Proceedings and Data From The Schizophrenia Summit: A Critical Appraisal to Improve the Management of Schizophrenia

In mid-February 2008, a panel of 10 nationally recognized schizophrenia research experts was assembled in a Schizophrenia Summit to focus on controversies that exist in treating patients with schizophrenia. The current literature related to the diagnosis and etiopathology of schizophrenia was evaluated regarding the identification of a prodromal phase, brain changes, cognitive impairments, genetic factors, and use of neuroimaging in patients with schizophrenia. Further, consideration was given to evidence supporting the neuroprotective benefits of atypical antipsychotic medications, the benefits of treating patients during the prodromal period, the use of combination antipsychotic medications, the need to improve cognitive function, and the management of substance abuse. Summit faculty member opinion is compared with field survey results, and recommendations are made for future research.
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INTRODUCTION

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How many of the commonly held clinical beliefs about schizophrenia are actually supported by Level-I research evidence? This was the overarching question that prompted the inception of this continuing medical education (CME) project. To examine this issue, 10 brief statements concerning schizophrenia were constructed, 5 dealing with the diagnostic and etiopathologic issues and 5 focusing on the therapeutic interventions for patients with schizophrenia (Table 1). Additionally, an online survey of clinical psychiatrists within the United States (N = 1064) was conducted in January 2008. Survey participants were invited by e-mail alerts sent to the member lists of *Current Psychiatry* and the *Journal of Clinical Psychiatry*, as well as by a dedicated landing page posted on the Web sites of these publications. The online survey was available for approximately 1 month, and participation in the survey was voluntary. In the survey, respondents were asked to rate the validity of the 10 statements on a 5-point scale, as detailed in Table 2.

Along with the collection of survey data, a panel of 10 nationally recognized experts was assembled, each with an established track record in schizophrenia research. Each faculty member was assigned 1 of the 10 statements and was asked to conduct a review of published Level I to Level V evidence, as defined in Table 2, in support of their statement. A 2-day, face-to-face meeting titled "The Schizophrenia Summit" was held in mid-February of 2008. At the beginning of the Summit, the 10 research experts were surveyed to ascertain their beliefs regarding the validity of all 10 statements in a manner similar to what was done with the clinician survey. Following this initial survey, the faculty members divided into 2 subgroups (i.e., 5 in the diagnostic/etiopathologic group, 5 in the therapeutic intervention group). Each faculty member had conducted a literature review for their statement, and they presented evidence for or against the statement to the members of the subgroup. A discussion of the presented evidence followed among the members of each subgroup.

On the second day, the entire faculty reconvened, and each faculty member summarized the literature and the critique/discussion that took place on the preceding day. After each presentation, the 10 Summit members voted on the validity of each statement in light of the strength of the available evidence in support of the statement. The ratings of the research experts were then compared to the survey results of the national sample of clinical psychiatrists on the same statement. Comparative results were displayed in a bar graph.

Interesting differences emerged between the survey results of clinicians and those of the research experts. These discrepancies are described in the following detailed and scholarly reviews of the level of evidence for each statement. Although some difference in opinion was expected, the extent of the disparity between psychiatric clinicians and researchers has rarely been quantified in this manner. Readers of this article not only will glean a plethora of important findings about the biology, diagnosis, and treatment of schizophrenia, they also will appreciate the thin line that sometimes separates myth from reality or half-truths from evidence-based facts.

This summary of how all 10 statements were viewed both by practicing clinicians and by research experts should illuminate the need for better educational efforts to properly inform clinicians about the rapidly changing scientific landscape in the field of schizophrenia research. A hard-nosed perspective on widely held beliefs should be adopted, as the diagnosis and treatment of patients with

Table 1. Schizophrenia Summit Statements for Evaluation

Workshop 1: Diagnosis and Etiopathology Statements (Statements 1–5)	
1.	Identification of the earliest prodromal phase of schizophrenia is feasible
2.	Schizophrenia is a neurodegenerative disease resulting in brain changes that parallel symptom progression and functional decline
3.	Cognitive impairment, especially executive dysfunction and memory loss, is a key diagnostic component of schizophrenia
4.	Genetic factors are the best established etiologic determinants of schizophrenia
5.	Neuroimaging is a tool for elucidating biological and genetic mechanisms of illness and treatment response
Workshop 2: Therapeutic Interventions (Statements 6–10)	
6.	Atypical antipsychotic drugs are neuroprotective in patients diagnosed with schizophrenia
7.	Treatment in the prodromal phase of schizophrenia improves patient outcomes
8.	Patients with treatment-resistant schizophrenia require combination antipsychotic treatment
9.	Improvement in cognitive function is an essential treatment target in patients with schizophrenia
10.	Managing substance abuse is a key target of treatment

Table 2. Voting Schemes Used in the Schizophrenia Summit

Category	
	Nature of evidence
I	Evidence obtained from at least 1 well-designed, randomized, controlled trial
II	Evidence obtained from well-designed cohort or case-control studies
III	Evidence obtained from case series, case reports, or flawed clinical trials
IV	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
V	Insufficient evidence to form an opinion
	Level of support for the statement
1	Accept recommendation completely
2	Accept recommendation with some reservations
3	Accept recommendation with major reservations
4	Reject recommendation with reservations
5	Reject recommendation completely

schizophrenia, or any other psychiatric disorder, can be influenced significantly by what a psychiatrist believes to be true and valid. This is particularly important for a thriving medical discipline like psychiatry in which scientific advances are emerging so rapidly that the dissemination of this information to clinicians sometimes can be done prematurely or in a distorted or overly confident manner. As can be seen in the following summaries, the gap between the research and clinical realms is evident, and efforts to close the gap are clearly needed.

STATEMENT 1: IDENTIFICATION OF THE EARLIEST PRODROMAL PHASE OF SCHIZOPHRENIA IS FEASIBLE

Diana O. Perkins, M.D., M.P.H., was the contributor of this section.

Rationale and Definition of Statement

Schizophrenia is a common disorder, affecting approximately 1 out of every 100 people, with a typical onset during adolescence and early adulthood.[1] The personal and societal costs of schizophrenia are extremely high. Schizophrenia frequently results in social and occupational disability, and it is listed among the 10 most common causes of disability.[2] Family members of patients with schizophrenia also are affected both directly and indirectly.[3] The economic burden of schizophrenia on society is considerable. The 2002 estimated annual direct and indirect economic costs of schizophrenia were over $63 billion in the United States.[4] Prevention of schizophrenia, therefore, would offer substantial benefits to patients, their family members, and the community at large.

Retrospective studies of patients with schizophrenia indicate that approximately 80% to 85% report experiencing subsyndromal symptoms for a period lasting several months to several years prior to onset of the illness.[4,5] The reported subsyndromal symptoms include impaired perception, thought processes, subjective cognitive function, and mood. Retrospective studies also suggest that much of the functional decline associated with schizophrenia occurs during this prodromal stage.[4,5]

Identification of individuals at the prodromal stage of illness (i.e., prior to the onset of schizophrenia-level symptoms) would offer clinicians the opportunity to provide preventive interventions. While the evidence base for specific interventions is weak (see discussion of Statement 7, "Treatment in the prodromal phase of schizophrenia improves patient outcomes"), patients in the schizophrenia prodrome are symptomatic and frequently experience functional impairment. To the extent that the diagnostic criteria are valid, sensitive, and specific, it may be possible to address the functional impairments associated with the psychotic prodrome and to develop and test specific preventive interventions with clinical trials.

Literature Search

A PubMed database search to locate studies related to schizophrenia prodrome identification was completed on January 8, 2008. The text words and resulting articles included

- "prodrome," with 710 articles;
- "ultra high risk," with 279 articles; and
- "ultra high-risk," with 102 articles.

These terms were combined with "OR" for a total of 981 articles. In a second search, the text words and identified articles included

- "schizophrenia," with 77,568 articles, and
- "psychosis," with 38,375 articles.

These terms were combined with "OR" for a total of 104,801 articles. When the 2 searches were combined with "AND," a total of 184 articles were returned. Limiting these results to articles written in English yielded a total of 168 articles. From these, 12 articles were selected that were deemed relevant to the statement.

Evidence

Three areas of evidence were evaluated in the current literature. These included

- evidence for reliable diagnosis of schizophrenia prodrome,
- evidence for the predictive validity of the Criteria for Prodromal States (COPS)[6] and At-Risk Mental State (ARMS)[7] diagnostic criteria, and
- evidence that COPS/ARMS specificity can be increased by consideration of other clinical factors.

Evidence for reliable diagnosis of the schizophrenia prodrome. The COPS and the ARMS are 2 very similar sets of diagnostic criteria that identify a clinical state of elevated risk for psychosis. A comparison of these criteria is detailed in Table 3. The ability of various clinicians (e.g., psychiatrists, psychologists, master's-level clinical social workers) to reliably apply the COPS criteria was investigated in 2 studies.[6,8] In total, more than 40 clinicians were trained, with an overall κ coefficient averaging 0.9. This indicates excellent ability of trained clinicians to reliably diagnose the COPS-defined clinical at-risk state. In a 2005 study by Yung et al.,[7] researchers investigated the reliability of clinicians to evaluate specific symptoms used in ARMS ratings. Similarly, they found excellent reliability, with intraclass correlation coefficients ranging from 0.62 to 0.93 for symptom domains.

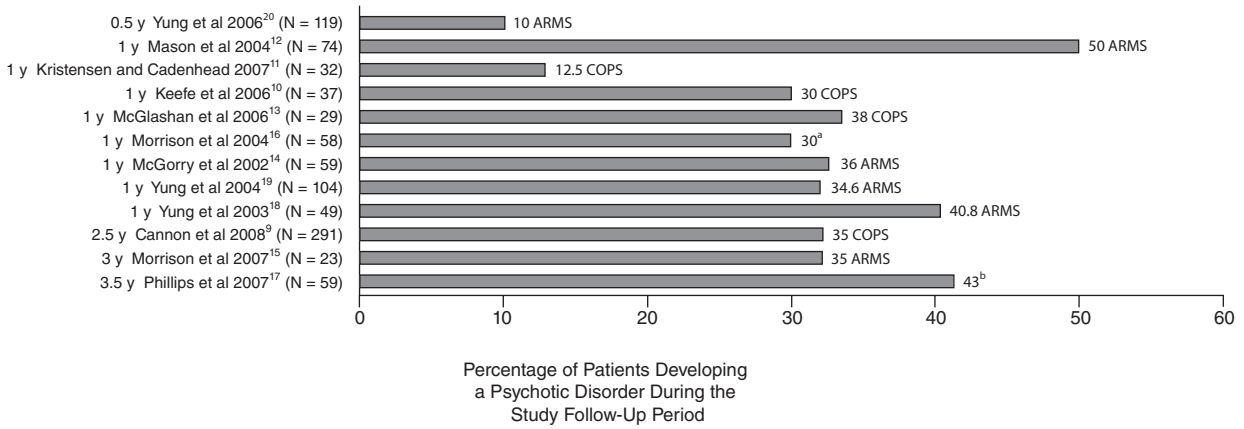
Evidence for the predictive validity of the COPS and ARMS diagnostic criteria. Figure 1 summarizes the results of several studies[9–20] that examined the predictive validity of the COPS and ARMS diagnostic criteria for psychosis prodrome. There are 4 prospective studies in which

Table 3. Comparison of the Criteria for Prodromal States (COPS) and the At-Risk Mental States (ARMS) Criteria for Clinical At-Risk State for the Development of a Psychotic Disorder

Criteria	COPS	ARMS
Attenuated Positive Symptom		
	Presence of at least 1 of 5 SOPS-positive[a] symptoms meeting clinical at-risk severity criteria	Presence of at least 1 of 3 CAARMS-positive[b] symptoms meeting clinical at-risk severity criteria
	AND	AND
	Symptoms began or worsened in the past year	*(Symptoms occurring at least twice during a 1-week period and lasting less than 1 hour)*
	AND	OR
	Symptoms have occurred at least once per week for the last month	*(Symptoms occurring at least twice during a 1-month period and lasting less than 1 hour)*
		AND
		Symptoms present in the past year, and duration of symptoms is less than 5 years
Brief Psychotic Symptom Syndrome		
	Presence of at least 1 of the 5 SOPS-positive symptoms meeting psychotic severity criteria	Presence of at least 1 of 3 CAARMS-positive symptoms meeting psychotic-level severity
	AND	AND
	Symptoms began in the last 3 months	Duration more than 1 hour per occasion and occurring less than daily
	AND	AND
	Symptoms occurring currently at least several minutes per day at least once per month	Episode duration is less than 1 week
		AND
		Symptoms present in the last year, and duration of symptoms is less than 5 years
Genetic Risk and Deterioration Syndrome		
	(A first-degree relative with a history of any psychotic disorder)	*(A first-degree relative with a history of any psychotic disorder)*
	OR	OR
	(Schizotypal personality disorder in patient)	*(Schizotypal personality disorder in patient)*
	AND	AND
	Global Assessment of Functioning Scale (GAF) drop of 30 points from premorbid level, sustained for at least 1 month	GAF drop of 30% from premorbid level, sustained for at least 1 month
Psychosis		
	Presence of at least 1 of the 5 SOPS-positive symptoms meeting psychotic severity criteria	Presence of at least 1 of 3 CAARMS-positive symptoms meeting psychotic-level severity
	AND	AND
	(*Symptoms occurring currently at least 1 hour per day at least 4 days a week for at least 1 month)*	Duration more than 1 hour per occasion and occurring less than daily
	OR	AND
	(Symptoms are disorganizing or dangerous)	Episode duration is more than 1 week

[a]SOPS = Schedule of Prodromal Symptoms. Positive symptoms include unusual thought content/delusions, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, disorganized communication.
[b]CAARMS = Comprehensive Assessment of At-Risk Mental States. Positive symptoms include disturbance of thought content, perceptual abnormalities, disorganized speech.

Figure 1. Comparison of Studies and Patients Experiencing Psychotic Disorders



[a]The 2004 study by Morrison et al.[16] is detailed further in the 2007 study by Morrison et al.[15]
[b]The study by Phillips et al.[17] is a follow-up to the McGorry et al.[14] study.
Abbreviations: ARMS = At-Risk Mental State, COPS = Criteria for Prodromal States.

the predictive validity of the COPS criteria was reported.[9–11,13] The primary outcome studied was the development of psychosis (i.e., as defined by the COPS criteria), which reflects the symptoms listed in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criterion A for schizophrenia psychosis. The North American Longitudinal Prodrome study combined data from 8 National Institute of Mental Health–funded projects.[8,9] Study participants included 291 patients who met the COPS criteria for a clinical at-risk state and who were followed for a minimum of 6 months to a maximum of 2.5 years. Development of psychosis occurred in 84 (35%) of the patients, with the mean time to conversion being 275 days.

In an earlier, randomized clinical trial by McGlashan et al.,[13] the researchers compared olanzapine to placebo in the prevention of psychosis in 60 patients who met the COPS criteria. They found that 11 of 29 (38%) of the placebo-treated patients developed psychosis during the 1-year follow-up period. In another study by Keefe et al.[10] of 37 patients who met the COPS criteria, 11 patients (30%) developed psychosis by the 1-year follow-up. In a separate study by Kristensen and Cadenhead[11] of 48 patients who met the COPS criteria, 6 patients (12.5%) developed psychosis within a year.

