treatments showed similar response rates.
- The global assessment scale measuring level of functioning showed results that exactly corresponded to the remission rates. There was a clear advantage of the combination treatment over the other three treatments, which did not differ from each other in the level of functioning.
- The adolescents rated themselves on their quality of life. Those scores again showed a clear advantage for the combination treatment over the other three treatments, which did not differ from each other in the adolescent's perception of improvement in quality of life across 12 weeks of treatment.
- TADS contributed substantially to the debate regarding selective serotonin reuptake inhibitor (SSRI) treatment of depression and treatment-emergent suicidal behavior. At week 12, suicidal ideation had declined in all of the treatment groups. The FLX group did not improve as much as the other treatment groups. The most dramatic improvement was the combination group, which went from significantly more suicidality to

significantly less relative to FLX; that finding suggests that CBT, when given with FLX, in some way buffers any treatment-emergent risk associated with the drug. Suicidal events—interrupted suicide attempts or a clinically significant worsening of suicidal ideation—showed an identical pattern. There was an excess of suicidality in the FLX-treated adolescents relative to the combined treatment, CBT, and placebo. At 36 weeks, the same indicator showed similar results: slightly more than 14 percent of the FLX-treated patients had a suicidal event, compared with 8 percent of those who received combination treatments and 6 percent of those who received CBT alone. Most of the risk occurred early in treatment, with relatively little risk during maintenance treatment.

Summarizing the TADS findings, Dr. March said that accelerating improvement in moderate to severely depressed teenagers requires medication. Combined treatment provides better outcomes than medication alone. This proved to be true across multiple domains of outcome. CBT is an effective treatment but requires more time to produce a treatment response. Combined treatment confers striking protection against suicidal events, particularly the risk for treatment-emergent suicidal events. When both risk and benefit are taken into account, the combination of FLX and CBT appears to be superior as a treatment for major depression in adolescents. Significant public health benefits should accrue if severely to moderately severe depressed teenagers are identified and receive the combined treatment. Much of medicine relies on combined treatment using medication management and a target-specific psychosocial intervention designed to rehabilitate the somatic substrate of the illness, such as the use of diet and exercise in diabetes and physical therapy for arthritis. Dr. March said there is no reason why the same model should not be used in psychiatry.

He concluded his presentation with the observation that good clinical practice requires the careful monitoring of the benefits and potential harms of treatment. It is clear that psychiatric illness tends to be best conceptualized as a neurodevelopmental set of disorders, Dr. March said, that begin in childhood and extend into adulthood. The earlier the onset, the more likely the course of illness will be severe. Preventing mental illness will depend on a shift to more research earlier in the life span.

*Sequenced Treatment Alternatives to Relieve Depression (STAR*D)*

Results of the STAR*D trials were presented by Dr. A. John Rush, Vice Chair, Department of Clinical Sciences, Professor, Department of Psychiatry, and Betty Jo Hay Distinguished Chair in Mental Health at the University of Texas Southwestern Medical Center at Dallas.

Dr. Rush explained that the STAR*D trial, conducted at 41 clinical sites with 18 of them in primary care settings, represents the largest prospective study of a broadly representative adult outpatient sample with non-psychotic depressive disorder.

The main objective of STAR*D was to determine prospectively the next best treatment steps for depressed patients who experience an unsatisfactory clinical outcome following an initial and, if needed, subsequent treatment step(s). When the trial began, it was unclear whether patients who require more treatment steps in order to get better differ from those who require fewer steps. In addition, it was unclear whether patients who require more steps have lower remission rates, take longer to achieve remission, or have poorer long-term outcomes. The role of baseline moderators—clinical or biological characteristics including genetics that might influence decisions about treatment selection—was also explored. A final objective was to define long- term outcomes in a representative broad population of patients with depression. For that reason, inclusion and exclusion criteria were minimally restrictive, and a wide array of treatment settings beyond traditional research ones were used in the study.

