Drug Initiatives to Improve Cognitive Function

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Unlike for other chronic illnesses, the development of new medications for the treatment of schizophrenia has been relatively dormant since the 1950s. Recently, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program was established by the National Institute of Mental Health (NIMH) in order to facilitate the development of treatments for cognitive impairment and functional outcome in schizophrenia. Although effective medications for managing the positive symptoms of schizophrenia have permitted many patients to live in the community, these medications often fail to improve social and vocational function. As a result, some experts believe that research into new treatments should focus instead on the functional outcomes of patients by improving cognitive abilities and social competence. The MATRICS program brought together scientists from academia, government, and industry to discuss ways of promoting the development of new treatments for schizophrenia and gain consensus on treatment targets. The initiatives that have come out of the MATRICS program include focusing on adjunct medications, addressing regulatory issues with the U.S. Food and Drug Administration, determining the best way to measure functional outcomes, classifying symptoms, developing a battery of cognitive tests for assessing outcomes in clinical trials, and ranking promising targets for new treatment development.

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The first antipsychotic, chlorpromazine, was introduced in Paris about 50 years ago.[1] Although this medication and other antipsychotics have altered the symptom course of schizophrenia, the social and vocational functioning of many patients with schizophrenia remains impaired. Today, patients may be less likely to reside in hospitals than in previous decades, but only about 20% of patients with schizophrenia are able to work.[2] In addition, the clinical practice of psychiatry focuses largely on positive symptom control. Clinicians may be more inclined to focus on positive symptoms because drugs have the most effect on these symptoms, rather than focus on other domains of psychopathology in schizophrenia.

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LIMITATIONS OF CURRENT PHARMACOTHERAPY

As treatment limitations have emerged, patients and their family members have become more critical of mental health providers for focusing on symptom control and stabilization rather than other goals of treatment, such as recovery. Harvey et al.[3] defined a management strategy in which treatment efficacy would be based on improvements of various domains of life, such as social functioning, independent living, and employment. Similar to recovery in chronic diseases such as arthritis, pulmonary disease, and chronic heart disease, recovery in schizophrenia would be a process whereby patients regain and improve functions that have been compromised as a result of their illness. Recovery is not necessarily about curing chronic illness but rather helping patients to live an improved life at the highest possible function despite the burden of a chronic illness.

Second-Generation Antipsychotics

The introduction of a second generation of antipsychotic medications led to hopes that these medications were substantially better than older medications. The results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[4] funded by the National Institute of Mental Health (NIMH) indicate that the advantages for these newer medications may have been overestimated. In addition, although there is some evidence that newer antipsychotics are more effective for improving cognition,[5] it is unclear that this advantage is

sufficient to affect functional outcomes. For example, a quantitative review[6] found that patients with schizophrenia performed 1.5 to 2.0 or more standard deviations below the mean on selected neuropsychological tests. Improvements associated with newer antipsychotics may vary between 0.5 to 1.0 standard deviations.[3] This finding indicates that antipsychotics are limited in their ability to treat cognitive impairments.

Stagnant Progress of Pharmacologic Development

A possible explanation for the lack of beneficial pharmacologic treatments is the small number of innovative drugs that have been developed during the past several years. As a comparison, few advances in drugs with new mechanisms of action for the treatment of depression and schizophrenia have been developed, whereas much more substantial advances have been made in other therapeutic areas.[7] Insel and Scolnick[7] suggest that mental health researchers from both academia and industry have focused on modest goals such as developing agents with incremental improvements in their side effect profile, whereas investigators in cancer and other fields have focused on strategies for altering the course of the illness.

It is also important to acknowledge that problems in drug development are not just confined to psychiatric medications. A recent article in the *New York Times*[8] noted the stagnation in drug development. Although pharmaceutical companies have funded the development of new drugs, there has been a gradual decrease over the past several years in the number of drugs that are actually approved. In addition, a monograph[9] from the U.S. Food and Drug Administration (FDA) explained pipeline stagnation of new medications and why it exists. According to the monograph, the needs of the applied sciences for medical product development have not met with commensurate advances in basic sciences. New advances are not being used to guide the technology of drug development and have not been used to accelerate the discovery process. In many cases, drug developers have no choice but to use the tools and concepts of the last century to develop new drugs for this century.

Drug development is a long process that involves risk, which may, consequently, hinder innovation. Pharmaceutical companies often focus on a proven method of action and a proven indication in order to develop a drug that is incrementally better than its predecessors, which increases the likelihood of getting the drug to launch. A drug or mechanism that is new and innovative might be a greater investment in time and resources, which leads to greater risk, so the pharmaceutical company may decline to develop it. The time course of drug development from first human use to launch is approximately 7 years, and only about 9% of the drugs under development actually make it to market.[10] The cost of drug development can be over one billion U.S. dollars.[10]

MEASUREMENT AND TREATMENT RESEARCH TO IMPROVE COGNITION IN SCHIZOPHRENIA (MATRICS) PROGRAM

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program is funded by the NIMH and has the specific goal of facilitating the development of new compounds for improving cognition and functional outcome in schizophrenia. The remainder of this article describes the processes used to establish consensus and promote new treatment development.