There were 6 prospective studies that investigated the predictive validity of the ARMS criteria.[12,14,15,18–20] As with the COPS criteria studies, the primary outcome in these studies was the development of psychosis in the patient population, as reflected by the development of DSM-IV criteria for schizophrenia psychosis. A 2006 study by Yung et al.[20] details a 6-month prospective study of 119 patients who met the ARMS criteria. Of the total number of patients, 12 (10%) developed psychosis by the 6-month follow-up. In a prospective study published in 2003 by Yung et al.[18] of 49 patients who met the ARMS criteria, 20 patients (40.8%) developed psychosis by the 1-year follow-up, and 2 more developed psychosis by the 25-month follow-up for a total of 22 (44.9%). The DSM-IV diagnoses of the patients with psychosis included

- schizophrenia in 13 patients (65%),
- schizoaffective disorder in 1 patient (5%),
- bipolar disorder with psychotic features in 1 patient (5%),
- major depression with psychotic features in 2 patients (10%),
- brief psychotic disorder in 1 patient (5%), and
- psychotic disorder not otherwise specified in 1 patient (5%).

A 2004 article by Yung et al.[19] records the results of a 12-month prospective study of 104 patients who met the ARMS criteria. Of these, 36 patients (34.6%) developed a psychotic disorder. Similar to the 2003 study by Yung et al.,[18] most patients developed schizophrenia spectrum diagnosis, with 20 (19%) developing schizophrenia, 2 (2%) developing schizoaffective disorder, 2 (2%) developing brief psychotic disorder, 2 (2%) developing psychotic disorder not otherwise specified, 5 (5%) developing bipolar disorder, 4 (4%) developing major depression with psychosis, and 1 (1%) developing substance-induced psychosis.

In another study by Mason et al.,[12] researchers investigated 74 patients who met the ARMS criteria, and 37 (50%) developed psychosis by the 1-year follow-up. Diagnostic outcomes included

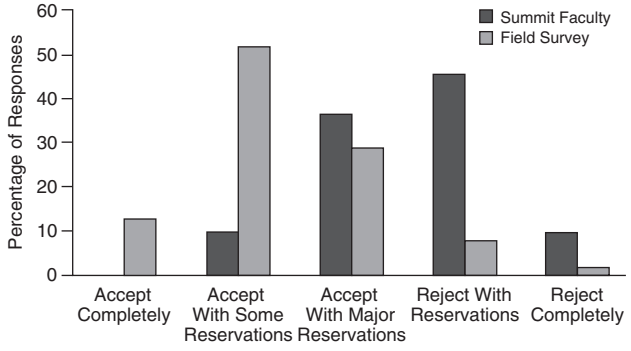
- schizophrenia in 7 patients (9%),
- schizoaffective disorder in 10 patients (14%),
- depression with psychotic features in 7 patients (9%), and
- bipolar disorder in 4 patients (6%).

In a randomized clinical trial by McGorry et al.,[14] researchers compared risperidone and psychotherapy to needs-based intervention. During the study, 10 out of 28 patients (36%) in the needs-based intervention group developed psychosis by the 1-year follow-up. Additionally, 2 more patients in that group (for a total of 12 out of 28 or 42%) developed psychosis by 3- to 4-year follow-up.[17] In a separate, randomized trial by Morrison et al.[15] that compared cognitive behavioral therapy to monitoring, 6 out of 23 patients in the monitoring group developed psychosis by the 1-year follow-up, and 7 out of 23 (30%) developed psychosis by the 3- to 4-year follow-up.

In summary, 4 published studies investigated a total of 405 patients who met COPS criteria, with 112 of these patients (28%) developing psychotic disorders during a follow-up period that ranged from 6 months to 2.5 years. Similarly, there were 6 studies that investigated a total of 397 patients who met the ARMS criteria, with 124 of these patients (31%) developing psychotic disorders during a follow-up period that ranged from 6 months to 4 years. In the studies that provided follow-up diagnoses for the patients who developed a psychotic disorder, a total of 68% of the patients developed schizophrenia, schizoaffective disorder, or brief psychotic disorder. An additional 28% developed a mood disorder, and 4% developed an unspecified psychotic disorder. Several of these studies also followed comparison patients who did not meet the clinical at-risk diagnostic criteria.[9,10,20] Only 1 out of 354 of these patients (0.3%) developed a psychotic disorder, which is similar to the expected risk of psychosis in the general population during adolescence and young adulthood (i.e., approximately 1 per 1000 per year).[21]

Evidence that COPS/ARMS specificity can be increased by consideration of other clinical factors. Almost all of the studies examining psychosis risk prediction also evaluated whether the presence of specific clinical factors

Figure 2. Level of Support for Statement 1, "Identification of the Earliest Prodromal Phase of Schizophrenia Is Feasible"



can improve the identification of those patients at highest risk in the at-risk groups (e.g., improved specificity and positive predictive value). In patients who met the COPS or ARMS criteria, these studies indicated that more severe at-risk symptoms,[9,12,18,19] longer duration of at-risk symptoms,[19] increased social and occupational role function impairment,[9,12,19] objective neurocognitive dysfunction,[22] subjective attentional deficits,[19] substance abuse,[9,11] family history of psychotic disorders,[9] and cortical gray matter volume decline[23] could be used to identify patients at increased risk of psychosis. However, no studies have prospectively tested these clinical factors as part of the at-risk diagnostic criteria.

Grading of Evidence

Based on a review of the studies cited above, 1 of the 5 Summit faculty members of this workshop (20%) considered the evidence available to support this statement to be Category II (evidence obtained from well-designed cohort or case-controlled studies). Of the remaining faculty, 3 (60%) considered the evidence to be Category III (evidence obtained from case series, case reports, or flawed clinical trials), and 1 considered it to be Level V (insufficient evidence to form an opinion).

Level of Support

When voting on the support for this statement, none of the Summit participants voted to accept the statement completely, 9% voted to accept the statement with some reservations, 36% voted to accept the statement with major reservations, 45% voted to reject the statement with reservations, and 9% voted to reject the statement completely. In comparison, of the 1064 clinical psychiatrists who participated in the online survey, 12% voted to accept the statement completely, 51% voted to accept the statement with some reservations, 28% voted to accept the statement with major reservations, 7% voted to reject the statement with reservations, and 1% voted to reject the statement completely (Figure 2).

Discussion

The first wave of studies examining the predictive validity of the psychosis prodrome indicates that approximately one-third of treatment-seeking patients who meet the COPS or ARMS criteria will develop a psychotic disorder. Data reveal that these patients have an approximately 30-fold increase in risk of developing a psychotic disorder—primarily schizophrenia. However, there are important caveats to these findings. First, the results of these studies cannot be generalized to members of the general population who are not seeking treatment for their symptoms. There is preliminary evidence that broader recruitment strategies would result in lower psychosis conversion rates.[24]

In addition, in those patients who develop psychosis, the eventual diagnosis often is schizophrenia, but mood disorders with psychotic features also do occur. Finally, the COPS and ARMS diagnostic criteria have small differences that, for practical reasons, need to be reconciled to produce a single, optimal set of diagnostic criteria (see Table 3).

As an example of this discrepancy, in order for a patient to meet the "Attenuated Positive Symptom" criteria under the COPS diagnosis criteria, he or she must demonstrate either the emergence of a new symptom or the worsening of an existing symptom within the past year. In contrast, to fulfill the diagnosis of an "Attenuated Positive Symptom" using the ARMS criteria, the patient's symptoms must have been present in the past year but have persisted no more than 5 years. In addition, both the COPS and the ARMS criteria have 3 separate categories to define the clinical at-risk state; however, more than 90% of the patients enrolled in these studies met the "Attenuated Positive Symptom" risk criteria. Further, the value of the "Genetic Risk and Deterioration" criteria and the "Brief Intermittent Psychosis" criteria in the prediction of psychosis risk is reduced because of the low base rate of these criteria in the help-seeking population. Finally, these systems do not have a consensus definition of the term *psychosis*, which limits the ability to make comparisons between studies that use different systems and criteria.

Future Directions

The next wave of studies likely will focus on refinements of the diagnostic criteria for the clinical at-risk state and the clinical definition of *psychosis*. High priority should be given to the differentiation of risk factors for schizophrenia spectrum psychosis versus mood disorders with psychotic features. In addition to the most promising clinical risk predictors (e.g., neurocognitive function, at-risk symptoms severity, substance abuse), these studies will also need to include biological risk predictors such as brain structure, brain function, DNA structure, and gene expression. As understanding of the underlying neurobiology of schizophrenia increases, it is likely that novel

clinical and biological risk factors will be identified, and their value in psychosis risk prediction will need to be examined. The likely end result will be a risk prediction algorithm, similar to the one currently used to identify individuals at high risk for cardiovascular disease.[25]

A valid and specific set of clinical at-risk diagnostic criteria will help pave the way for preventive intervention studies. Three such studies already have been published,[13–15] and the results of several other ongoing or recently completed clinical trials are anticipated in the next few years. Under the currently available clinical at-risk diagnostic criteria, only a minority of the general population will be diagnosed with a psychotic disorder. A substantial minority of patients who do develop psychosis will not develop schizophrenia spectrum disorders, which may limit the potential usefulness of these criteria in routine clinical practice.

To substantially improve sensitivity of early identification, it will be necessary to focus on risk identification in nonclinical populations. Future studies should focus on criteria that can be used to screen the general population of adolescents and young adults for psychosis risk. Further complicating the situation is that studies in which the general population is screened for these criteria likely will face ethical concerns, particularly in mitigating the potential consequences of being identified as vulnerable to a stigmatizing disorder.

STATEMENT 2: SCHIZOPHRENIA IS A NEURODEGENERATIVE DISEASE RESULTING IN BRAIN CHANGES THAT PARALLEL SYMPTOM PROGRESSION AND FUNCTIONAL DECLINE

Francine M. Benes, M.D., Ph.D., was the contributor of this section.

Rationale and Definition of Statement

This statement consists of several components including whether there are brain changes in schizophrenia and whether those changes correlate with clinical changes. Probably most controversial is the inclusion of the word *neurodegenerative* in the description of those changes. It has long been suspected that schizophrenia involves alterations of brain structure. Although the exact nature of these defects was elusive during the first half of the twentieth century, research efforts during its last 2 decades began to unravel some of the mysteries concerning the pathophysiology of this complex disorder.

Brain imaging studies have been particularly effective in provoking investigations into the causes of schizophrenia. However, they yield maximum utility only when the results of postmortem studies are factored into the interpretation of imaging results obtained from structural and functional approaches.

One of the most replicated findings in schizophrenia research is that of brain tissue volume loss. The first evidence for this came from a series of studies in which pneumoencephalography was employed to demonstrate ventricular enlargement and sulcal widening in patients with schizophrenia.[26,27] Many investigators have interpreted these changes as evidence of a neurodegenerative process that occurs in the brains of patients with schizophrenia. Studies conducted in the early part of the twentieth century yielded inconclusive findings in this regard; however, a quantitative microscopic investigation that measured the numerical densities of neurons and glia in the prefrontal cortex and other cortical regions failed to demonstrate neuronal loss or gliosis in patients with schizophrenia.[28] Subsequent evidence suggested that this volume loss is related to a contraction of the neuropil where synaptic connections are largely located.[29]

In the review that follows, the relationship of both gray matter loss and white matter changes to the onset and progression of schizophrenia is discussed. Questions that are addressed here include whether gray and white matter changes in schizophrenia are present early enough in the disease process to be considered etiologic in nature, and whether the gray and white matter changes that are related either directly or indirectly to normal postnatal maturational changes in the brain serve as "triggers" for the expression of the schizophrenic phenotype.

Literature Search

A PubMed database search was conducted on January 24, 2008. A search using the terms "schizophrenia" and "pathology" yielded 2306 articles. The combination of this search with a subsequent search for the terms "brain" and "pathology" yielded 1762 articles. Adding the search term "disease progression" yielded 39 articles, and these were narrowed to 35 by limiting the results to studies published in English and to those involving human subjects.

Evidence

The available studies can be categorized according to their focus on gray matter or white matter. Specifically, evidence falls into 3 broad categories: studies investigating the gray matter volume loss in first-episode schizophrenia patients, longitudinal studies, and studies of myelin content in patients with first-episode schizophrenia.

Gray matter volume loss in patients with first-episode schizophrenia. In an article by Molina et al.,[30] the relationship between illness duration and gray matter loss was addressed using a cohort consisting of 44 healthy control patients; 22 patients with first-episode schizophrenia; 29 patients with short-term, chronic schizophrenia; and 30 patients with long-term, chronic schizophrenia. Overall, the data demonstrated that patients with first-episode schizophrenia did not show any significant differences in volumetric measurements, whereas patients with

short-term chronic and long-term chronic schizophrenia showed a decrease in prefrontal gray matter volume when compared to normal control patients. These findings suggest that volume loss in the prefrontal cortex may be secondarily related to the illness—the longer patients with schizophrenia are ill, the more likely they are to show deterioration in their prefrontal cortex.

Nakamura et al.[31] conducted a study in which neocortical volumes in patients with schizophrenia, patients with affective disorder (i.e., first-episode affective psychosis), and healthy patients were followed for 1.5 years. At the outset, the patients with first-episode schizophrenia had smaller neocortical gray matter volumes and larger cerebrospinal fluid volumes when compared to healthy control patients. Furthermore, at follow-up, the patients with first-episode schizophrenia showed a 1.7% decrease in the neocortical gray matter volume, while patients with first-episode affective psychosis showed a slight increase. These results suggest that loss of cortical tissue volume may progress, at least in some patients with schizophrenia, during the course of the illness.

Longitudinal studies. In a study by Farrow et al.,[32] first-episode schizophrenia patients seen at the 2-year follow-up demonstrated extensive gray matter volume loss in the lateral and medial frontal regions as well as the left inferior temporal and middle temporal gyri. This loss occurred after the initial assessment of the patients, when a slight decrease was noted in the patients with schizophrenia, and before their 2-year follow-up. However, researchers found that there was a corresponding increase in white matter volume.

Another study by van Haren et al.[33] reported the results of a 5-year follow-up study of 96 patients with schizophrenia and 113 healthy control patients. Among the patients with schizophrenia, extensive decreases were seen in gray matter volume in the superior frontal area (i.e., Brodmann areas 9/10), the left superior temporal gyrus (i.e., Brodmann area 42), the right caudate nucleus, and the right thalamus. The decreased gray matter volume in the superior frontal gyrus was directly associated with the number of hospitalizations and, by inference, the severity of the patient's illness.

Lastly, reporting on a 10-year follow-up study of patients both with and without schizophrenia, Saijo et al.[34] recorded a 22.9% increase in the size of the lateral ventricles of patients with schizophrenia versus only a 5.1% increase in healthy control patients. Ventricular volume also was somewhat correlated with the Brief Psychiatric Rating Scale (BPRS) assessments of negative symptoms ($r = 0.43$, $p \leq .1$). This study suggests that volume loss over time in a patient with schizophrenia is associated with deterioration in clinical status. Although it is tempting to speculate that the volume loss reflected in increased ventricular size may be a marker for a neurodegenerative process, it is important to emphasize that detailed microscopic histopathological assessments are needed to establish such a relationship.