The design of the study was complex. In Level 1, patients received the SSRI citalopram (CIT). Patients who either did not have an adequate response to or could not tolerate CIT were eligible for random assignment to Level 2 treatments where they could switch to another treatment [sertraline (SERT), bupropion-sustained release (BUP-SR), venlafaxine-extended release (VEN-XR), or cognitive therapy (CT)] or continue to receive CIT with the addition of another augmenting compound (BUP-SR, buspirone, or CT). Patients without a satisfactory response to Level 2 treatment were eligible for Level 3 treatment that offered random assignment to two switch options [mirtazapine (MIRT) or nortriptyline (NOR)] or to two augment options (lithium or triiodothyronine). Patients who had not done sufficiently well by the end of Level 3 were eligible for Level 4 random assignment to tranylcypromine or MIRT plus VEN. Patients with adequate improvement at any step could enter a 12-month naturalistic follow-up phase. The number of patients declined as the study progressed: 2,876 participated in Level 1; 1,438 in Level 2; 390 in Level 3; and 109 in Level 4.

The study patients were widely representative of the kinds of patients who have depression and who seek treatment in the community. Their average age was 40.8 years, ranging from 18 to 75; those over 75 were excluded because of problematic efficacy, safety, and dosing data that were available. Sixty-four percent of patients were female; 76 percent were Caucasian, 18 percent African American, and 13 percent Hispanic. They had a relatively long-standing illness, averaging 16 years. Twenty-five percent had been in the current episode for 2 years or more. Almost 40 percent of the study participants had their first major depressive episode before age 18. One in five had a substance abuse or a dependence problem, and such patients were not excluded from the study as long as they were suitable for antidepressant medication treatment. About 52 percent had private insurance and 14 percent had public insurance; the remainder had no insurance. The socioeconomic range was wide. Patients were seen in both primary and specialty care settings.

Two-thirds of the patients had general medical conditions, which are known to be a major risk for developing depression. Individuals with schizophrenia and bipolar disorder were excluded, but two-thirds had at least one other Axis-1 disorder, primarily anxiety and somatiform-type disorders. Such a high level of comorbidity is unusual in efficacy trials where patients with multiple comorbidities are typically excluded from study. Dr. Rush said that analyses are underway of study participants who would have been eligible for standard efficacy trials. Those results are not yet available.

The investigators did not necessarily seek out chronically ill people or those with very early onset. They did require that participants meet criteria for major depressive disorder such that medications would be recommended for treatment. During the study, the research team regularly measured symptoms and side effects. Using simple measures that included self-reports from patients, which engaged them and helped to retain them in treatment, and an algorithm that recommends to the physician when dose increments should be made, high-quality care was delivered at no significantly increased expense.

Patients were given maximally tolerated dosages, which were higher than doses commonly used in practice, to ensure that optimal treatment was provided before a determination was made that participants would proceed to the next treatment level.

Remission was chosen as the major outcome measure and was determined by scores on the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) ratings done by the patients. At the end of 12 to 14 weeks, a third of the patients on CIT in Level 1 achieved remission of symptoms, a result similar to those obtained in efficacy trials with patients who are not treatment resistant and who did not have comorbid illness. The remission rate at Level 2 was also about a third. At Level 3, 14 percent had remitted, and at Level 4, 13 percent remitted. The time to remission in those who did remit was slightly greater for patients requiring more treatment steps.

Dr. Rush said that it can be argued that if patients do not discontinue treatment, it is possible to achieve a remission rate of about 70 percent after four treatments. However, patients do discontinue treatment. Either they do not tolerate treatment, or in the case of STAR*D where patients had to give consent at every level, when confronted with the possibility of tranylcypromine at Level 4, an MAO inhibitor with dietary restrictions, there was a higher decline rate for consenting to go forward. The other consideration is that each acute treatment level lasted up to 12 to 14 weeks—it may be possible to more rapidly achieve remission.

