New Paradigms for Treatment Development

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Wayne Fenton believed that government—particularly National Institute of Mental Health (NIMH)—could play a critical role in addressing important public health problems where the current system of treatment development was inadequate. Earlier experiences in HIV/AIDS convinced him and others that the NIMH can effectively facilitate the rapid development of new research in critical areas. This report will demonstrate how the work of Fenton and others brought together representatives from industry, government, and academia to address issues that included new preclinical approaches to drug development and defining new therapeutic targets in schizophrenia. An initiative to facilitate the development of new pharmacological agents to address the cognitive impairments in schizophrenia—titled Measurement and Treatment Research to Improve Cognition in Schizophrenia or MATRICS—is used as an example of a new paradigm for treatment development.

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Despite the introduction of a new generation of antipsychotic drugs, the outcome of schizophrenia has not improved to a substantial degree. That is not to say that there have not been advances in antipsychotic medications. Clinicians and patients can select among a number of agents. In the process, most patients are able to find an agent that is reasonably well tolerated. However, there is little to suggest that these improvements have had a substantial impact on the ability of patients to function in the community.1 Most patients with schizophrenia who are treated with antipsychotic medications are unmarried and unemployed, and many live with persistent psychotic and negative symptoms and cognitive impairments. These observations indicate that there are substantial limitations to what we can expect from currently available antipsychotic medications.

These limitations of antipsychotic medications are not a result of a lack of activity in the pharmaceutical industry. In recent years, there has been a substantial increase in spending by the drug industry. For example, between 1993 and 2004 the inflation-adjusted expenses by pharmaceutical companies for research and development increased from $16 billion to $40 billion. However, during this same period, the number of new molecular entities as well as the number of new drug applications to US Food and Drug Administration (FDA) decreased.2 Most of the new drug applications were for modifications of existing drugs rather than for innovative new agents. A report from the Government Accountability Office classified only 12% of the submissions as substantial innovations.2,3

National Institute of Mental Health and HIV/AIDS

Even though AIDS and schizophrenia are both prevalent in approximately 1% of the population, schizophrenia has not enjoyed the same sense of urgency that has characterized the AIDS pandemic for more than 25 years. The approach taken in AIDS can be seen as a model for schizophrenia research programs. The efforts of National Institute of Mental Health (NIMH) began in 1983 to reduce the fear and panic that occurred as a result of the disease. The response to reduce the suffering from AIDS has been profound and has resulted in the integration of many disciplines of science, from immunology to psychiatry. It has encouraged scientists to think about big picture issues and to demand that research be relevant to saving lives. The treatments have led to AIDS no longer being an acute death sentence to prolonging the quality of life and living with a chronic illness. The AIDS community was mobilized to fight a common enemy. There was a realization that research was not prevention and it was not until evidence-based prevention programs were implemented by public health clinics that the disease would be stopped. Therefore, NIMH-supported studies are systematically disseminated through the Centers for Disease Control.4

AIDS required that a new multidisciplinary field be built where none had existed. There were no experts, and research on sexual behavior was not active. There was also involvement from the community and activism,
not evident in schizophrenia research. Funds were set aside beginning in 1983 and continue to this day. NIMH established research centers with multidisciplinary teams and community representatives, who helped frame the research questions. AIDS also has an international perspective that makes it quite unique.

Another lesson learned in HIV research is that a quick “fix” does not work and that large-scale, multisite trials were needed to answer questions to develop culturally sensitive behavioral interventions to reduce risky behaviors and pharmacological treatments to deal with the neurocognitive problems, not addressed by Highly Active Antiretroviral Treatment. Another event that transformed the field was a 1997 National Institutes of Health (NIH) consensus conference on HIV prevention, the first behaviorally oriented conference in its history.5

Mental health and AIDS affect people who are marginalized and stigmatized. However, more than 99% of the people in our country are aware of how HIV is transmitted, while far fewer are aware of the characteristics of schizophrenia. It is difficult in both arenas to get professional and public support for the issues. Numerous areas that we developed for HIV research, such as adherence,6 behavior change and functioning,7 comorbidity,8 and stigma,9 are now being supported in schizophrenia through initiatives at the NIMH.