Early onset schizophrenia. In a study of patients with early onset schizophrenia, Salisbury et al.[35] reported that there were no differences in mismatch negativity in the patients with schizophrenia versus healthy control patients during the first hospitalization. However, when the patients were followed longitudinally for 1.5 years, the patients with schizophrenia showed a significant decline in mismatch negativity ($r = 0.60$, $p = .04$). The amplitude of mismatch negativity correlated positively with the volume of the left hippocampal gyrus (i.e., the lower the amplitude, the greater the volume reduction). In healthy control patients, there was no relationship between these 2 parameters.

In a 5-year prospective study of very early onset schizophrenia, which was sponsored by the National Institute of Mental Health, Thompson et al.[36] reported that the rate of gray matter loss in 12 patients with schizophrenia with an average age of 13.9 years was compared to 12 age- and gender-matched control patients. The patients with schizophrenia showed an accelerated loss of gray matter volume (approximately 5% per year) encompassing the frontal eye fields and supplementary motor, sensorimotor, parietal, and temporal cortices in both hemispheres ($p = .00002$). Using the Childhood Global Assessment of Functioning Scale, these researchers found that the faster loss rates of frontal cortex strongly correlated with more-severe negative symptoms ($p = .038$, using the Scales for the Assessment of Positive and Negative Symptoms score at final scan). Patients who had the least overall tissue deficit showed the best cognitive performance in terms of full-scale IQ at follow-up. Patients with the worst deficit on magnetic resonance imaging (MRI) scanning had the lowest full-scale IQ at follow-up ($r = 0.62$, $p = .016$). These investigators concluded that overall gray matter quantity at initial scan is a good predictor of full-scale IQ in patients with very early onset schizophrenia.

In dynamic mapping of the development of the hippocampus in 29 patients with childhood-onset schizophrenia, Nugent et al.[37] performed serial MRIs on patients every 2 years between the ages of 11 and 26 years. The MRI results demonstrated at the outset that the volume of the hippocampus in patients with schizophrenia was smaller when compared to normal patients and remained so throughout the period of the study. This occurred to an equivalent degree in both the left and right hemispheres.

Myelin content in patients with first-episode schizophrenia. In a study by Federspiel et al.,[38] intervoxel coherence mapping was employed to evaluate potential white matter changes in patients with first-episode schizophrenia. The intervoxel coherence values were measured and found to be increased in 3 fiber bundles, including the anterior thalamic peduncle, optic radiation, and posterior part of the external capsule. Eleven other loci in the frontal, temporal, cingulate, and occipital regions, as well as several other fiber bundles, showed significant decreases

in intervoxel coherence. The authors interpreted these findings as an indication that that there is a preponderance of decreased fiber organization in the brains of patients with first-episode schizophrenia. This suggests that there may be disturbances in cerebral connectivity related to white matter changes in patients with schizophrenia.

In a study of patients with chronic schizophrenia, Mori et al.[39] used diffusion tensor imaging to assess fractional anisotropy in the white matter. Patients with schizophrenia showed decreased fractional anisotropy in the white matter of the frontal and temporal regions as well as the uncinate fasciculi, cingulum bundles, and the genu and splenium of the corpus callosum. Fractional anisotropy showed a negative correlation with the duration of illness, suggesting that these changes may be progressive in nature and may reflect the deterioration in functioning that often occurs in schizophrenia.

Myelination is a normal developmental event that continues to occur during childhood, adolescence, and adulthood. A postmortem study of myelination in the hippocampal formation was conducted by Benes et al.[40] in 164 neurologically and psychiatrically normal patients who ranged in age from 0 to 76 years. The area of myelin staining in the superior medullary lamina found along the surface of the subiculum and presubiculum was measured and was found to increase by 100% between the first and second decades of life. Following a plateau during the third and fourth decades, the myelin staining again showed another 50% increase during the fifth and sixth decades of life. These results suggest that the postnatal development of the human brain continues much longer than had heretofore been suspected. The superior medullary lamina is of particular interest because it contains fibers that link the anterior cingulate cortex with the hippocampal formation, which contributes to the integration of emotional experience and cognitive functioning.

Additional support for these conclusions comes from an MRI study by Paus et al.[41] in which computational analysis was performed of structural MRI images obtained in 111 children and adolescents. Analysis demonstrated age-related increases in white matter density in the fiber tracts that constitute putative corticospinal and frontotemporal pathways. The maturation of the corticospinal tract occurred bilaterally, whereas the maturation of the frontotemporal pathway was found to occur predominantly in the left (i.e., the speech-dominant) hemisphere. These findings provide evidence for a gradual maturation of fiber pathways during late childhood and adolescence. This development presumably occurs in those regions that support motor and speech functions.

Bartzokis et al.[42] measured the ratio of gray matter to white matter volume in 55 healthy male control patients and in 35 male patients with schizophrenia approximately 4.5 years after the onset of illness. Significant decreases in the ratio of gray matter to white matter were present in the frontal and temporal regions of the brains of patients with schizophrenia. Additionally, the normal expansion of white matter with age did not occur in these patients.

In a study by Whitford et al.,[43] T1-weighted structural MRI scans were performed on 41 patients with first-episode schizophrenia compared with 47 age- and gender-matched healthy comparison patients. Of the baseline participants, 25 patients with first-episode schizophrenia and 26 comparison patients returned in 2 to 3 years for a follow-up scan. To identify regional volumetric white matter volume differences between the 2 groups at baseline, voxel-based morphometry in statistical parametric mapping-2 was used, while tensor-based morphometry was used to identify the longitudinal changes over the follow-up interval. In addition to volumetric deficits in the white matter volume of the frontal and temporal lobes at baseline, the patients with first-episode schizophrenia lost considerably more white matter over the follow-up interval relative to comparison patients. This occurred in both the middle and inferior temporal cortices bilaterally. The researchers interpreted these results to indicate that patients with first-episode schizophrenia exhibit white matter volume abnormalities at the time of the first presentation of their psychosis and that these abnormalities degenerate further over the initial years of illness. In consideration of the role that white matter plays in neural communication, the authors suggested that white matter abnormalities may contribute to the dysfunctional neural connectivity, which has been proposed as an underlying cause of the symptoms of schizophrenia.

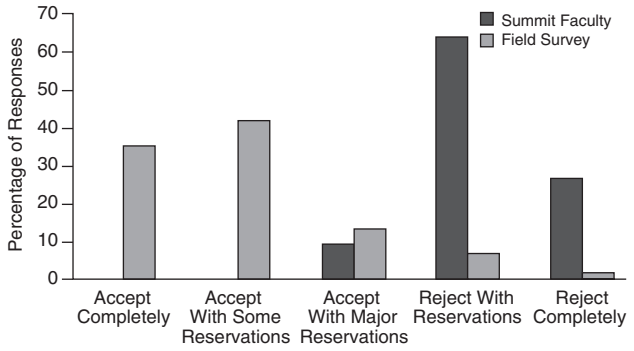
Grading of Evidence

Based on a review of the literature cited above, 2 of the 6 Summit faculty workshop members (33%) considered the evidence available to support this statement to be Category II (evidence obtained from well-designed cohort or case-controlled studies). Of the remaining faculty members, 1 (17%) considered the evidence to be Category III (evidence obtained from case series, case reports, or flawed clinical trials); 1 (17%) considered it to be Category IV (opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees), and 2 (33%) considered it to be Level V (insufficient evidence to form an opinion).

Level of Support

When voting on the support for this statement, no summit participants voted to accept the statement either completely or with some reservations. In comparison, of the 1064 clinicians who participated in the online survey, 35% voted to accept the statement completely, and 42% voted to accept the statement with some reservations. A total of 9% of the summit participants voted to accept the statement with major reservations, 64% voted to reject the statement with reservations, and 27% voted to reject the

Figure 3. Level of Support for Statement 2, "Schizophrenia Is a Neurodegenerative Disease Resulting in Brain Changes That Parallel Symptom Progression and Functional Decline"



statement completely. Of the clinicians who participated in the online survey, 13% voted to accept the statement with major reservations, 7% voted to reject it with reservations, and only 2% voted to reject it completely (Figure 3).

Discussion

It is clear from the data shown in Figure 3 that there is a highly significant disparity between the field survey and the faculty votes as to whether schizophrenia is a neurodegenerative disorder. It is likely, however, that those who participated in the field survey did not have the opportunity to scrutinize the data from the many brain imaging and histopathologic studies demonstrating that neurodegenerative changes, as defined by neuropathologists, are not present in the brains of patients with schizophrenia.

Based on the studies reviewed here, it is clear that a decrease in gray matter volume does occur in patients with schizophrenia. Further, this decrease already is present in first-episode patients and gradually progresses over time. The fact that these changes occur in parallel with a worsening of symptoms and deterioration in cognitive functioning implies that the functional integrity of the brain is being compromised as these changes occur. It is important to emphasize, however, that a cause-and-effect relationship has not been established.

The critical question, therefore, is whether the well-documented loss of gray matter volume is attributable to a neurodegenerative process, defined by the presence of neuronal loss and gliosis. Brain imaging studies are unable to demonstrate these types of changes because they lack the requisite level of spatial resolution that is possible with a bright field microscope. It is clear from postmortem studies, however, that there is an insufficient loss of neurons to adequately explain the volume losses reported. Additionally, neither an increase in glial numbers nor an increase in reactive glia has been found in quantitative microscopic studies of postmortem brain tissue sampling of patients with schizophrenia.

The question of how to reconcile these differences remains. It certainly is possible that some regions of the brain of patients with schizophrenia show a contraction of the neuropil,[29] the area in which most synaptic connections are located. In addition to shrinkage of neuropil, there also is a decrease in the number of dendritic spines and synaptic proteins.[44,45] In the hippocampus, synaptophysin[46] is reduced, whereas a specific synaptosomal-associated protein (SNAP-25) is decreased in both the hippocampus[47] and prefrontal cortex.[48] Interestingly, not all regions of the brain necessarily show similar changes. For example, in the anterior cingulate cortex, where increases of neuropil may be present,[49,50] increases of SNAP-25 and syntaxin also have been found.[51] In some regions, the neuropil might be decreased, while in others, it might be increased.

Using sophisticated new technologies, current postmortem studies are beginning to identify complex changes in the molecular regulation of neurons and glia in the brains of patients with schizophrenia. The types of changes that are being identified are likely associated with dysfunction of neurons in the absence of widespread neuronal degeneration. It is likely that the significant degree of volume loss detected by brain imaging technology will be explained as the result of more subtle changes in the distribution of synaptic terminations, dendritic spines, and other cellular elements that contribute to the functional composition of the neuropil.

For patients with schizophrenia and the clinicians who treat them, the implications of this tautology are of critical importance. For a neurodegenerative disorder such as Alzheimer's disease, the prognosis is typically quite grim, but for a brain disorder in which the "lesion" is probably related to cellular and molecular regulatory mechanisms, the overall outlook can be quite optimistic. It is now well established that the brain is capable of marked degrees of neural plasticity. Changes that occur in axons, dendrites, synapses, and molecular regulatory mechanisms are all capable of being reversed. It is essential to learn more specifically what these changes are, where they are located, and how to manipulate the genome appropriately in order to restore complex neural circuits to a state of optimal cognitive function in patients with schizophrenia.

STATEMENT 3: COGNITIVE IMPAIRMENT, ESPECIALLY EXECUTIVE DYSFUNCTION AND MEMORY LOSS, IS A KEY DIAGNOSTIC COMPONENT OF SCHIZOPHRENIA

Matcheri S. Keshavan, M.D.,
was the contributor of this section.

Rationale and Definition of Statement

Cognitive measurement has been considered to be a core feature of schizophrenia ever since the illness was originally defined over a century ago with the earlier

name, "dementia praecox," which literally means "cognitive decline with onset in youth." Impairment or deficit is seen consistently in a range of neurocognitive functions including psychomotor *S*peed, *M*emory (e.g., working memory, visual and verbal memory), *A*ttention, *R*easoning, and *T*act (i.e., social cognition). Note the mnemonic "SMART." However, it is only in recent years that the neurobiological underpinnings of cognitive impairment have been recognized, and the cognitive deficits have only recently been considered as potential targets for therapeutic intervention.

DSM-IV makes reference to cognitive impairment as an accompanying feature of schizophrenia. To date, however, cognitive deficits have not been included among the diagnostic criteria for this illness. Proposals have been made in recent years to include cognitive deficits as part of the diagnostic criteria for schizophrenia. The strength of the existing evidence for the potential diagnostic value of cognitive impairment in patients with schizophrenia is discussed herein.

Literature Search

A PubMed database search was conducted on January 15, 2008, to identify studies relating to the diagnostic value of cognitive impairment in identifying schizophrenia. The search terms "schizophrenia" or "cognition" returned a total of 170,625 articles. The search terms "schizophrenia" and "cognition" yielded 5143 articles. Using the terms "schizophrenia," "cognition," and "diagnosis," and limiting the results to reviews or meta-analyses because of the large numbers of articles in the literature, yielded 379 articles. When these results were limited to articles written in English, 347 articles were identified. Nine articles deemed relevant to Statement 3 were reviewed.

Evidence

Schizophrenia is a complex, highly debilitating disorder manifesting itself primarily in cognitive impairment. While generalized intellectual deficits occur in schizophrenia, there are prominent impairments in select domains of cognition, including psychomotor speed, memory, attention, reasoning, and social cognition. To date, cognitive deficits are not part of the criteria for a diagnosis of schizophrenia. The candidacy of cognitive impairment to the diagnostic criteria may be evaluated on the basis of whether it (1) is a frequent feature of the illness; (2) is a robust feature of the illness; (3) reflects "trait" aspects of the illness (i.e., being longitudinally stable and present in unaffected relatives as well); (4) is related to the outcome of the illness as evaluated longitudinally; and (5) is discriminatory between schizophrenia and other psychotic disorders.

Cognitive impairment is seen in the majority of patients with schizophrenia. While cognitive deficits are seen in many patients with schizophrenia, some patients are classified as unimpaired by traditional definitions of impairment. Keefe et al.[52] determined the percentage of patients with schizophrenia who met the criteria for cognitive decrement (i.e., those who tested below the level expected in premorbid estimates) based on maternal and paternal education and reading scores. With the latter 2 parameters, 42% of patients in the control group and 98% of patients with schizophrenia had cognitive function below expectations. Thus, it is likely that a majority of patients with schizophrenia have cognitive deficits, defined by a failure to reach the expected level of functioning. Some patients with schizophrenia who perform within the normal range on cognitive tests still may have cognitive decrements below their potential, an important point to remember when planning therapeutic interventions to improve cognition.