Dr. Rush said the study demonstrated the following:

- High-quality measurement-based care can be implemented in routine care settings.
- Patient preference should be encouraged. In this study, some patients did express a preference for switching to another antidepressant or augmenting their medication with another drug or CT. Under study conditions, the question of whether to augment or switch turns out not to be difficult to answer if one listens to the patient.
- Vigorous medication doses produced reasonably good outcomes, although the percentage of new patients in remission decreased over multiple steps.
- Treatment should be continued until the patient achieves remission.

- Response and remission take longer than the commonly held belief of 4-6 weeks; a third of the responses to medication and half of the remissions occurred after 6 weeks. When asked at 6 weeks how they were doing, patients responded that they didn't think a medication was working when they had not experienced at least a 50 percent reduction in depressive symptoms. In real-world settings, it takes longer to see a benefit, even when patients are vigorously dosed and given high-quality care.
- Early efforts are needed to enhance patient retention. Patients who left acute treatment early have greater illness burden (patients with more comorbid conditions) and tended to have less education, be in the lower socioeconomic classes, and be members of ethnic minorities and socially disadvantaged groups.
- Non-remitting patients relapse at twice the rate of patients who do remit.
- Children of mothers with depression improve when mother's depression improves [see Weissman, M.M., Polowaky, D.J., Wickramaratne, P.J., Talati, A., Wisniewski, S.R., Fava, M., Hughes, C.W., Garber, J., Malloy, E., King, C.A., Cerda, G., Sood, A.B., Alpert, J.E., Trivedi, M.H., Rush, A.J., and STAR*D-Child Team. "Remissions in Maternal Depression and Child Psychopathology: A STAR*D-Child Report." *Journal of the American Medical Association* 22:295(12): 1389-1398, 2006].
- Collaborations with NIMH investigators have produced interesting genetic findings [see McMahon, F.J., Buervenich, S., Charney, D., Lipsky, R., Rush, A.J., Wilson, A.F., Sorant, A.J., Papanicolaou, G.J., Laje, G., Fava, M., Trivedi, M.H., Wisniewski, S.R., and Manji, H. "Variation in the Gene Encoding the Serotonin 2A Receptor is Associated with Outcome of Antidepressant Treatment." *American Journal of Human Genetics* 78(5): 804-814, 2006].
- Subsequent trials should be designed with long-term outcomes as the primary research focus.
- Two study patients committed suicide, many fewer than what might have been expected in this population. Eight other participants died from non-psychiatric causes.

Among the public health implications of the study is that individuals with serious, complicated, or life-threatening illness can safely be included in studies with a proactive risk-management approach. However, better treatments are needed for treatment-resistant depression, Dr. Rush said. Echoing Dr. Hyman's comments, Dr. Rush urged better delivery of available treatments. STAR*D did not exhaust all possible combination treatments that are widely used in practice, although little evidence exists for their comparative efficacy, safety, and tolerability.

Dr. Rush concluded his talk by noting that the study's dosing procedures, manuals, rating scales, and other aspects of the study are in the public domain and available at www.star-d.org and www.ids-qids.org.

Dr. Insel noted that the ancillary studies have turned out to be a very important component of the practical trials. He noted that genetic components were initiated in response to a recommendation by Council that DNA be collected on all participants in the studies.

*Next Steps in Determining Optimal Care*

Council member Dr. Susan Essock, who served as chairperson of the Council Workgroup on Services and Clinical Epidemiology Research, suggested that NIMH can optimize its investment in the large practical trials in a number of ways. The trials are "stunningly relevant—virtually

everyone knows someone for whom the results are relevant." She noted that there are significant health care dollars at stake given the cost the illnesses reported on today as well as the interventions to treat them.