New NIMH Approaches in Schizophrenia

Experiences in HIV/AIDS and other disorders indicated that NIMH could play a leading role in setting a research agenda in an area of great clinical need. In this case, the clinical need was in schizophrenia where there was a recognition that current treatments were inadequate. In March 2001, Steve Hyman asked Wayne Fenton and Ellen Stover to develop an NIMH program in treatment development. This led to the selection of cognitive impairment as a particularly promising new target and a request for proposals to address some of the important obstacles that should be addressed to facilitate drug development in this area. The contract was awarded to University of California Los Angeles (UCLA) with Stephen Marder and Michael Green as the coprincipal investigators. They assembled a diverse group of individuals from academia, government, and industry to organize a series of 6 conferences on various aspects of treatment development for cognitive impairment in schizophrenia. Approaches to addressing drug development were explored at one of these meetings on Government-Industry Collaboration, convened on January 22, 2004. Organized by Ellen Stover and Wayne Fenton and the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) group, this meeting included representatives from NIMH, the pharmaceutical industry, and academia. (A transcript of the meeting is available at http://www.matrics.ucla.edu.) The goal was to reach agreement on how these different groups with different perspectives could contribute to a process of drug development that would lead to more effective treatments for mental illnesses. One model involving consensus building comes from the HIV/AIDS arena. In developing the schizophrenia initiatives, Ellen Stover and Wayne Fenton drew from principles of this model.

Lessons From MATRICS

There was a widespread agreement at all the MATRICS meetings10 that the current paradigm for drug discovery was leading to the development of agents that were only small incremental advances. The first effective drug for schizophrenia, chlorpromazine, was first administered to patients in Paris about 50 years ago. Since that time, dozens of other antipsychotics have been developed and introduced into clinical treatment. Although—as mentioned above—these drugs have improved the options for clinicians, all these agents—with the exception of clozapine—demonstrate similar efficacy in clinical populations. Recent large clinical trials such as the NIMH-Clinical Antipsychotic Trials of Intervention Effectiveness trial11 have reinforced the notion that these agents are similar. The lack of success in developing more effective antipsychotics is not surprising because all these agents appear to act at the same target, the dopamine D2 receptor. The drug discovery process has generally focused on preclinical models to identify agents with activity at this site.

In the January 2004 NIMH meeting (see Government-Industry Collaboration meeting transcript at http://www.matrics.ucla.edu), Thomas Insel, the NIMH Director, pointed out that there are potentially hundreds of thousands of targets for drugs. In his talk, Insel noted that drugs in all medicine have focused on fewer than 120 targets. This suggests that there may be extraordinary opportunities for therapeutics because research in genetics and molecular biology identifies the molecular pathophysiology that affects vital processes.

It is also important to note that it is not necessary to understand the etiology of an illness to develop drugs to treat the illness. With the exception of drugs for infectious illnesses and perhaps drugs for cancer, most effective drugs do not affect the basic processes that are causing the illness. For example, antihypertensive drugs lower blood pressure by mechanisms that are unrelated to the cause of the hypertension. The same is true for antipsychotic medications. They are not antischizophrenia agents. Rather, they are effective drugs for reducing psychotic symptoms regardless of the cause of the illness. In other words, a process for translating basic science findings into improved therapeutics can begin with improving our understanding of the processes that underlie the functions that can be worsened by an illness. This model suggests the importance of linking basic science discovery
to drug development. One of the important lessons of MATRICS was that there was considerable interest among basic and clinical scientists in participating in a broad initiative to improve drug development.

Functional genomics approaches are beginning to identify risk factors for schizophrenia that may offer valuable insights into the molecular-, cellular-, and systems-level pathogenesis of schizophrenia. Understanding functional pathways and mechanisms offer the promise of new targets for therapeutic development. A recent article by LeNiculescu et al12 provides an example of an approach to identify genes of pathophysiological relevance to schizophrenia. The authors use a convergent functional genomics approach to identify candidate genes by integration of brain gene expression data from pharmacogenetic mouse models (treated with phencyclidine, clozapine, the combination, or placebo) with human genetic linkage and postmortem brain data. Many of the gene candidates identified with the Bayesian strategy of cross-validation of findings are within pathways implicated in the pathophysiology of schizophrenia (eg, γ-aminobutyric acid and glutamates’ neurotransmission, synaptic function, myelin/glial function, and lipid metabolism). The genetic approach for validating targets for psychopharmacological intervention in schizophrenia harkens back to an article coauthored by Hyman and Fenton.13

NIMH Strategies

Over the past 10 years, NIMH has developed a number of strategies for exploring potential targets and preclinical drug discovery efforts for mental disorders. These strategies have included initiatives that specifically encourage research aimed at drug discovery and early preclinical testing of compounds with therapeutic potential studies aimed at design, synthesis, and preclinical testing of compounds; development of novel delivery systems; development of assays that permit the preliminary screening of candidate compounds; development of models that permit further evaluation of candidate compounds and/or toxicology studies; and initial testing of candidate compounds for efficacy using cell-based assays and/or preclinical models (http://grants.nih.gov/grants/guide/pa-files/PAR-07-048.html, http://grants.nih.gov/grants/guide/pa-files/PAR-07-049.html).