Cognitive impairment is a robust feature of schizophrenia. Recent meta-analyses show that cognitive impairment distinguishes patients with schizophrenia from healthy comparison patients to a significant degree (i.e., an effect size of approximately 1 with approximately 1 standard deviation, although some studies show 2 to 3 standard deviations in some domains[53]). Effect sizes represent standardized mean differences—usually, an effect size of 0.2 is considered to be small, 0.5 to be medium, and 0.8 to be large. Average effect sizes for cognitive impairments are about twice as large as those obtained in structured MRI studies.[54] However, not all patients have cognitive impairments of robust magnitude. This variation perhaps relates to the heterogeneity in the clinical manifestations as well as etiopathology of schizophrenia.

Cognitive impairment is a stable, trait-related aspect of schizophrenia, being present in nonpsychotic relatives as well. Cognitive impairment may be related to a patient's genetic susceptibility to schizophrenia, and this genetic susceptibility is considered to be the candidate intermediate phenotype for the illness. Snitz et al.[55] compared relatives of patients with schizophrenia and patients in the control group on 43 cognitive test scores from 58 studies. Small to medium effect sizes were seen, especially for complex tasks involving demands on complex executive functions, including set shifting and inhibition of prepotent responses. Cognitive deficit, seen as a potential intermediate phenotype, may prove to be a valuable "foothold" in our search for genetic factors underlying schizophrenia illness.

Cognitive impairment is also stable during the longitudinal course of schizophrenia. Cognitive deficit is present in the premorbid phase of the schizophrenic illness and persists during the long-term course. In a review of 15 studies with a follow-up of at least 1 year (i.e., follow-up ranged from 1 to 15 years), Rund[56] found that patients' cognitive deficits remain relatively stable, with no evidence for either decline or improvement. In general, this

observation supports the view that the long-term course of schizophrenia may not be associated with substantial neurodegenerative processes. However, the longitudinal studies reviewed thus far may not be adequate to confidently rule out the possibility that progressive functional decline may occur in a small subgroup of patients with schizophrenia.

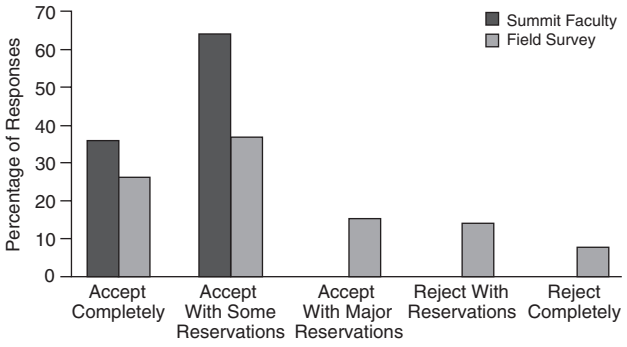
Cognitive impairment predicts outcome as evaluated longitudinally. In a review of 18 longitudinal studies with a minimum of a 6-month follow-up, Green et al.[57] examined the relationship between longitudinal outcome and cognition. Cognitive deficit did predict outcome as measured by social and vocational effectiveness. Though the effect size for individual measures was modest, global cognitive dysfunction had a moderate effect size as a predictor. This study suggested that social cognition may have a particularly strong relation to functional outcome. These observations provide a rationale for developing psychopharmacological and psychosocial interventions to improve cognition in patients with schizophrenia. However, functional outcome is also affected by a plethora of factors other than cognition, such as negative symptoms (e.g., the so-called deficit symptoms) as well as the educational and vocational opportunities available to the individual.

Cognitive impairment is more robust in schizophrenia compared to other psychiatric disorders. Relatively few studies have directly compared neurocognitive measures between schizophrenia and other psychiatric disorders. Some studies have compared schizophrenia versus psychotic and nonpsychotic affective disorders. In a study examining antipsychotic-naive, first-episode psychotic patients, MacDonald et al.[58] reported that prefrontally mediated dysfunctions related to context processing were found only in patients with schizophrenia when compared to psychotic patients who do not have schizophrenia. These dysfunctions were related to disorganization symptoms. Another study by Hill et al.[59] showed that patients with psychotic depression have cognitive decrements similar to those seen in schizophrenia, but to a lesser extent. The data showed that nonpsychotic depressive patients had neuropsychological profiles similar to those of healthy patients in the control group. The diagnostic groups overlap significantly, however, suggesting that there is no "point of rarity" needed for utility as a marker to distinguish between disorders.

Grading of Evidence

Based on a review of the studies cited above, 2 of the 6 (33%) Summit faculty members in this workshop rated the evidence available to support this statement as Category I (evidence obtained from at least 1 well-designed, randomized, controlled trial). Of the remaining faculty members, 3 (50%) considered the evidence to be Category II (evidence obtained from well-designed cohort or case-controlled studies), and 1 (17%) considered it to be Category III (evidence obtained from case series, case reports, or flawed clinical trials).

Figure 4. Level of Support for Statement 3, "Cognitive Impairment, Especially Executive Dysfunction and Memory Loss, Is a Key Diagnostic Component of Schizophrenia"



Level of Support

When voting on the support for this statement, 36% of the total Summit faculty members voted to accept the statement completely, and 64% voted to accept the statement with some reservations. In comparison, of the 1064 clinicians who participated in the online survey, 25% voted to accept the statement completely, 36% voted to accept the statement with some reservations, 14% voted to accept the statement with major reservations, 13% voted to reject the statement with reservations, and 7% voted to reject the statement completely (Figure 4).

Discussion

This review indicates that neurocognitive impairment may be a core component of schizophrenia, but is it a core component of the diagnosis of this illness? The purpose of diagnosis is to predict the cause, pathogenesis, course, response to treatment, and familial factors associated with a disease. Cognitive function is severely to moderately impaired in patients with schizophrenia compared with healthy control populations. A majority of patients with schizophrenia manifest cognitive decrement relative to their expected level of functioning. Cognitive impairment in these patients appears early, persists during the illness, and tends to be stable. Cognitive deficits in patients with schizophrenia are more severe and pervasive compared to patients with psychotic and nonpsychotic affective disorders. Cognitive deficits predict some part of the variance in functional disability and are associated with a familial risk for this illness. In this sense, cognitive impairment meets many of the key components of the diagnostic process as outlined by Robins and Guze[60] decades ago.

Keefe and Fenton[61] recently have suggested that a specific criterion pertaining to cognitive impairment be

included in the DSM-V criteria. Specifically, they recommend "a level of cognitive functioning suggesting a consistent severe impairment and/or a significant decline from premorbid levels considering the patient's educational, familial, and socioeconomic background"[61(p912)] as the criterion. A majority of the Summit participants supported this proposal. The inclusion of such a criterion may help more clearly discriminate schizophrenia and nonschizophrenia psychoses. Increased clinician awareness of cognitive deficit also may lead to the choice of more appropriate treatment modalities and thereby improve patient outcomes.

Future Directions

Some of the lack of consistency in neurobiological abnormalities across the multiple diagnostic criteria in schizophrenia may be related to the fact that many criteria are based on consensus ratings of cross-sectional symptoms. Cognitive impairment appears to be more strongly associated with a definition of schizophrenia that incorporates some aspects of the longitudinal course of the illness (e.g., the Feighner, Langfeldt, or French diagnostic systems) than definitions that do not take the course of the illness into consideration.[62] Future refinements in diagnostic criteria for schizophrenia need to consider such observations.

Several cognitive assessment methods are now available for clinicians, including brief assessments and interview-based assessments. However, assessment of cognitive deficit by clinical rating scales such as the Positive and Negative Syndrome Scale (PANSS) may not be an adequate substitute for neuropsychological testing in order to reliably ascertain cognitive deficits in patients with schizophrenia.[63] The reliable determination of cognitive impairment as part of a standard diagnostic evaluation, therefore, could be difficult for clinicians in community settings with inadequate expertise or limited resources. More research is needed to implement such criteria in practice.

STATEMENT 4: GENETIC FACTORS ARE THE BEST ESTABLISHED ETIOLOGIC DETERMINANTS OF SCHIZOPHRENIA

David L. Braff, M.D.,
was the contributor of this section.

Rationale and Definition of Statement

It is now widely accepted that schizophrenia results from interactions between a genetically mediated neurobiological vulnerability and nongenetic "second hits" or stressors.[64] Family and twin studies have established that familial genetic factors account for the fact that schizophrenia is approximately 80% heritable. The key data that have supported Statement 4 come from many family studies and from the finding that monozygotic (MZ) twins raised apart have a concordance rate (i.e., if 1 MZ twin has schizophrenia, so does the other) far higher (41% to 65%) than dizygotic (DZ) twins raised either together or apart (0% to 28%).[65,66]

While family studies tell us that schizophrenia is highly heritable, more information is needed to better understand the

- identity of and the percentage of the variance attributable to specific genes responsible for schizophrenia vulnerability,
- mechanisms by which these genes produce the neurobiology of schizophrenia, and
- basis for the 20% to 30% of schizophrenia risk that is nongenetic.

Nongenetic contributors to the etiology of schizophrenia include diverse factors from postconception epigenetic methylation events[67] to viremias and nutritional deficiencies that impact a vulnerable fetus in the second trimester of gestation. In general, Zubin's "stress diathesis" model[64] has stood the test of time. Also, it appears that with greater polygenic vulnerability, less stress is needed to precipitate schizophrenia.

Schizophrenia is a "common" disorder with an incidence of approximately 1% or greater. It also appears to be highly polygenic (i.e., many genes apparently contribute to the schizophrenia vulnerability). It is likely that common base pair changes or "single nucleotide polymorphisms" (SNPs) contribute greatly to a patient's risk for schizophrenia. In extreme cases, a single, highly penetrant, rare allele may create risk for schizophrenia as suggested by the "common disease/rare mutation" hypothesis.[68]

High levels of heritability do not mean that it is an easy process to map exactly which genes or combination of genes (i.e., oligogenetic interactions) create the highly heritable trait that precedes the onset of schizophrenia. In fact, exact mapping of genes has proven to be difficult in most medical and neuropsychiatric disorders.

Thus, Statement 4, "Genetic factors are the best established etiologic determinants of schizophrenia," appears to be both true and challenging in all its complexities.

Literature Search

A literature search was performed on January 28, 2008, using PubMed via the National Center for Biotechnology Information (NCBI) Entrez retrieval system. This retrieval system was developed by NCBI at the National Library of Medicine, located at the US National Institutes of Health. The text words used for the literature search were

1. "schizophrenia," yielding 77,766 articles;
2. "genetic factors," yielding 148,843 articles;

3. "psychosis," yielding 38,477 articles; and
4. "etiologic determinants," yielding 192 articles.

When any of these 4 text words were combined with "OR," the query search resulted in 251,926 articles.

A search was done using text words 1 and 2. When combined with "AND," the query resulted in 1939 articles. When the results were limited to articles written in English, this yielded 1732 articles. Next, a search was performed using text words 1 and 3. When these words were combined with "AND," the query resulted in 11,195 articles. When these results were limited to articles written in English, the results narrowed to 9111 articles. Another search was conducted using text words 1 and 4. When these text words were combined with "AND," the query returned only 4 articles. After the query was limited to articles written in English, the 4 articles remained. When results were limited to human subjects, 4 articles were returned by the query. However, when the query was limited to clinical trials, only 1 article was identified.

Lastly, a search was conducted combining text word 1 and text word 2, and then combining the results with "OR" and text word 4. This query search resulted in 2130 articles. The results then were limited to articles written in English, which resulted in 1913 articles. By limiting the results to human subjects, 1795 articles were returned. Of these articles, approximately 68 were deemed relevant to this statement.

Evidence

The evidence for this statement comes from a sizeable number of studies and strong inferences. These include studies of twins and families; linkage, association, and candidate gene studies; and the endophenotype or intermediate phenotype strategy of gene discovery in patients with schizophrenia.

Twin and family studies. In addition to studies of DNA, genetic evidence also comes from epidemiological, observational, and family studies. Gregor Mendel's study of pea colors and texture first illustrated lawful Mendelian heritability patterns long before the structure of DNA was elucidated.[69] Cardno and Gottesman[65] summarized twin/family studies of schizophrenia and showed that there are "proband concordance rates" of 41% to 65% in MZ twins, but only 0% to 28% in DZ twins. This percentage is close to the rates in nontwin siblings, as would be expected. These results reinforce the known established heritability and genetic basis of schizophrenia, but they do not address the question of which specific genes are involved. Cardno and Gottesman[65] also noted that there is discordance in the data of MZ twins, which presents a valuable opportunity to study the nongenetic etiologies or protective factors related to schizophrenia.

Subsequently, Sullivan et al.[66] conducted a meta-analysis of 12 large studies of twins and found that there was substantial evidence for additive genetic effects (i.e., the point estimate of heritability in liability to schizophrenia was 81%) and a corresponding lower level of nongenetic effects in schizophrenia. This raises a second challenging issue: exactly what is the nature of the polygenic contributions to schizophrenia risk?

Linkage, association, and candidate gene studies. After the advent of the "genetics era" with the identification of the DNA double helix,[69] genes, and mRNA with base pair coding of proteins, the search for genetic units of heritability for human diseases blossomed. Mendelian-dominant disorders like Huntington's disease proved relatively easy to decode genetically. Despite the fact that there are hundreds of very rare Mendelian-dominant disorders that occur in much less than 1% of the population, most highly heritable diseases have complex genetic bases. In fact, with 3 billion base pairs, only 1% to 2% of base pairs form protein-coding genes. Thus, much of the genome is somewhat paradoxically "silent" in terms of the actual coding of proteins, which are the building blocks of life.

Additionally, there are approximately 30,000 genes, 16,000 of which are expressed in the human brain, and 6000 of these genes are expressed only in the brain.[70] Thus, scientists are faced with the profound problem of identifying which genes and combinations of genetic interactions form the substrate of risk in "non-Mendelizing" polygenic disorders. These consist of diverse conditions including hypertension, cancer, type II diabetes, bipolar disorder, and schizophrenia.

An initial approach to this problem was somewhat "atheoretical" in that it consisted of linkage studies. Across the genome, locations of known base pairs were mapped. Then, across often large families, schizophrenia was found to be linked with a genomic region. Schizophrenia, therefore, was linked to a specific genomic region, but that region harbored more than 1 gene. It had yet to be determined which specific or general genetic risk marker or markers were involved in schizophrenia. The arduous, statistical bar having been met for positive linkage studies, scientists then took on the task of genetic "fine mapping." This process is analogous to increasing the power of a microscope. Although family-based linkage studies were quite informative in identifying genes of interest, the function of these risk genes remained largely unknown, unlike model organism and endophenotype studies. Neurobiology and gene function, therefore, needed to be added to linkage studies in order to fully exploit this rich and informative area of scientific inquiry.[71,72]

In addition, a plethora of other analytic problems presented themselves related to base pair frequency differences across different racial populations, which necessitated analytical strategies using "population stratification" by race.[72] One solution to this "admixture" problem was to study "population isolates" from geographically disparate and isolated areas such as the Central Valley of Costa Rica

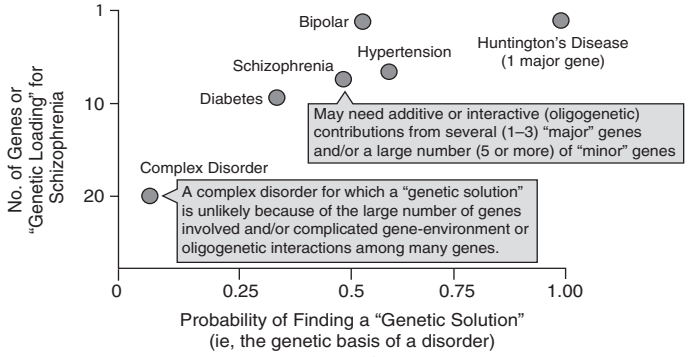
or Papua, New Guinea. In population isolates, "founder populations" of relatively few individuals are the progenitors of a discrete population, so that background genetic noise (i.e., diversity) is minimized and, in theory, the genetic signal-to-noise ratio is amplified.[73] This makes disease genes easier to identify. While useful, this approach is limited when applied in the real world, where admixture of different racial groups is so prevalent.