Dr. Essock highlighted themes that emerged from the trials. The trials showed that more needs to be known about addressing residual symptoms and unmet needs. STAR*D is compelling in showing that complete remission should be the goal of treatment for depression. At the same time, each of the trials shows that there are many individuals whose symptoms do not remit with treatment. They and their clinicians need to be provided with information on pharmacological and psychosocial interventions that can be tried as next treatment steps. Another theme across the trials is that this is newsworthy science. It is clear that consumers and payers are anxious for unbiased comparative trials providing good data on the effectiveness of alternative treatment approaches to guide treatment choices. Each of the speakers talked about current prescribing patterns that lack an evidence base for treating people who have not responded to the first, second, or third treatment.

These studies have produced data that already have begun to serve as national resources, Dr. Essock continued. Three networks—the Depression Network, the Bipolar Network, and the Schizophrenia Trial Network, each evolving respectively from CATIE, STAR*D, and STEP-BD, are ongoing resources. The question is how to maximize the impact of the investments in these networks. As an example, she referenced the schizophrenia network that provided the opportunity for Dr. Essock and her colleagues to mine the CATIE data to address a very common clinical quandary—whether to switch to another medication. Some participants who entered the CATIE trial were randomly assigned to stay on the same medication that they had been taking at study entry. Dr. Essock's group was able to use the CATIE data to look at the relative benefits and risks associated with staying on a given antipsychotic versus switching to another one. Another question that can be addressed with the CATIE data relates to antipsychotic polypharmacy, a common clinical practice without an adequate database to support it. A third question concerns the use of a conventional injectable antipsychotic versus an injectable second-generation medication. Other benefits associated with the CATIE trial include faster recruitment of more diverse samples, availability of trained raters, and greater ease in overcoming bureaucratic hurdles such as indemnification language since contracts with sites had already been worked out in the CATIE study.

The practical clinical questions addressed in the large trials are relevant to the recommendations contained in the report of the Council Workgroup on Services and Clinical Epidemiology Research. Those recommendations included enhancing research responsiveness to stakeholders, including large payer groups, which each of the trials has done. Although the trials were expensive, payers also are facing increasing treatment costs and are looking for guidance. The Workgroup called for engaging payers as potential funding partners in leveraging scarce NIMH resources. Science and services can coexist, she said, as shown in the September 2006 issue of *Psychiatric Services.* That issue was devoted to the public health response to the September 11, 2001, terrorist attacks. Project Liberty, funded by the Federal Emergency Management Agency (FEMA), was created in the aftermath of September 11 to provide community-based disaster relief for the people of New York who experienced psychological distress after the attacks. Project Liberty, Dr. Essock said, was an example of how one can leverage a small amount of research dollars to translate science into services. In this case, NIMH contract funds were used to provide rapid research support. Overcoming practical hurdles efficiently and effectively will

depend largely on the wisdom of NIMH staff and its advisors to seize research opportunities and implement them in real-world settings. It is imperative, she said, that the collective wisdom gained from the successes and failures of the trials reported on at this session be shared throughout the research community.

Dr. Essock concluded her remarks by suggesting that in the future, NIMH should consider cost-sharing projects with public partners through Requests for Proposals that might be issued jointly with them. Also needed are strategies for more rapid translation of research findings into practice. The networks, she reiterated, are national resources that can help keep (research) traffic flowing smoothly on the road ahead.

*Discussant Comments*

Council member Renata Henry, Director of the Delaware Division of Substance Abuse and Mental Health, said that the large investment made by NIMH in the trials was worth the investment of time and resources because the results and outcomes have clear public mental health policy relevance. However, she continued, there are real challenges in translating the research outcomes and interventions to the public mental health sector. Partnerships are needed with State mental health directors and payers including Medicare and Medicaid to explore the key elements for implementing an intervention as well as strategies for accelerating implementation. Meeting that challenge can only be done if NIMH commits to partnerships with consumers and families, administrators, policymakers, and payers to explore these issues.