Wayne Fenton played a key role in the design and coordination of NIMH programs to advance the development and testing of fundamentally new, rationally designed medications and treatments for mental disorders. These programs provide a vehicle for industry and academic scientists to pool intellectual and material resources for the translation of basic science findings into the conceptualization, discovery, and evaluation of new chemical entities and promising clinical candidates in preclinical proof of mechanism, first in human, and proof of concept studies in patients with mental disorders. The National Cooperative Drug Discovery Group Program (http://grants1.nih.gov/grants/guide/pa-files/PAR-04-009.html) was implemented in response to the Strategic Plan for Mood Disorders to support preclinical ligand discovery for novel molecular targets implicated in mood and anxiety disorder. Not long afterward, a more broad-based, complementary Cooperative Drug Development Group (http://grants.nih.gov/grants/guide/pa-files/PAR-05-010.html) Program was developed to support proof of concept studies of new investigational new drug-ready drugs for the treatment of core symptoms associated with mental disorders. The newest program, codeveloped by Wayne Fenton and Ellen Stover, the Centers for Intervention Development and Applied Research (http://grants.nih.gov/grants/guide/pa-files/PAR-05-039.html) was developed to support the development of interdisciplinary research teams to define predictors and understand the mechanism of treatment response in major mental disorders, create and refine biomarkers to assess the presence and/or extent of mental illness, and hasten the development of novel treatments for mental disorders. This triad of programs has been an effective strategy for NIMH to assist the academic and private sector effort to fill the drug discovery pipeline with novel mechanism of action compounds for the treatment of mental disorders.

NIMH-MATRICS Approach to Treatment Development

For the most part, drugs in psychiatry have been targeted at psychiatric disorders that are categorized in diagnostic manuals such as Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. This has been accepted by regulatory authorities such as the FDA and has guided the development of drugs for psychiatric disorders as well as agents in other areas of medicine. A 2003 article by Hyman and Fenton13 questioned whether this was the best strategy for drug development. Because researchers attempt to connect human phenotypes as defined by diagnostic category to genetics, the limitations of this method have become more apparent. Psychiatric disorders tend to have complex phenotypes with patients demonstrating abnormalities in multiple areas of brain functioning. This is particularly true in schizophrenia, a disorder that includes psychopathology in different dimensions. Although researchers continue to debate about the number of dimensions, there is agreement that individuals with schizophrenia are vulnerable to having impairments in their perceptions of reality (or psychotic symptoms), in their cognitive abilities, and in their basic drives (or negative symptoms).14

The proposal of Hyman and Fenton13 suggests a strategy for advancing drug development by dissecting Diagnostic and Statistical Manual of Mental Disorders into component dimensions of psychopathology that may be more proximate to pathophysiological processes.
These more circumscribed areas of psychopathology may cut across diagnostic boundaries. For example, the pathophysiology of cognitive disturbances in schizophrenia and Alzheimer disease may have similarities and so may the apathy in schizophrenia and major depression. Therefore, pharmacological approaches to these dimensions may cross diagnostic boundaries. This novel approach to addressing psychopathology is actually reflected in clinical practice. As mentioned above, antipsychotic medications are not antischizophrenia medications. Rather, they are effective agents for any type of psychosis. Antidepressant medications are not just effective for major depressions. They are effective for depressive symptoms in a number of psychiatric disorders.

This more pragmatic approach to drug development suggests a number of promising targets. Hyman and Fenton\textsuperscript{13} viewed the cognitive impairments in schizophrenia as particularly promising. These impairments affect nearly every individual with schizophrenia to some degree.\textsuperscript{15,16} Moreover, the severity of these impairments is related to the ability of individuals with schizophrenia to function in the community.\textsuperscript{17} They raise the very compelling question as to whether a drug that improved cognition might, in turn, improve functioning. It is important to note that this proposal by Hyman and Fenton\textsuperscript{13} has helped to reorient treatment development. As will be noted below, Fenton was the individual, who demonstrated extraordinary leadership within NIMH by translating these ideas into effective Institute initiatives.