Key studies. Because of space constraints, only several key studies will be reviewed here. In a study from 2006, Suarez et al.[72] conducted a genome-wide linkage scan of 409 families of European ancestry (EA) and African American (AA) descent with a history of schizophrenia. Families included a schizophrenia proband and 1 or more siblings with schizophrenia or schizoaffective disorder. A simple, tandem, repeat polymorphism interval of 9 cM was used with follow-up fine mapping. The linkage analysis of 403 independent, full-sibling affected sib-pairs was a major focus of this study. Nonparametric, multipoint linkage analysis of all families revealed evidence of linkage at loci 8p23.2-q12 and 11p11.2-q22.3, as well as 2 other regions of interest, based on Z likelihood-ratio scores which separated along AA/EA family lines. This finding suggests the existence of population (i.e., racial) differences in schizophrenia. Fine mapping was then performed on the full sample to examine the 2 strongest identified peaks (i.e., multipoint 2 (1r) of 2.25 D8S1771 at 50 cM), and both were telomeric to neuregulin 1 (*NRG1*). The authors performed many other complex statistical analyses that can be reviewed by the interested reader. This study clearly illustrates the steps typically utilized in robust linkage studies.

The neurobiological function and significance of *NRG1* in schizophrenia remain uncertain, however. In this sense, linkage and association studies are "agnostic" in that they are not designed to inform the issues of function, as are endophenotype and some model organism studies. Once a disorder is identified as highly polygenic in origin (i.e., each gene accounts for only relatively small amounts of the cumulative heritability), more detailed and fundamentally relevant information is needed in order to integrate the complex genetic tapestry of "risk" or vulnerability into a coherent neurobiological picture of vulnerability (see Figure 5).[74,75]

There are a number of other approaches that are useful for honing in on the functional impact of schizophrenia genes. For example, the high statistical genetics bar for "positive findings" in linkage studies and association in case-control studies obviously should be lowered once multiple studies have confirmed the significance of the same genes. Harrison and Weinberger[71] and Cardno and Gottesman[65] have done an excellent job of summarizing

Figure 5. "Ease" of Defining the Genetic Architecture of Single-Gene, Mendelian-Dominant Disorders (eg, Huntington's) Versus the More Daunting Task of Understanding the Genetic Architecture of Complex Disorders Such as Schizophrenia[a]



[a]Reprinted with permission from Braff et al.[74]

the extensive literature. It turns out that many of the genes identified atheoretically have meaningful expression in the brain and can be linked to schizophrenia.

In the case of *NRG1*, Stefansson et al.[76] followed up on 5 studies that showed an association between schizophrenia and chromosome 8P. In this context, *NRG1* was identified as a candidate gene for schizophrenia in a large Icelandic population via fine mapping of the 8p locus, haplotype association analysis, and a technique called TDT (transmission/disequilibrium test) analysis. In this study, *NRG1* was associated with prepulse inhibition (PPI) deficits, which is an endophenotype in schizophrenia. Furthering its strength as a candidate gene for schizophrenia, *NRG1* has shown a clear role in neurotransmitter expression involving *N*-methyl-D-aspartic acid (NMDA) and dopamine neurotransmitters, which are central to most models of receptors in schizophrenia.

In parallel model organism studies, investigators "knocked down" or decreased the expression of *NRG1* and its receptor ErbB4. These "hypomorphs" showed behaviors typical of animal models of schizophrenia, including decreased PPI with its known neurobiological substrates.[74,77,78] In addition, clozapine normalized the PPI endophenotype in these hypomorphs, providing further support for *NRG1* as an important candidate gene in schizophrenia.

Weinberger et al.[79] have added compelling support for catechol-*O*-methyltransferase (*COMT*) as a schizophrenia vulnerability gene. These investigators have shown that the *COMT* val$^{(108/158)}$ met allele/SNP (rs4680) affects dopamine-regulated prefrontal cortical activity, which appears to be impaired in schizophrenia.[80] Building on previous work, the National Institute of Mental Health (NIMH) group examined a number of SNPs in the *COMT* gene in 325 patients with schizophrenia, 359 of their siblings, and 330 control patients. Overall, val homozygotes

(i.e., val/val) exhibited dysregulated cerebral metabolism and deficits in working memory—a core neurocognitive feature of schizophrenia. This effect occurred across all subject groups. This finding suggests that *COMT* val$^{(108/158)}$ met SNPs in schizophrenia confer a small but important part of a patient's risk for schizophrenia.

The acetylcholine receptor epsilon subunit (AChR) α-7 gene "story" elucidated by Leonard and Bertrand[81] is another example of the power of understanding the function of genetic variation in schizophrenia. First, these researchers made a dramatic, widespread clinical observation that 80% of patients with schizophrenia smoke and thereby achieve nicotine receptor stimulation. Initial linkage studies were followed up by association studies between the diagnosis of schizophrenia and, on fine mapping, the promoter region of the α-7 nicotinic receptor. This established the α-7 nicotine receptor as a functionally rational risk gene in schizophrenia.[82]

Endophenotype/intermediate phenotype strategy of gene discovery in patients with schizophrenia. In addition to linkage studies, genome-wide association studies and candidate gene studies (e.g., the "endophenotype strategy" utilized by the Consortium of Genetics in Schizophrenia [COGS]) offer a rich complementary gene-finding strategy.[75] Gottesman et al.,[83] relying on information from the glucose tolerance test in diabetes and plant biology, first used the term *endophenotype* in the neuropsychiatric literature. Endophenotypes, defined as "deficits" not visible to the naked eye, occur in patients with schizophrenia and their "non-affected" relatives at greater frequency than in control groups. Ideally, endophenotypes also cosegregate with the illness. In many other biomedical fields, these associations are called intermediate phenotypes (i.e., deficits intermediate between the gene and the full disease). The distinction between these terms has been a point of some contention.[84,85] More important is the underlying idea that endophenotypes probably, but not invariably, have a simpler genetic architecture than do complex and clinically heterogeneous disorders such as schizophrenia.[74,82,85,86]

As an example, the COGS project has identified 12 neurocognitive and neurophysiologic "quantitative" endophenotypes that are significantly heritable in families. These endophenotypes were ascertained via a proband with schizophrenia and at least 1 "unaffected" (i.e., nonschizophrenic) sibling.[87] Prepulse inhibition, P50 suppression, oculomotor function, California Verbal Learning Test, Letter-Number-Sequencing, Continuous Performance Test–Identical Pairs Version, and the University of Pennsylvania Computerized Neurocognitive Battery all were obtained on these subjects. Results showed that schizophrenic deficits were significantly heritable.[88]

The next issue that needed to be determined was the identification of the genes that accounted for these heritable deficits. Two approaches are currently being used to identify these genes: genomic linkage scans from the Center for Inherited Disease Research and association studies using the 1536 SNP chip.[89] The SNP chip approach uses 1536 SNPs from 94 candidate genes with either established or strong inference-based relationships to schizophrenia. Similar work is being done using a drug abuse SNP chip.[75,90] As discussed in the article by Greenwood et al.,[89] *NRG1* and its ErbB4 receptors are associated with 8 and 10 of the 12 COGS endophenotypes, respectively, at the $p < .01$ to $p < .00001$ level. They also associate with the qualitative diagnosis of schizophrenia itself. Five genome-wide association studies showed $p < 10^{-7}$ level associations of *NRG1* to schizophrenia, so it could be argued that a replication using endophenotypes requires only a $p < .01$ or even $p < .05$ to be viewed as significant. Surely, when 8 to 10 of 12 endophenotypes associate with *NRG1* and ErbB4 at $p < .01$ to $p < .00001$, the significance of *NRG1* in schizophrenia and its functional importance is evident.

The gene *NRG1* also reflects pleiotropy in that it is associated across multiple endophenotypes of schizophrenia. Still, some would take an "ahistorical" approach and demand a 10^{-7} p value on replications; however, this seems gratuitous. Importantly, if schizophrenia risk also is rooted in complex neural networks like the cortico-striato-pallido-thalamic circuitry,[78] each site and its multiple neurotransmitters may be affected by many different SNPs, as has been described for *COMT*.[71,80] It is possible, or perhaps it even is likely, that new "neurobiologically informed" medications may modulate the common output pathway of several hundred or even thousands of SNPs and many genes across widespread neural circuits.[75,91] Thus, dopamine D_2 receptor antagonists (e.g., haloperidol) have antipsychotic properties and act to regulate output from a frontal structural circuitry.

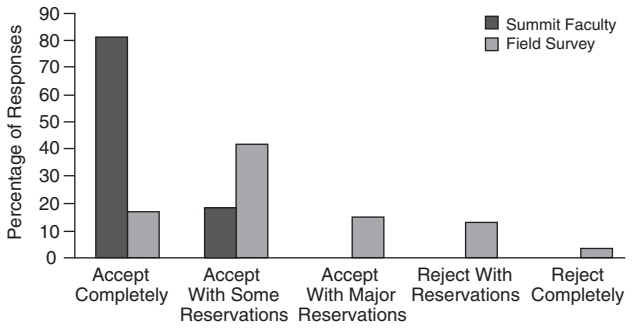
Currently, based on the P50 suppression/α-7 nicotinic associations in patients with schizophrenia, a number of potential α-7 agonists are being used in multiple medication studies. Results of these studies will influence future schizophrenia treatment options.

The fact that this statement has a complicated back story reflects the daunting complexity of brain-behavior relationships. The genetic influences that cause schizophrenia risk, however, are foundational to a new understanding of the neurobiology and potential treatments of schizophrenia.

Grading of Evidence

Based on a review of the literature cited above, 4 of the 6 Summit faculty workshop members (67%) considered the evidence available to support this statement to be Category I (evidence obtained from at least 1 well-designed, randomized, controlled trial). The remaining 2 faculty members considered the evidence to be Category II

Figure 6. Level of Support for Statement 4, "Genetic Factors Are the Best Established Etiologic Determinants of Schizophrenia"



(evidence obtained from well-designed cohort or case-controlled studies).

Level of Support

A total of 83% of the Summit faculty members accepted the statement completely, and 17% accepted this statement with some reservations. This translates to 100% of the faculty supporting the statement. Results from the field survey of 1064 clinicians, however, indicated that 17% accepted the statement completely, while 42% accepted the statement with some reservations. In addition, 15% of the field survey respondents accepted the statement with major reservations, 12% rejected the statement with reservations, and 5% rejected the statement completely. It appears that possibly 9% of the field survey respondents did not vote (Figure 6).

Discussion and Future Directions

As discussed, the future direction of genomics in schizophrenia will rely on a challenging and rich platform. This platform, however, is in its early adolescence. The explosion of genomic, proteomic, epigenetic, and gene-environment knowledge[68,71,72,74,76,91,92] promises a hopeful future for the application of our knowledge of schizophrenia genomics. In the future, research should be conducted to

- identify the genomic regions that harbor risk genes, identify these genes, and specify the many SNPs within those genes that each contribute to the high heritability levels (i.e., 80%) of schizophrenia;
- specify the neurobiological significance and neural network locations of those "risk" genes, which may act alone or in concert with other genes and environmental factors (e.g., methylation); and
- use this knowledge as a robust platform for the development of new, strong, inference-based molecules for the treatment of schizophrenia.[74]

STATEMENT 5: NEUROIMAGING IS A TOOL FOR ELUCIDATING BIOLOGICAL AND GENETIC MECHANISMS OF ILLNESS AND TREATMENT RESPONSE

Daniel R. Weinberger, M.D.,
was the contributor of this section.

Rationale and Definition of Statement

The clinical diagnosis of schizophrenia is based on the phenomenological characteristics of people who are ill. As such, it is subjective and imprecise. Its clinical features traditionally have been difficult to attribute to specific biologic processes, and it is reasonable to assume that the underlying biology is not specific to the diagnostic symptoms and the symptoms are not necessarily the result of a singular biology.

Prior to the discovery of antipsychotic medications, biologic research on mechanisms of schizophrenia was very limited and was based on low-resolution biologic assays and physiologic measurements of limited relevance to brain function. After the discovery of antipsychotic medications, researchers focused on neuropharmacological and biochemical assays in relation to the mechanism of the therapeutic action of these agents. However, these techniques could not address brain function directly, because most assays were based on the collection of peripheral body fluids.

The advent of neuroimaging techniques introduced the first methods and strategies for the direct examination of brain structure, function, and chemistry in living human beings. This permitted a much more interpretable research paradigm for understanding the relationship of brain biology to illness states, illness manifestations, and the therapeutic actions of available and experimental medications. While neuroimaging techniques are phenomenological and observational, the opportunity to use imaging to map the effects of genetic variations associated with a clinical diagnosis has opened a new area of investigation related to understanding the neurobiological mechanisms by which genes are related to the neuroscience of mental illness. Statement 5 reflects these developments in the application of neuroimaging to clarify brain mechanisms of illness, treatment response, and genetic associations.

Literature Search

Several PubMed literature searches of articles dating back to 1992 were conducted on March 1, 2008, to sample the medical literature concerning this statement. Search queries included "neuroimaging and schizophrenia," which yielded 637 citations; "brain imaging and schizophrenia," which yielded 3222 citations; "neuroimaging and schizophrenia genes," yielding 42 citations; "brain imaging and schizophrenia genes," yielding 103 citations; "neuroimaging and schizophrenia treatment," which

yielded 176 citations; and "brain imaging and schizophrenia treatment," which yielded 854 citations. Combining the results of these searches identified 35 articles relevant to this statement.

Evidence

Neuroimaging studies related to schizophrenia have addressed several key issues. These include localizing the structural pathology associated with schizophrenia, characterizing the associated functional abnormalities, identifying neurochemical aberrations related to the illness, characterizing functional and neurochemical effects of treatment, and most recently, describing the effects of genetic variations associated with schizophrenia on the putative phenotypes defined by structural and functional imaging.

Structural pathology and illness state. Since the advent of the computed tomography (CT) scan in the mid-1970s, literally hundreds of studies have appeared comparing patients with schizophrenia to healthy control populations, including unaffected relatives of patients with schizophrenia.[93–97] These studies have focused on quantitative measures of brain structure—the so-called cerebral morphometry. Most of this literature involves MRI technology.[93,94,96] Measures in these studies include the volume of brain structures such as the hippocampus, thalamus, neocortex, and ventricles; the shape of brain structures including the hippocampus and thalamus; and the surface area of cortical structures.