The second discussant, Council member Dr. Suzanne Vogel-Scibilia, Medical Director of the Beaver County Psychiatric Service in Pennsylvania and President of the Board of Directors of the National Alliance for Mental Illness, noted the importance for NIMH to have a clear focus on the most serious mental illnesses in both pediatric and adult populations. Attacking these illnesses as first priorities increases the likelihood of making substantive progress given the grave morbidity and mortality associated with them. She advocated expanding the opportunity for practical real-life studies, including the trials reported on at the session, which delivered more bang for the buck than was originally anticipated. In addition, Dr. Vogel-Scibilia continued, the U.S. Government is the only organization that can realistically support such studies because of its unbiased goals, financial resources, and ability to disseminate important research findings to the end users of research. It is critical that a comprehensive strategy for research dissemination be in place to transmit important findings to treatment providers outside of specialty mental health settings, including family practitioners and internists who are handling a tremendous amount of severe and persistent mental illness. Treatment adherence, Dr. Vogel-Scibilia continued, is a big problem that may relate to the public's perception of undue influence by the pharmaceutical companies in the conduct of research and metabolic and safety concerns associated with currently available treatments. She concluded her remarks by emphasizing the importance of effective communication strategies to address these public concerns.

*Question-and-Answer Period*

During the general discussion that followed, Dr. Wagner asked Dr. March whether a paper from TADS would be published focusing on CBT for moderate to severely depressed children that would highlight the length of time needed to achieve a response. Dr. March replied that the take-home message from TADS is that a rapid response requires medication. Patients are likely to do

just as well with CBT in 4-6 months as they would on medications during a shorter period. One question that arises is who would respond best with initial treatment of CBT and with the addition of medication as needed, and who requires a combination treatment from the outset? He also emphasized that all CBT is not the same. A recent meta-analysis showed that the effect sizes for CBT are small in depression. Dr. March said he would like to see more research done on the effectiveness of CBT in depression using data from the network, the hardware for which is now in place.

Dr. Rush said that the outcome data from the psychotherapy arm of the STAR*D trial will be published soon. He said he and his colleagues were surprised by the lack of popularity of CT; only 60 to 100 study patients actually received CT. Another problem, he said, was that more than 40 cognitive therapists were trained but they were not at the sites where the care was being delivered, and thus patients had to go to two different practitioners and make two co-payments to receive CT.

Dr. Aguilar-Gaxiola asked Dr. Rush about the special attention needed to retain patients who are minorities or who have low income and educational levels. He said that failure to stay in treatment is a huge problem in some populations. Among Latinos, for example, up to 75 percent of those who began treatment did not return for a second time. Dr. Rush said that to improve retention, his group developed a brief patient booklet, which is on the Web site. Also, all of the study forms and rating scales were produced in English and Spanish. The entire 28-page protocol was presented at the first visit, which was burdensome. About eight percent never came back. That group is being analyzed separately. Another subset dropped out of treatment early. Those analyses show that it is not just ethnicity that predicts study discontinuation, it is also being socially disadvantaged. Dr. Rush said that the variant that was most powerfully related to outcome was the presence of comorbid illnesses.

Dr. Levitt said that he believes that the public does not understand that psychotherapy, like medications, can qualitatively and quantitatively alter brain chemistry and that part of the reason for the reluctance to seek cognitive therapy may be related to this lack of understanding. Dr. Sachs said that mental health treatment can be seen as stigmatizing to some patients but that providing quality services and the rationale for treatment can lessen some of those perceptions.

Dr. March said that he hopes that over the next 10 years, research will demonstrate the mechanisms of action of psychotherapy to explain the impact of learning-driven models on mental illnesses. Recent research has shown, for example, that over-learning strategies are effective in processing language among individuals with dyslexia. The same strategies can be used to teach people, such as those with social phobias, the skills to help them manage their illness.