An interesting byproduct of the current process of drug discovery relates to the development of clinical measures. The drugs that treat schizophrenia are reasonably effective for attenuating or even eliminating psychotic symptoms. As a result, clinical investigators have learned to measure hallucinations, delusions, and other psychotic symptoms with good accuracy. Dimensions of psychopathology that are less affected by antipsychotics—particularly cognitive impairments and negative symptoms—can be measured using a number of instruments. However, it is unclear how these instruments are when they are used as endpoints in clinical trials. Instruments that are reliable and valid for measuring psychosis such as the Positive and Negative Symptom Scale\textsuperscript{18} and the Brief Psychiatric Rating Scale\textsuperscript{19} are widely accepted within the academic community, in industry, and by FDA. Until recently, there was little agreement on the best instruments for measuring cognition and negative symptoms.

The NIMH-MATRICS initiative was a direct result of the strategy proposed by Hyman and Fenton.\textsuperscript{13} The goal of this program (awarded as a competitive contract to UCLA with Stephen Marder and Michael Green as co-principal investigators) was to facilitate the development of pharmacological treatments for the cognitive impairments that are common in schizophrenia by addressing key obstacles. These obstacles included the lack of agreement regarding how to measure cognition in a clinical trial; concerns about the willingness of regulators such as the FDA to accept cognition in schizophrenia as a drug indication; a lack of agreement regarding the best molecular targets for drug development; and concerns about the clinical trial design that would be appropriate for demonstrating the effectiveness of a drug. During the 2-year period from 2003 to 2004, 6 MATRICS conferences addressed all these issues. (Each meeting is described at http://www.matrics.ucla.edu).

The MATRICS Consensus Cognitive Battery (MCCB) may be the most tangible result of this initiative. A committee of experts cochaired by Michael Green and Keith Nuechterlein first achieved agreement about the domains of cognition that were impaired in schizophrenia and which should be the focus of measurement.\textsuperscript{20} This was done through a process that included both expert opinion and factor analysis. The committee also achieved agreement regarding the selection criteria for tests within each domain. Using a process developed by RAND to measure the appropriateness of medical treatments,\textsuperscript{21} the group convened a panel to compare each candidate test with the selection criteria. This led to the development of a beta version of the battery, which included 20 of the most promising tests. This version was evaluated in a 5-site study, where the battery was first administered to patients with schizophrenia on 2 test occasions separated by a month. The battery was then administered to a large community sample to collect normative data.

At this time, the MCCB is the only battery that has been accepted by FDA as an instrument developed through broad consensus building. For the convenience of researchers, the battery has been assembled into a single kit, which can be purchased through major test publishers. The battery is currently used in a number of large studies of putative cognition enhancing drugs.

A similar effort was used by MATRICS to achieve agreement on the most promising molecular targets for drug development. A Neuropharmacology Committee cochaired by Carol Tamminga and Mark Geyer surveyed experts in the field regarding promising targets. The survey results (available at http://www.matrics.ucla.edu) were used to develop the agenda for a meeting that was held at the NIH Clinical Center on June 23–24, 2003. At the meeting, experts presented evidence supporting each targets. The proceedings of the meeting were assembled into a special issue of Psychopharmacology in 2004.\textsuperscript{22} A recent review also provides an overview of the targets recommended by MATRICS.\textsuperscript{23}
MATRICS meeting, a representative from FDA, Dr Thomas Laughren, agreed that impaired cognition is a core feature of schizophrenia and that if a drug demonstrated that it could improve cognition it could be approved. In April 2004, NIMH-FDA representatives from both industry and academia as well as government reached agreement on clinical trial designs that could support an efficacy claim for either a comedication that could be added to an antipsychotic to improve cognition or an agent which was effective for treating psychosis and improving cognition.

Supporting Collaborations Among Government, Industry, and Academia

MATRICS also focused on approaches to improving collaborations among government, industry, and academia. At a meeting at NIMH on January 22, 2004, representatives from each of these sectors addressed the opportunities and the barriers to collaboration. (A transcript of the meeting can be found at http://www.matrics.ucla.edu.) Edward Scolnick, MD, provided an industry view on how NIMH could assist industry in drug development. He suggested that the Institute support research on surrogate markers which indicate that a drug is affecting a target. This would require improving our understanding of the pathophysiology of illnesses that are drug targets. These biomarkers would be useful to industry because they screen compounds and attempt to estimate the effective clinical doses. He also pointed out the importance of NIMH supporting epidemiological studies that characterize the natural course of psychiatric disorders such as Minimal Cognitive Impairment or schizophrenia. This would be valuable information for drug companies and others who study the long-term effects of a drug. Others pointed to the need for the development of new radioligands that could be useful for drug development.