Establishing Consensus Among Researchers

Several approaches were used to determine which promising molecular mechanisms for improving cognition in schizophrenia should be researched. Establishing consensus included defining separable domains of cognition, developing outcome measures in each domain appropriate for clinical drug trials, and improving the understanding of the neurobiology of normal behavior in disease states and in animal models.[11,12]

The consensus-developing process adopted by MATRICS, called the RAND Panel Method,[13] provided a strict path that assured a working product at the end of the consensus-building process. Variations of this method were used to develop consensus in a number of areas, including the development of a consensus cognitive battery and recommendations for the design of clinical trials and molecular targets for drug development. In each area, we assembled and interviewed experts and reviewed relevant literature to reach a consensus using guidelines developed before the process was initiated. In all of these areas, the process adhered to certain principles. First, the process included a broad range of experts from industry, government, and academia. More than 300 people from these sectors participated in MATRICS meetings and committees. The process was also transparent. Meetings were open, presentations were available on the MATRICS Web site,[14] and results were published relatively rapidly. Finally, wherever possible, consensus development was guided by data.

Defining Psychopathologic Targets

An important step in treatment development involves improving the definition of psychopathologic targets. Although clinicians tend to focus on positive symptoms such as hallucinations, careful studies have found that both cognition[15] and negative symptoms[16] (such as blunted affect, alogia, avolition, and anhedonia) are stronger predictors of functional outcome. The study by Fenton et al.[16] found that positive symptoms did predict the need for hospitalization and the likelihood of suicide.

One of the first steps in characterizing a symptom dimension such as cognitive impairment or negative symp-

toms is to understand its components. For cognitive impairment, a neuropsychology group chaired by Keith H. Nuechterlein, Ph.D., used both factor analysis and expert opinion to define 6 separable cognitive factors.[17] These included speed of mental processing, attention and vigilance, working memory, verbal learning and memory, visual learning and memory, and reasoning and problem solving. At a large conference of experts, there was a consensus that social cognition should be added as a seventh factor even though this factor had received the attention of other factors. The reason for adding this factor was that recent findings[18] indicate that social cognition, which includes facial recognition and recognizing affects in others, is a key contributor to social adjustment.

A less formal process was used to define the domains of negative symptoms. Again, factor analysis and expert opinion were surveyed. The results indicated that negative symptoms can be divided into at least 2 main domains.[19] One domain is characterized by diminished expression, which consists of flat affect and alogia. The other domain reflects a social dimension, which is manifested by apathy and anhedonia. Some research[20] suggests that anhedonia is a key factor in recognizing negative symptoms and that patients with schizophrenia and negative symptoms have a relatively normal ability to experience pleasure when they are engaged in activity, such as eating a meal or watching a movie. However, these patients seem impaired in their ability to anticipate pleasure.

Instrument Development

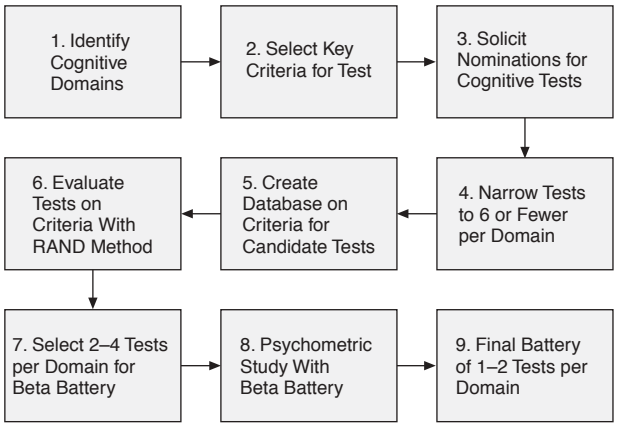
The cognition group also used a consensus process to define the essential criteria for selecting a test of cognition.[21] The group concluded that cognitive tests for clinical trials should have high test-retest reliability, a tangible relationship to functional outcome, the potential to change in response to pharmacologic agents, and a high level of tolerability and practicality to make the tests acceptable to patients.