There also have been a number of recent studies using diffusion tensor imaging (DTI) to survey white matter tract orientation.[98–101] Although some data discrepancy exists, most studies show that patients with schizophrenia, including patients at the onset of the illness, have small reductions in cortical volumes, particularly in the frontal cortex and hippocampus, on the order of 3% to 10%. These patients also have a slight enlargement of their cerebrospinal fluid spaces. These changes are not diagnostically specific and, therefore, have an uncertain pathologic origin. Although the DTI studies report differences between patients and control populations in most studies, they are inconsistent in terms of which long white matter tracts are implicated.

Cortical volume loss based on MRI measurement has been shown to advance over the first few years of illness in several recent studies.[79,95,102] In some studies, this has been demonstrated even in later years of chronic illness.[103] The origin of these so-called progressive changes is unknown, and artifacts related to such factors as medication effects, dietary changes, smoking effects, and exercise have not been excluded as potential causes. All of these factors have been shown to affect MRI measurement of cortical volume in nonschizophrenic patients as well. It is widely assumed that these progressive changes do not reflect neurodegeneration per se.

Thus, structural imaging has served to highlight particular brain regions and structures that appear to be specifically linked to the illness state, and it has helped to identify illness-related brain systems. While schizophrenia-specific brain structures or systems cannot be identified with certainty from these studies, the frontal lobes with the prefrontal cortex in particular, and the temporal lobe with the peri-hippocampal cortex in particular, most often are implicated.[79,93,95,104–107]

Functional abnormalities associated with illness. Electroencephalographic (EEG) studies were the first functional brain studies conducted on patients with schizophrenia,[108] but EEGs do not permit exact localization and are not precise imaging procedures. The development of cerebral blood flow measurement techniques including positron emission tomography (PET) and now predominately functional (f)MRI, permits high-resolution, 3-dimensional imaging of brain function. Hundreds of studies have identified functional differences between patients with schizophrenia and normal volunteers tested using these methods.[79,93–97,104–107,109–113] Studies have included measurements of brain activity both during rest and during the performance of specific information-processing paradigms, especially cognitive paradigms.[104,106,107,110,111]

The breadth of data and study details is enormous. In general, frontal (including cingulate) and hippocampal functional differences between patient and control populations have been documented in many studies, both for patients with schizophrenia near the onset of illness and in those with chronic illness.[71,93,95,105–107,110,111,114]

Recent studies have attempted to characterize these differences in greater detail, focusing on patterns of activity across brain regions (i.e., the so-called connectivity analyses), and to parse the physiologic responses based on experimental cognitive paradigms.[71,107,110,115] These reports have suggested that frontal cortical engagement in patients with schizophrenia is inefficient or poorly tuned, which leads to relatively greater activation for a particular level of task performance.[116] Because cognitive capacity in patients with schizophrenia is generally less than that of control populations, cortical engagement also tends to diminish as capacity is exceeded.[106,116] It has been proposed that this pattern of overactivity (i.e., inefficient) and underactivity (i.e., hypofrontal), depending on capacity constraints, explains much of the functional imaging data seen in patients with schizophrenia.[79,106]

Patterns of functional connectivity across regions of the brain, particularly the prefrontal and temporal regions, also tend to be abnormal, but it is unclear whether this is an inevitable manifestation of local cortical processing deficits or a reflection of distributed, circuit-related pathophysiology. Recently, there has been interest in whether these patterns of brain activity in patients could be used to predict treatment outcomes or individual responsiveness.[117] In general, the prediction of outcomes based on imaging has

not met with consistent success; however, successful treatment tends to improve these abnormal activity patterns.

Chemical abnormalities associated with schizophrenia. Neuroimaging techniques include several approaches to in vivo neurochemical measurement. Studies using radioreceptor imaging techniques typically involve PET and single photon emission CT. Most studies have focused on the D_2 receptor; however, early reports of increased D_2 receptor binding were subsequently shown to likely be an artifact of neuroleptic treatment.[118]

Imaging of the D_2 receptor has also been used extensively to characterize the in vivo binding affinity of available and experimental antipsychotic medications. This has confirmed that all effective antipsychotic medications bind in vivo to D_2 receptors. The degree and temporal dynamics of the binding data predict some of the variability in side effect profiles of the various agents.[119,120] While the degree of D_2 occupancy does not predict treatment response, no response is seen unless at least 50% of available D_2 receptors are occupied for at least several hours per day.

There have been several independent studies of the effect of amphetamine treatment on D_2 binding in the stratum, constituting an indirect assay of presynaptic dopamine (DA) release.[118,121] These studies found evidence of increased presynaptic DA responsivity in patients, and the differences between patients and the control group disappeared during psychosis remission.[118] These data add to the evidence that regulation of DA responsivity is abnormal in patients with schizophrenia.

Studies of other receptor systems in patients with schizophrenia have not produced a consistent body of data. Researchers have used PET imaging to assay presynaptic DA activity using the metabolic substrate F-8 fluorodopa.[122] There have been at least 5 similar studies conducted, and the data consistently have shown an increased uptake within the striatum of this substrate. These results again add to the evidence that, at least in actively psychotic individuals, the activity of DA terminals in the striatum is increased. Whether this is a primary or secondary phenomenon is unclear.

In addition to radionuclide-based neurochemical imaging, MRI techniques have been adopted to obtain information about various metabolites within the brain, an approach referred to as magnetic resonance spectroscopy (MRS). Most studies using MRS have focused on measures of *N*-acetyl aspartate (NAA), a glutamate metabolite and correlate of glutamate concentrations and neuronal synaptic density.[104,105,109–111] In many studies, but not all, patients have lower NAA concentrations in the prefrontal and hippocampal cortices. In some studies, these NAA measures were shown to predict clinical symptoms including working memory and also other physiologic imaging parameters.[104] Magnetic resonance spectroscopy techniques also have been adapted to measure other metabolites, including glutamate and γ-aminobutyric acid (GABA).[123,124] These results have been inconsistent, and the specific component of the glutamate and GABA signals related to the neurotransmitter pools is not clear.

Neuroimaging as an approach to identifying genetic mechanisms of schizophrenia. Studies of unaffected relatives of patients with schizophrenia, including siblings and cotwins, provide insight about findings that are state related (i.e., found only in association with manifest illness) and findings that are trait related (i.e., found in individuals who are at increased risk of manifesting illness but do not).[106] The latter set of associations might identify changes in the brain that are linked to genetic susceptibility factors. Examination of healthy cotwins of patients with schizophrenia shows that structural changes in prefrontal and temporal cortices associated with illness are heritable and, to a lesser degree, can be observed in healthy cotwins.[95,96] This suggests that genes related to schizophrenia affect the development of these cortical regions. Studies in siblings, who are less genetically related than twins, have shown similar but less-consistent results.[106,125]

A newer strategy has been to use imaging as a phenotyping tool to search for association of genetic variation with variation in brain imaging phenotypes.[126] Using standard clinical genetics strategies, imaging genetics allows researchers to explore how genes associated with schizophrenia alter brain structure and function in patients with schizophrenia and in their relatives.

The *COMT* gene, which has been inconsistently associated with schizophrenia, is associated with prefrontal and hippocampal physiologic changes associated with schizophrenia (e.g., reduced hippocampal activation during memory, inefficient prefrontal cortical engagement during frontal lobe cognitive tasks).[127] These associations with imaging phenotypes have been observed consistently, even in normal subjects, illustrating the power of imaging genetics. Another promising schizophrenia susceptibility gene, *DISC1,* has been associated with frontal and hippocampal structural and physiologic phenotypes.[128,129] Once again, *DISC1* has also been found in normal individuals carrying risk-associated alleles, suggesting that the gene is linked to schizophrenia via its impact on these cortical systems.

A number of other associations of genetic variations in candidate susceptibility genes have been reported, including the following:

- *NRG1*, which has been linked with cingulate response[130];
- *GAD1,* which has been linked with prefrontal response[131];
- *GRM3*, which has been linked with hippocampal and prefrontal structural and functional MRI measurements and spectroscopic signals from

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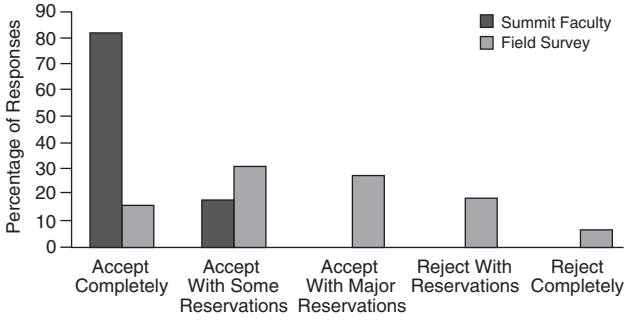
NAA-containing compounds[112,113];
- *DAOA*, which has been linked with hippocampal fMRI responses[132]; and
- *AKT1*, which also has been linked with prefrontal response.[133]

The literature is in its infancy, and most of the results, with the exception of those involving *COMT*, should be considered preliminary and in need of much more investigation. However, these studies suggest that imaging can elucidate biologic epistasis between genes affecting schizophrenia-related physiologic patterns (e.g., *COMT* with *GRM3* exaggerate cortical inefficiency and neurotransmitter pathways, *COMT* with *AKT1* and *COMT* with *RGS4* exaggerate DA signaling abnormalities).[134]

Figure 7. Level of Support for Statement 5, "Neuroimaging Is a Tool for Elucidating Biological and Genetic Mechanisms of Illness and Treatment Response"



Grading of Evidence

Based on a review of the literature, 2 of the 6 Summit faculty workshop members (33%) considered the evidence available to support this statement to be Category I (evidence obtained from at least 1 well-designed, randomized, controlled trial). The remaining 4 faculty members (67%) considered the evidence to be Category II (evidence obtained from well-designed cohort or case-controlled studies).

Level of Support

When voting on the support for this statement, 82% of the Summit participants voted to accept the statement completely, and 18% voted to accept the statement with some reservations. In comparison, of the 1064 clinicians who participated in the online survey, 16% voted to accept the statement completely, 31% voted to accept the statement with some reservations, 27% voted to accept the statement with major reservations, 19% voted to reject the statement with reservations, and 6% voted to reject the statement completely (Figure 7).

Discussion

Neuroimaging has been an essential tool in schizophrenia research and has influenced our understanding of this disorder profoundly. Structural imaging has identified target areas and systems that are affected by the disease state, particularly the frontal and temporal lobes. Findings also suggest that some of these changes may be linked to the genetic architecture of risk. Functional neuroimaging has provided a more specific illustration of how neuronal systems and circuits abnormally handle information in patients with schizophrenia. These various results place schizophrenia in the realm of neuroscience and have fundamentally changed how we approach this illness. Neuroimaging is observational and phenomenological and, as such, cannot differentiate cause from effect. The underlying mechanisms for the various findings are still unknown and most likely will never be definitively determined using neuroimaging approaches. For example, we still do not know what accounts for brain volume changes, as postmortem studies of actual brain tissue do not show volume changes consistent with what is seen in vivo. Likewise, functional abnormalities do not suggest a single, specific causal mechanism. Overall, despite the early expectations of imaging technology, neuroimaging has not proven to be as useful a clinical tool in the practice of psychiatry.

With the discovery of genetic links to mental illness as the first compelling clue to the etiology of various disorders, the use of neuroimaging as a tool for differentiating patients from control subjects is likely to be of less interest. Recent studies that have investigated putative susceptibility genes and their effects on brain structure and function have made it possible to understand what genetic susceptibility might mean in terms of brain development and function. The presence of these genetic factors increases the likelihood of a patient's brain having schizophrenia-like characteristics. Although the number of studies will expand rapidly, a number of caveats and concerns must be addressed when considering the results of so-called imaging genetics studies. These include the heritability of the imaging phenotype, the choice of genetic variation, and the statistical difficulty inherent in multidimensional datasets.

It is noteworthy that the Summit faculty and the field survey responses differed somewhat in their confidence in this statement. While the faculty tended to accept the statement, the field survey respondents were less certain. There likely are a number of reasons for these differences. In general, the Summit faculty members are academic researchers familiar with both the research applications of neuroimaging and the recent literature about imaging genetics. The field survey respondents are less likely to be as up-to-date with the literature, as much of it has emerged only in the past few years.

Future Directions

Neuroimaging is still evolving with many new methods and applications, and it is expected that DTI methods will become more reliable and informative. The study of tract development, particularly in the context of genetic variation, most likely will emerge as a novel approach in schizophrenia research. High-field magnets are becoming available for use on human subjects, and high-sensitivity spectroscopy will make measurement of low-abundance metabolites possible. This may provide novel targets for treatment monitoring and the development of more individualized therapeutic regimens. Large datasets are currently being acquired as part of multicenter clinical trials and genetic association studies. These data will make it possible to explore genetic interactions in brain phenotypes and will help to further dissect the genetic architecture of relevant brain developmental and functional abnormalities implicated in schizophrenia.

STATEMENT 6: ATYPICAL ANTIPSYCHOTIC DRUGS ARE NEUROPROTECTIVE IN PATIENTS DIAGNOSED WITH SCHIZOPHRENIA

This section was adapted from a Summit presentation by Henry A. Nasrallah, M.D.

Rationale and Definition of Statement

Schizophrenia, a chronic and disabling mental illness that influences virtually all aspects of patients' lives, is associated with a significant burden of disease. It has been rated as 1 of the 10 most disabling disorders[135] and can last a lifetime, affecting patients, families, and society. Additionally, the quality of life associated with schizophrenia ranks as among the worst of any chronic medical illness.[136] If a window of opportunity exists where interventions could reverse, attenuate, or slow the progression of the disease and its sequelae, this would transform the treatment of schizophrenia and improve the outcome of patients treated for this complex brain disease.

Emerging evidence suggests that the loss of function in schizophrenia is not a static phenomenon. Multiple studies have documented the changes of brain structural morphology, which have included a progressive loss of brain tissue and an increase in ventricular volume, from the initial prodromal phase and continuing through the chronic phase of schizophrenia.[36,137–149] Progressive deterioration resulting from neurostructural changes also parallels the patient's functional decline.[36,150]

Changes in gray matter morphology also progress with the illness,[136,151–153] and brain volume reduction is associated with prognosis and functional outcomes.[36,138,139,149,154] Recent research also has implicated white matter changes in the pathology of schizophrenia.[151] Emerging evidence suggests that pharmacologic interventions may minimize neurotoxicity and, therefore, the possibility of related brain morphology changes associated with this disease.[151,153,155,156]

Literature Search

An initial PubMed database search was conducted and was augmented in February 2008 to identify studies related to neuroprotection and schizophrenia. A search using the text words "antipsychotics" or "antipsychotic agents" yielded 91,179 articles. A second search inclusive of "schizophrenia," "psychosis," or "psychotic disorders" produced 106,100 publications, and a third search consisting of "brain," "neuroprotection," "myelination," "gray matter," "grey matter," or "neuronal plasticity" generated 1,069,864 articles. The first 3 searches were combined with the "AND" function, which resulted in 3297 publications. Review articles were excluded, and the search results were further limited to English-language publications, producing 2402 citations. Finally, 1105 articles were identified by limiting the search results to those published since 2000. Eleven citations were deemed pertinent to the statement. Abstracts from recent meetings also were reviewed.