A number of participants also agreed that the field might benefit from research that focuses on better definitions of phenotypes and an improved understanding of the pathophysiology of disease phenotypes.

There is a momentum for effective, practical approaches for treatments that address the cognition difficulties in schizophrenia. Many of the components of the successful collaborations used in the prevention and treatment programs for AIDS are now evident in the area of schizophrenia. These include a greater sense of urgency among individuals in industry, academia, and government. Methodological advances have been made including measurement and identification of new clinical targets that may translate into improved clinical outcomes. A multidisciplinary group of scientists and representatives from industry and government are actively participating in a new research agenda for schizophrenia.

Post-MATRICS Activities

More than 300 individuals from academia, government, and industry participated in MATRICS activities. Many found the model for addressing issues in therapeutic development to be useful and became involved in activities that used the consensus building process to address other important issues. A final MATRICS meeting in September 2004 focused on the NIMH research agenda. The program (cochaired by Mark Geyer and Robert Heinssen) was titled “New Approaches” and focused on some of the critical scientific issues that had been identified through the MATRICS process. (It is summarized in a special section of the Schizophrenia Bulletin for October 2005). At least 2 important initiatives developed directly from this meeting.

The first initiative led to the development of a new initiative to evaluate animal models for each of the cognitive domains from MATRICS. The work is being carried out by a subgroup of Treatment Units for Research on Neurocognition in Schizophrenia—chaired by Mark Geyer. A completed survey of preclinical tasks for rodents is currently available at http://www.turns.ucla.edu). A similar document is under development for nonhuman primates.

Discussions at the New Directions meeting also led Deanna Barch and Cameron Carter to develop a research program that addressed an important concern among cognitive neuroscientists. That is, the MCCB included well-standardized neuropsychological tests most of which had been used for years in clinical practice and in research. These tests had considerable strengths including a lack of ceiling and floor effects. On the other hand, these tests are relatively complex and probably tap more than a single domain of cognition. More specific tests have been developed in cognitive neuroscience. However, most of these are relatively new and will require study of their psychometric properties before they are suitable for large-scale clinical trials. The other hand, these newer tests may have the advantage of being clearly linked to specific neural systems and are probably easier to translate into animal models.

An NIMH program titled “Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia” or CNTRICS (http://cntrics.ucdavis.edu/index.shtml)—led by Carter and Barch—is focused on developing these newer measures for clinical trials. The hope is to develop tests that are more specific measures of brain functions and to assure that these measures are ready for clinical trials. The first meeting of CNTRICS occurred in February 2007, and future meetings are scheduled.

Other post-MATRICS activities include an initiative to improve the measurement of negative symptoms. A consensus-building meeting sponsored by NIMH indicated that negative symptoms in schizophrenia was an area where there was a need for better treatments. In addition, the current instruments for measuring this domain
of psychopathology were based on constructs that had been developed during the 1980s. The group agreed that the development of new therapeutic approaches could be aided by a data-driven approach—similar to MATRICS—for developing a new instrument. An early version of an instrument has been developed, and a validation process is being developed.

A New NIMH Collaboration With Industry and Academia

Discussions among individuals from industry and academia revealed 2 remaining obstacles to drug development: first, the MCCB was only available in English, but most drug development was international; and second, the MATRICS process did not adequately address the need for measures of functioning and functional capacity that could be used in large international trials. This led to the development of MATRICS CT (for Coprimary selection and translation of the battery). This NIMH program—led by Stephen Marder and Brendon Binneman—is being supported by the Foundation for NIH, which is able to use private funds to support research carried out by NIH institutes. The first meeting is scheduled for August 21–22 in Bethesda.

Summary

Wayne Fenton had a vision for NIMH. It included new approaches to addressing some of the important obstacles that have interfered with the development of new treatments that could change the course of illness for individuals with serious psychiatric disorders. As a direct result of his leadership, important new initiatives are underway that have substantially changed the paradigms for treatment development. The effectiveness of his efforts should become apparent in the relatively near future.

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References