The accompanying article by Green[22] in this supplement describes the process used to develop the battery (Figure 1). A separate consensus group led by Brian Kirkpatrick, M.D., is developing a new instrument for measuring negative symptoms; the activity of this group can also be monitored on the MATRICS Web site.[14]

Measuring Functioning in Schizophrenia

In one of the early MATRICS meetings, a representative from the FDA stated that the agency would be reluctant to approve an agent as effective for cognitive impairment in schizophrenia based on improvement in a neuropsychology test. The FDA would need a better indication that the medication can improve functional outcomes. There was agreement that it would not be necessary to demonstrate that a drug led to a patient's getting a job or enriching his or her social interactions. Success in these areas is unlikely to occur during the time course of a drug trial and may require opportunities that patients may not be exposed to during that time. However, the FDA representative did say that improvements in a patient's capacity to function in an area or the patient's perception of improvement could be considered evidence supporting a claim by a company.

Figure 1. Steps to NIMH-MATRICS Consensus Cognitive Battery[a]



[a]Adapted with permission from Green et al.[21]
Abbreviations: MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, NIMH = National Institute of Mental Health.

The MATRICS group reacted to this message from the FDA by developing a task force (chaired by Alan S. Bellack, Ph.D.) to select measures of functional capacity. The task force selected 2 measures of functional capacity. One approach is the University of California San Diego Performance-Based Skills Assessment,[23] which is a test of cognitive abilities that assesses the capacity of a patient to perform daily living tasks, such as preparing a meal, taking mass transportation, managing medications, and demonstrating social competence. The other approach, the Maryland Assessment for Social Competence,[24] uses video vignettes in order to have a patient actually show social abilities and degrees of social competence.

Prioritizing Molecular Targets

In selecting molecular targets, some principles about how treatments are developed in medicine should be remembered. For nearly every chronic illness, treatments do not target the cause of the disease but rather the mechanisms that generate symptoms or the mechanisms that alleviate symptoms. A better understanding of the neurobiology of the basic processes that generate symptoms across diagnostic categories, therefore, may lead to more or better treatments. By understanding the biology of working memory or attention, attention or working memory may be improved in schizophrenia as well as in other disorders.

A MATRICS conference[25] of industry scientists and researchers from academia met to form a consensus on the most promising compounds for the treatment of impaired cognition in schizophrenia. The group also focused on models for use in drug development, including animal models, nonhuman primate models, and human models. The consensus was that the most promising target compounds are α_7-nicotinic receptor agonists and D_1-receptor agonists. Other targets of interest include α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid glutamatergic receptor agonists, α_2-adrenergic receptor agonists, *N*-methyl-D-aspartate glutamatergic receptor agonists, metabotropic glutamate receptor agonists, and glycine reuptake inhibitors. For more information on promising target compounds, please see "The Neurobiology of Cognition in Schizophrenia" by Carol A. Tamminga, M.D., in this supplement.[26]

Regulatory Issues

At an FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia,[27] there was a focus on the design of trials that would lead to approval of cognition-enhancing drugs for schizophrenia. As mentioned earlier, an FDA representative again stated that improvements that were solely based on neuropsychological testing data would not be sufficient to demonstrate efficacy. A drug should also be demonstrated to improve a patient's functional capacity or his or her own assessment of cognitive impairment. Since negative symptoms can be assessed by clinicians in an office environment, this would probably not be a requirement for approval of a drug for negative symptoms.

The FDA also addressed other important regulatory issues for study subjects and design for both trials of adjunct medication (that is, a medication that would be added to an antipsychotic to enhance cognition) and broad-spectrum treatments (or an agent that is effective for both psychosis and cognition). For example, studies should include patients who are stable on antipsychotic treatment. The best design for studies of adjunct medication would be a placebo-controlled trial of the study drug added to the antipsychotic. The best design for studies of broad spectrum antipsychotics would be a double-blind trial of the experimental drug versus an antipsychotic that does not impair cognition. In both study designs, the objective would be to discover which intervention led to greater improvement in symptoms.

Psychosocial Approaches to Improving Cognition

In an area such as cognition, psychosocial treatments can also improve some of the domains described by MATRICS. A study[18] from Germany that found that facial affect recognition can be enhanced with special training also found indications that the metabolism in the fusiform facial area, which is used for facial recognition, actually increased after patients received training. Cognitive training has been found to improve working memory[28] and attention.[29] Cognitive-enhancing therapies can improve a number of domains of cognition and processing speed. As this field of therapeutics continues to develop, it is also possible that the best treatments will involve combinations of pharmacologic and psychosocial interventions.

CONCLUSION

Current treatments for schizophrenia, particularly pharmacologic agents, are limited in their ability to improve functional outcomes. Some of the changes in symptomatology associated with psychosocial treatments are actually more substantial than the changes from drug treatments. Improvements in functional outcomes in patients with schizophrenia are more likely to be accomplished by focusing on cognitive impairments and negative symptoms than by focusing on positive symptoms. Innovative new treatments may emerge through a better understanding of the neurobiology of basic cognitive and motivational processes.

Drug name: chlorpromazine (Thorazine, Sonazine, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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