Evidence

To evaluate the evidence supporting this statement, 2 areas of evidence were assessed. These included preclinical and clinical data related to neuroprotection associated with antipsychotic agents.

Preclinical evidence. Results from a variety of studies have suggested that it is not the typical antipsychotic agents but rather the atypical antipsychotic agents that induce favorable neuroplastic changes, including neurogenesis. Using bromodeoxyuridine (BrdU), which is incorporated into newly synthesized DNA and can be used as a surrogate to detect proliferating cells, a blinded, placebo-controlled study revealed that both risperidone 0.5 mg/kg/day and olanzapine 2 mg/kg/day administered for 21 days induced a significant increase in BrdU-positive cells in the subventricular zone (SVZ) of rats ($p < .0038$).[157] This increase was noted in comparison to results seen in rats given haloperidol 0.4 mg/kg/day or vehicle. The atypical neuroleptics stimulated a 2- to 3-fold increase of BrdU-positive cells when compared to control- or haloperidol-treated animals. No differences were seen between rats treated with haloperidol or with vehicle alone. In another study by Wang et al.,[158] the administration of olanzapine 10 mg/kg/day, but not haloperidol 2 mg/kg/day, resulted in an increase in the number of new BrdU-generated cells in the prefrontal cortex and the striatum of rats ($p = .032$) and in the density of these cells ($p = .013$).

In 1 abstract, Nasrallah and Pixley[159] also demonstrated significant neurogenesis with atypical agents. In one 3-arm study, risperidone 1 mg/kg/day or paliperidone

1 mg/kg/day for 28 days resulted in a significant increase in BrdU counts in the stem cell areas of neural tissue of the SVZ compared to vehicle in young male rats ($p < .05$). However, there was no significant difference between risperidone and paliperidone. In an abstract by Nasrallah,[160] a significant increase in BrdU counts occurred with paliperidone 0.6 mg/kg/day for 28 days in the stem cell areas of neural tissue in the SVZ and the olfactory epithelium compared to placebo ($p < .05$). There was no significant difference between placebo, risperidone (i.e., using a lower dose of 0.6 mg/kg/day compared to the earlier study), or fluoxetine 0.6 mg/kg/day.

Clinical evidence. The most robust study reviewed was a double-blind, 52-week study by Lieberman et al.[136] that evaluated whole brain gray matter volumes using MRI assessments at baseline and at weeks 12, 24, 52, and 104 in 161 patients diagnosed with first-episode schizophrenia. Data were compared to those of 58 healthy control patients. Patients randomly received haloperidol 2 to 20 mg/day (N =79) or olanzapine 5 to 20 mg/day (N = 82). Compared to baseline values, patients receiving olanzapine had significantly greater gray matter volume at all time points versus those receiving haloperidol (p values ranged from .01 to .008). The mean, maximum, whole-brain gray matter volume loss was –3.7 cm^3 versus –12.8 cm^3 in those receiving olanzapine and haloperidol, respectively. In the haloperidol-treated patients, the most significant reductions were observed in the first 12 weeks. When specific anatomical regions were evaluated, significant reductions were primarily observed in the frontal (i.e., –7.56 cm^3), parietal (i.e., –3.65 cm^3), and temporal (i.e., –1.33 cm^3) lobes in those receiving haloperidol. These regions in particular have been implicated in theoretical pathophysiologic models of schizophrenia, imaging studies, and postmortem studies. No change in gray matter volume was evident in the age- and gender-matched healthy volunteers.

Using voxel-based morphometric (VBM) methodologies, greater gray matter deficits were detected in patients treated with typical versus atypical agents in the epidemiologically based AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study involving patients diagnosed with first-episode psychosis.[161] At the time of the MRI scan, 32 patients received a typical agent (i.e., chlorpromazine, sulpiride, haloperidol, thioridazine, droperidol, trifluoperazine, zuclopenthixol), 30 patients received an atypical agent (i.e., risperidone, olanzapine, quetiapine, sertindole, amisulpiride), and 22 patients were left untreated. Compared to untreated patients, those receiving typical antipsychotic agents had 1 cluster of gray matter volume excess and 3 clusters of volume reductions ($p \leq .002$). Patients taking an atypical agent had a gray matter excess in the left and right thalami ($p = .002$). There were no differences in duration of illness, total symptom score, or length of treatment.

Compared to baseline MRI values, cerebral cortical gray volumes of 13 patients with schizophrenia increased by a mean of 20.6 mL ($p < .0005$) following 28 days of treatment with risperidone 4 mg/day or ziprasidone 60 mg twice daily.[162] A mean gray matter expansion of 25.1 mL and 15.3 mL was evident in the 7 patients receiving risperidone and the 6 patients treated with ziprasidone, respectively. There was no significant difference between these treatment groups ($p = .341$). No changes in cortical gray volumes were noted in the 6 patients who received haloperidol 7 mg/day ($p = .98$) or in the 7 control patients ($p = .93$). The 13 patients receiving an atypical antipsychotic agent demonstrated a diffuse and significant increase in gray matter involving the frontal, parietal, occipital, and temporal regions. The expansion of cortical gray matter was accompanied by a cerebrospinal fluid reduction ($p = .027$) and a reduction of white matter volumes ($p = .011$).

Compared to baseline values, a significant increase in gray matter and decrease in white matter volumes were documented in a small, longitudinal study by Molina et al.[163] involving 29 patients diagnosed with schizophrenia who received either risperidone or clozapine for 2 years. Treatment-naive patients (N = 17) received risperidone (mean dose 5 mg/day), and chronic treatment-resistant patients (N = 12) received clozapine (mean dose 260 mg/day). Compared to control patients, the risperidone-treated patients demonstrated a significant expansion of gray matter in the parietal lobes (1.2%, $p < .05$) and occipital lobes (6.2%, $p < .05$). The clozapine-treated patients demonstrated gray matter expansion overall (4.2%, $p < .05$) and in the frontal lobes (6.8%, $p < .05$), parietal lobes (7.3%, $p < .01$), and occipital lobes (14.9%, $p < .001$) compared to control patients. In the treatment-naive patients who received risperidone, there was a significant inverse relationship between the total increase in gray matter and the baseline deficit ($p < .02$).

Therefore, patients with a greater initial deficit demonstrated a greater expansion of gray matter. Compared to baseline values, both the clozapine- and risperidone-treated groups displayed significant reductions in total white matter volumes of 5.9% ($p < .001$) and 5.0% ($p < .01$), respectively. Significant reductions were evident in the frontal, parietal, and occipital lobes in the clozapine-treated patients. In the risperidone-treated group, however, the only significant white matter volume reduction occurred in the occipital lobe. In the control group, there was a small, insignificant change in brain morphology, a decrease in gray matter, and an expansion of white matter, which follows the expected trajectory in healthy patients. In addition, there was a significant improvement in symptoms in both treatment groups. In the treated patients, changes in gray matter and white matter were not related to an alteration in body weight.

In an exploratory, longitudinal study by Girgis et al.,[152] the short-term effects of risperidone on brain parenchyma

were evaluated by VBM methodologies on MRI scans from 15 neuroleptic-naive patients with first-episode psychosis. These were compared to scans from 15 age- and gender-matched volunteers. Compared to baseline, after 6 weeks of risperidone with a mean dose of 2.7 mg/day, increases in gray matter in the left superior temporal gyrus and the middle temporal gyrus were detected, while a reduction in gray matter occurred in the left rectal gyrus. Additionally, a reduction in white matter in the corpus callosum was observed. In contrast, no changes in gray matter or white matter were detected in the healthy patients.

According to Scheepers et al.,[164] caudate nucleus hypertrophy following the use of typical antipsychotic agents has been associated with a greater severity of symptoms and poorer neuropsychological test results. These researchers evaluated the relationship between caudate volumes and clinical symptoms in 22 patients who did not experience adequate response to typical antipsychotic medication treatment (i.e., with a 103-month mean duration). For these patients, clozapine was initiated for 52 weeks. It was noted in those patients who were responsive to clozapine that over time there was a significant reduction in the left caudate nucleus volume ($p < .05$). However, there was no corresponding reduction in the right caudate nucleus volume ($p = .11$). The change from baseline was significant after 24 weeks of clozapine treatment ($p < .005$), but no significant change occurred between 24 and 52 weeks ($p = .85$). However, the change in left caudate nucleus volume related to an improvement of symptoms at 52 weeks ($p < .05$), which may indicate a further clinically significant adaptation of the brain. Clozapine nonresponders did not exhibit any changes in caudate volumes.

In a study by Bartzokis et al.,[151] the differential effects that antipsychotic agents have on frontal lobe myelination were evaluated using an inversion recovery MRI imaging technique sensitive to the high cholesterol content found in myelin. The male participants were 18 to 35 years of age and included 71 patients diagnosed with schizophrenia. These patients received either fluphenazine decanoate ($N = 51$) for a mean of 3.3 years or risperidone ($N = 20$) for a mean of 1.3 years. Data were compared between these patient populations and 61 healthy, matched control patients. Based on residual z-scores, patients treated with risperidone had significantly greater frontal white matter volumes (i.e., +0.52) compared to those receiving fluphenazine (i.e., –0.39).

In a small, open-label, controlled study by Glenthoj et al.,[165] 16 drug-naive and 3 minimally treated patients diagnosed with first-episode schizophrenia randomly received zuclopenthixol (a typical antipsychotic medication available outside of the United States) with a mean dose of 7.8 mg/day or risperidone with a mean dose 3.6 mg/day for 3 months. An MRI scan was obtained at baseline, and another was obtained after treatment. These were compared to scans for 19 age- and gender-matched control patients. Caudate nucleus, nucleus accumbens, and putamen volumes were assessed. The results revealed no significant volume differences in the basal ganglia after treatment with low-dose zuclopenthixol; however, a significant increase in putamen volume was evident in the risperidone-treated group ($p = .018$).

In another open-label study by Massana et al.,[166] analysis was done on VBM methodologies on MRI in 11 first-episode, treatment-naive patients following the administration of high doses of risperidone (mean dose of 6 mg/day) for 3 months. Analysis revealed an increase in the basal ganglia, with specific emphasis in the left caudate and left accumbens.

Grading of Evidence

Based on a review of the studies cited above, 15% of the workshop attendees agreed that the evidence available to support this statement was Category II (i.e., evidence obtained from well-designed cohort or case-controlled studies). A majority of the workshop attendees (67%) ascertained that the evidence reflected Category III data (i.e., evidence obtained from case series, case reports, or flawed clinical trials), while 17% assessed the data as Category IV (i.e., opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees).

Level of Support

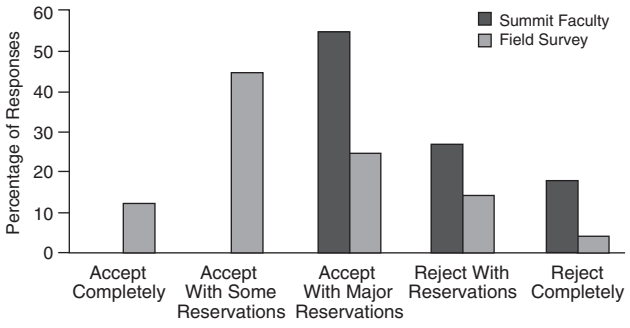
When voting on the support for this statement, 55% of the Summit participants voted to accept the statement with major reservations, 27% voted to reject the statement with reservations, and 18% voted to reject the statement completely. In comparison, of the 1064 clinicians who participated in the online survey, 12% voted to accept the statement completely, 45% voted to accept the statement with some reservations, 25% voted to accept the statement with major reservations, 14% voted to reject the statement with reservations, and 4% voted to reject the statement completely (Figure 8).

Discussion

The discussion at the Summit focused on a variety of topics. The central issue surrounded the lack of a clear and concise definition of neuroprotection and neurodegeneration. During the Summit, the 6 workshop participants were willing to accept that "neurodegeneration," defined not in the classic sense but more as a "deficiency in neuroplasticity," "the lack of adaptation," or "an accelerated form of aging," is present in patients with schizophrenia. This is based on the principle that neuroanatomical progression is associated with clinical progression.

A working definition of neuroprotection, therefore, included actions that "prevent clinical deterioration," "protect integrity," and "preserve the normal health of the

Figure 8. Level of Support for Statement 6, "Atypical Antipsychotic Drugs Are Neuroprotective in Patients Diagnosed With Schizophrenia"



brain." The workshop attendees also noted that treatment does affect the clinical and pathophysiologic course of schizophrenia. In addition, the preclinical data presented support the possibility of protective and trophic effects associated with atypical antipsychotic agents; however, it is unknown whether the neurogenesis that occurred produced functional neurons. The overall consensus was that atypical antipsychotic agents are protective and there may be some selective advantage to treatment with some of these agents. Overall, data suggest the neuroprotective effect of these agents.

Of the 6 participants in the workshop, 50% voted that there was fair evidence to support the statement, and 33% voted that there is poor evidence to support the statement, but recommendations may be made on other grounds. The remaining participant felt that there was fair evidence to reject the statement. The voting at the workshop level was different from the entire Summit faculty vote on level of support. This discrepancy was the result of the presentation on Statement 2, after which the participants concluded that schizophrenia is not a neurodegenerative disease. On the basis of that conclusion, the participants perceived an explicit link between neurodegeneration and neuroprotection. As a result, it was assumed that if neurodegeneration was not present, then neuroprotection also could not exist.

Discussions also ensued regarding the limitation of using MRI to assess brain morphological changes. It was noted that volume changes could be the result of tissue perfusion, increased fat or water content, changes in weight, or several other variables. These factors may confound the interpretation of morphological changes noted on MRI.

It is not surprising that there was divergent voting between the Summit participants and the 1064 field clinicians who answered the survey. The lack of clear and concise definitions of terms that are used ubiquitously in the medical literature likely contributed to these findings.

Future Directions

Future endeavors should focus on developing clear and concise definitions for neurodegeneration, neuroprotection, and neuroplasticity. It will also be important to establish methods of assessing brain morphological changes in a sensitive, specific, and robust manner and to determine the clinical significance of these changes. The ability to link neuroprotection to neurocognition following various interventions would enhance the understanding of the neurobiology of schizophrenia and possibly help optimize treatment for patients with schizophrenia. However, further clinical studies are required to assess the long-term effects of a variety of atypical antipsychotic agents on gray matter and white matter volumes and to determine whether patient neurocognition and quality of life can be improved.

STATEMENT 7: TREATMENT IN THE PRODROMAL PHASE OF SCHIZOPHRENIA IMPROVES PATIENT OUTCOMES

Peter J. Weiden, M.D.,
was the contributor of this section.