Dr. Levitt asked whether the data gathered in the reported trials can be useful in understanding retrospectively what developmental history contributes to these disorders in an effort to increase the relevancy of basic neuroscience, which develops and implements adult-based behavioral studies in model systems, to the developmental aspect of many complex behaviors and illnesses.

Dr. Lieberman said that most mental disorders have their origins in childhood and the patients involved in the schizophrenia, bipolar disorder, and depression studies represent the culmination of a lengthy process of pathogenesis and pathophysiology at an advanced stage. He suggested

that by partnering with the Substance Abuse and Mental Health Services Administration, the established networks would make it possible to initiate, for example, a CATIE study in children and quickly involve thousands of participants, thus more rapidly providing answers that could be disseminated into practice.

Dr. March added that the networks are ideally suited for doing studies, such as pharmacogenomics, which require large samples and involve moderator variables and segmenting of the population. He recommended that funding for future trials emphasize measurement models and designs that are specific to moderator and mediator variables and mechanisms.

Dr. March said that Dr. Kraemer has emphasized the importance of studies such as the TADS to consider the effects of mediators on treatment response. Dr. Kraemer added that some individual differences in responses to treatment have been ignored, resulting in small effect sizes and the necessity for large studies to detect those small effect sizes. However, she suggested, it may be possible to conduct more focused studies with smaller sample sizes. That may result in increased effect sizes, and more effective treatments could be identified for specific segments of the population.

Dr. Levitt said that he and a colleague have been using the CATIE sample to look at genetic moderators of treatment response as well as moderators across the sample and are discovering differences between Caucasians and African Americans in the sample.

Dr. Hellander said that families of children with bipolar disorder would be more willing to participate in research if they are offered genetic testing in an effort to guide the best choice of treatment and avoid lengthy trials of drugs at doses with troublesome side effects. She also asked if there was an effort to include younger children in the trials.

Dr. Sachs replied that including children below the age of 18 years creates many administrative and practical problems in research settings across the country. Many staff members are not certified in child psychiatry. In addition, there may be local consent requirements and other administrative difficulties that complicate the study of younger children but might be streamlined to encourage research participation.

In summarizing the day's presentations, Dr. Insel said they reflect Dr. Zerhouni's four Ps of medical care. The first two—*predictive* and *preemptive*—require the ability to take action before damage is severe. Most mental disorders are chronic or recurrent with onset by age 14 in half of patients and by age 24 in three out of four people with mental illness. Developmental neuroscience has shown that drugs have different effects on the developing nervous system and different behavioral effects in developing animals than they do in the adults. The third P is *personalized* treatment. There may be no greater mandate for NIMH, Dr. Insel said. Moderator data are needed that help predict treatment responders and non-responders. The data on CBT treatment of depression is striking. The question is how to predict who is not going to respond before a 9- or 6- week trial is conducted. In genetic studies, it is necessary to learn if variations are practically important. The final P, one that Dr. Zerhouni recently added, is *participatory*. Participation can ensure the relevance of research, give leverage, and provide venues and opportunities to do studies.

Dr. Insel then invited members of the public to share their remarks.

## Public Comments

Ms. Sheila McDonald, president of the Child and Adolescent Bipolar Foundation, said that she was frustrated to hear that Institutional Review Boards turn down studies with children because the research team is not board certified in child psychiatry. In reality, most children are not being seen by board-certified child psychiatrists. Children are subjected to polypharmacy with medications that have never been tested in children. IRBs and others may believe that they are insulating themselves against liability by not taking on children. The omission constitutes a greater liability, Ms. McDonald said.

Dr. Insel thanked the presenters and the NIMH staff that provided support to the clinical trials. He announced that the next Council meeting will be on January 11-12, 2007. With that, he adjourned the meeting.

**ADJOURNMENT**

Dr. Insel adjourned the 213th meeting of the NAMHC at 12:45 p.m. on September 15, 2006.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

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Thomas R. Insel, M.D., Chairperson