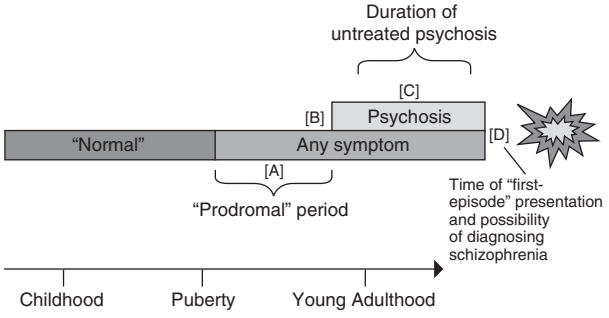
Rationale and Definition of Statement

The rationale for this statement is the recent publication of a series of controlled studies in which researchers investigated the prevention or delay of the onset of schizophrenia among individuals at high risk of developing schizophrenia or another serious psychotic disorder. These individuals are identified by either genetic risk or the presence of symptoms that are similar to those seen in patients with schizophrenia but not severe enough to meet the diagnostic criteria for psychosis.

Clinicians and researchers share a strong desire to have and employ established strategies to prevent the occurrence of this severe and disabling illness.[167] Nonetheless, the intuitive appeal of early intervention to prevent disease conversion in patients at risk for schizophrenia must be offset by the risks inherent in such treatments as well as the concern of treating patients who might not develop schizophrenia, thereby exposing them to the unnecessary risks of such treatments.[168] In this statement, the definition of treatment includes both pharmacologic and psychosocial approaches, such as the use of cognitive-behavioral therapy (CBT), to target the symptomatic presentation in this high-risk patient group prior to their meeting the diagnostic criteria for schizophrenia.

Defining the prodromal phase. This statement refers to the existence of a "prodromal phase" in persons who are deemed to be at high risk of developing schizophrenia in the future. In the review of evidence-based treatment studies, it was discovered that there is literature on the definition of "prodromal" as it pertains to patients who are at high risk for developing schizophrenia.[169–173] Before

Figure 9. "First-Episode" Schizophrenia: Definitions and Concepts[a]



[a]During the "prodromal phase" [A], the patient's signs and symptoms do not meet threshold criteria for psychosis but may include attenuated positive symptoms. The onset of acute psychotic symptoms [B] occurs when the patient has clearly defined psychotic symptoms. Intervention during this time is not considered a prodromal intervention. The duration of untreated psychosis [C] represents the gap between the onset of acute symptoms and initial clinical presentation [D], which often is triggered by an external event that is the result of worsening behavior.

moving forward in the discussion of the statement, it is helpful to address this controversy and clarify some potential areas of confusion regarding the definition of the prodromal phase. According to *Dorland's Medical Dictionary for Health Consumers*, a prodrome is "a premonitory symptom; a symptom indicating the onset of a disease."[174] By definition, after a patient meets the threshold criteria for a disease, then the term *prodromal* no longer applies. Therefore, being in the prodromal phase implies that there is some uncertainty about whether the disease will occur.

An important clinical point is that patients identified as prodromal for schizophrenia do not necessarily go on to have schizophrenia. Because it is the presence of full-blown psychotic symptoms (i.e., DSM-IV criterion A for schizophrenia) that confirms a diagnosis of schizophrenia, intervention studies of patients in the prodromal phase only will include individuals who have not yet had a defined psychotic episode.

Certainly, there are some individuals with particular symptoms or risk factors who have a much greater risk for developing schizophrenia. The question remains, however, whether the term *prodromal* is appropriate for these individuals. Some researchers object to the use of the term, because it is a clinical state that can only be confirmed in retrospect.[173] Their concern is that the term *prodromal phase* gives the impression that there is an inevitable progression that, in fact, does not exist. In a commentary by Yung,[173] the author states, "Many individuals who experience what appear to be early prodromal symptoms . . . do not develop psychotic disorders but instead have symptoms, which remit or remain stable. . . . [C]alling such symptoms 'prodromal' implies inevitable progression to psychosis, but . . . psychosis is not an invariable outcome of such symptoms."[173(p860–861)] As might be expected, some researchers prefer to use other terms instead. Terms such as *at-risk mental state* and *ultra high risk* (UHR) may be preferable to the use of the term *prodromal phase*. The important point for clinicians is to be sure that there is a clear understanding of what is meant by "prodromal phase" (see Figure 9).

Implications for the expert panel. Before the presentation of the literature and discussion of the evidence, the expert panel members agreed that *prodromal* refers to the period of time before the onset of full-blown psychotic symptoms. Further, the panel members acknowledged that once a patient's psychotic symptoms are identified and the patient is diagnosed with schizophrenia, prompt intervention using antipsychotic medications or other treatment options often improves patient outcomes. This can be seen in Figure 9 by the recommendation to reduce the duration of untreated psychosis (see section C in the figure). The remainder of this report pertains to treatment during the prodromal phase (i.e., any point during the period shown in section A). Early and prompt treatment is always indicated once the patient converts to full-blown psychosis (i.e., any point from section B and after).

Literature Search

A PubMed literature search was conducted on February 2, 2008, using the Medical Subject Headings (MeSH) database. The heading "schizophrenia/prevention and control" yielded 454 articles. The heading "psychotic disorders/prevention and control" yielded 328 articles. Combining these 2 headings with "OR" resulted in 735 articles. The MeSH headings "psychotherapeutics" or "therapeutics" returned 2,160,277 articles. Combining these results using "AND" with the 735 articles identified above yielded 258 articles. When these were limited to clinical trials written in English with human participants, 60 articles were identified. Case studies of low-dose antipsychotic treatments in high-risk patients were not included because of study design issues as well as the short-term nature of patient follow-up.[175,176] After the resulting articles were reviewed, only 3 were deemed relevant to the statement.

Evidence

The primary therapeutic target for this search was for an intervention or interventions that would delay or prevent the conversion of a patient deemed to be at high risk of schizophrenia to a full psychotic episode. Other secondary study criteria included reduction of current symptoms, retention rates in the interventions, and long-term outcomes. The 3 studies deemed relevant to the statement differed in the types of treatment given to patients. This included a combination of an antipsychotic medication treatment with CBT, a CBT-based psychosocial

intervention alone, and treatment with an antipsychotic medication alone.

Study 1: combination treatment. A study in 2002 by McGorry et al.[14] compared 2 treatment groups of patients identified to be at high risk of converting to schizophrenia. Patients were randomly assigned to 2 groups: one group received a combination of low-dose risperidone and CBT for 6 months (N = 31), followed by treatment as usual, and the control group received treatment as usual (N = 28) for the entire year. Treatment as usual comprised a needs-based intervention (NBI), in which medications or specific psychotherapies were given only when clear-cut symptoms emerged. The treatment clinic, a service specializing in patients at high risk of converting to schizophrenia, was part of the Early Psychosis Prevention and Intervention Centre (EPPIC) program in Melbourne, Australia. The specific program within EPPIC used in this study was the Personal Assessment and Crisis Evaluation (PACE) service.[177] This setting is pertinent in that all patients were carefully assessed and followed, and "treatment as usual" was above the usual services that typically would be available in the United States.

Patients who met the UHR criteria, therefore, were at high risk of developing schizophrenia within the next few years and were considered to be a prodromal equivalent. The UHR criteria consisted of having attenuated psychotic symptoms; a history of brief, limited, intermittent psychotic symptoms; or the presence of other trait or state risk factors.[20,178,179] The primary outcome measured was the proportion of patients who progressed to full psychosis as determined by a defined threshold of positive symptoms. The initial report included patient data for the first 12 months.[14] A later paper reported on an approximately 4-year follow-up (i.e., an average of 45.8 months) in 41 patients who were located and consented to participate in the study.[17]

At the end of the 6-month treatment period, 10 of the 28 NBI patients had converted to psychosis compared to only 3 of the 31 receiving preventive treatment (36% vs. 10%, p = .03). However, the conversion rates between the groups became equivalent within 4 years, with 12 (43%) conversions in the NBI group and 10 (32%) in the prevention group.[177] Of the 31 patients assigned to preventive treatment, 17 were nonadherent to treatment. An analysis of the 14 adherent patients showed that they were much less likely to convert.[178] It was unclear whether this benefit was related to direct treatment benefits or because adherent patients were more likely to do well over time.

In summary, almost 50% of the UHR patients converted to a full psychotic episode, suggesting that there is predictive validity to the UHR criteria, but conversion is far from inevitable. An intensive intervention that combines a low-dose antipsychotic such as risperidone with CBT appeared to delay but did not prevent conversion to full psychosis. In addition, the beneficial or protective effects of treatment were most pronounced for those patients who remained adherent during the course of follow-up. Finally, an increased level of treatment and care for high-risk patients enabled physicians to quickly recognize when the patient developed acute psychotic symptoms, which resulted in earlier intervention. In this type of treatment environment, the duration of untreated psychosis was greatly reduced for all patients.

Study 2: CBT-based intervention. In a trial by Morrison et al.,[16] researchers compared the course of UHR patients who were randomized to CBT intervention (N = 37) to those who received no treatment but were monitored monthly (N = 23). The study was conducted from 1999 to 2002 in Manchester, England, and patients were recruited using referrals from local primary care physicians, specialty psychiatry services, and school counselors. Further screening helped evaluate whether patients were at UHR using criteria similar to those established in the PACE study.[177] The goal of this study was to evaluate the efficacy of cognitive therapy in preventing transition to psychosis.

The CBT group received up to 26 treatments over 6 months using a "cognitive model most appropriate to the disorder that was prioritized on a problem list agreed upon between the therapist and patient."[16(p292)] The therapist and the patient, therefore, shared in the formulation of the problem list, and there was no emphasis on the possibly pathologic nature of the patient's symptoms; rather, the list placed the symptoms into a normalized context in a way that made the most sense for the distressed individual.[180,181] In this Early Detection and Intervention trial, all patients received monthly symptom monitoring with independent assessment of symptoms using the PANSS over the ensuing 12 months, as well as case management that "incorporated elements of case management in order to resolve crises regarding social issues and mental health risks."[16(p293)]

The first-year follow-up results showed a 1-year conversion rate of 6% in the CBT group compared to 22% in the control group (p = .03). However, these differences remained significant when using the alternate conversion criterion of a patient starting antipsychotic medication treatment within 3 years (e.g., 14% for CBT vs. 35% for control, p = .02). A secondary follow-up of these patients did not find sustained benefits of CBT. As in the PACE study, the differences between treatment groups did not persist on longer-term follow-up when PANSS symptom criteria were used (e.g., 20% for CBT, 22% for control), but attrition rates limited the ability to interpret the long-term effectiveness of the CBT intervention.[15]

One of the strengths of the study was that the control group's treatment approximated actual standard care (i.e., they did not receive intensive treatment beyond case management). Limitations included a small sample size, a randomization strategy that resulted in unbalanced

assignment (i.e., more patients were assigned to CBT than to monitoring), and that those who evaluated the outcomes of conversion were aware of the patients' assigned treatment method. Nonetheless, this is a significant controlled study showing that a specific intervention delayed conversion at 1 year. This research currently is being replicated in a multicenter study in the United Kingdom.

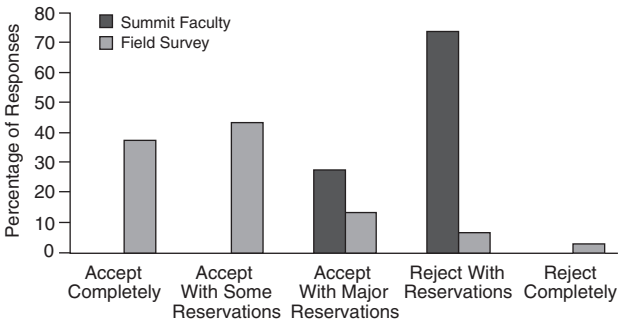
Study 3: antipsychotic medication. In 2006, McGlashan et al.[13] published the results of a randomized, multicenter trial that was conducted at 4 academic centers across the United States as part of the Prevention through Risk Identification, Management, and Education (PRIME) project. These centers provided specialty services that identified and treated help-seeking patients who were judged to be at high risk of developing schizophrenia. Patients were screened with the Scale of Prodromal Symptoms (SOPS), which operationalized the UHR criteria used in the PACE study. Patients received olanzapine 5 to 15 mg/day (N = 31) or placebo (N = 29) during a 1-year, double-blind treatment period, followed by a 1-year period of follow-up care. The primary outcome was the rate of conversion to psychosis both during the time of active pharmacologic treatment and during the subsequent follow-up year.

Among the patients who remained in the program for the first year, there was a trend-level reduction in conversion to psychosis in the group assigned to olanzapine. At the end of the initial year of treatment with olanzapine, 5 of the 31 (16%) patients met the criteria for psychosis compared to 11 of the 29 (38%) placebo-treated patients (p = .08). Olanzapine treatment also reduced the attenuated positive symptoms relative to the placebo group. However, these findings are tempered by high dropout rates in the first year (i.e., 27 [45%] of the initial sample, with a somewhat higher dropout rate in the treatment group [p = .13]). During the year after treatment was discontinued, the symptomatic benefits of olanzapine were not sustained.

Although this finding is equivocal, results from the follow-up year did not show that early medication intervention had any sustained protective benefits. Of the 17 patients who were treated in the second year, 3 of the 9 (33%) former olanzapine patients converted to full psychosis, whereas 2 of the 8 (25%) former placebo patients converted. Although the authors did not do formal statistical testing, it is clear that the 2-year conversion outcome results would not show any statistical benefit of earlier treatment with olanzapine if eventual conversion to psychosis is the primary outcome.

It is notable that there was a different time pattern of conversion depending on treatment status. As the authors state, "All 5 of the olanzapine-treated patients who converted to psychosis did so within the first 4 weeks, whereas the 11 placebo-treated patients converted to psychosis throughout the entire year."[13(p792–793)] This finding suggests that some patients actually may have had more psychotic symptoms than they initially reported, thereby causing them to have been misclassified as prodromal. Further, it could be that the treatment of these patients with olanzapine provided them the ability to report their psychotic symptoms.

Figure 10. Level of Support for Statement 7, "Treatment in the Prodromal Phase of Schizophrenia Improves Patient Outcomes"



Grading of Evidence

Based on a review of the 3 studies cited above, 3 of the 6 members of this workshop voted that the level of evidence for the statement was Category III (evidence obtained from case series, case reports, or flawed clinical trials), 2 voted for Category II (evidence obtained from well-designed cohort or case-controlled studies), and 1 voted for Category IV (opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees).

Level of Support

Among the 6 workshop members, 33% voted that there was fair evidence to support the statement, 50% voted that there is poor evidence to support the statement, and 17% voted that there is fair evidence to reject the statement. After the evidence was presented to the entire Summit faculty on the second day, 27% voted to accept the statement with reservations, and 73% voted to reject the statement with reservations.

In contrast, the field survey results were very different. The majority of the respondents accepted the statement, either completely (38%) or with some reservations (43%). Another 13% accepted the statement with major reservations, 6% rejected the statement with some reservations, and 1% voted to reject the statement completely (Figure 10).

Discussion

Of all of the statements reviewed during this Summit, the voting results on this statement showed one of the

largest divisions between the Summit faculty members and the general survey respondents. The nature of the survey precludes precise understanding of the source of this difference, but this discrepancy may be the result of the faculty members' concerns about the inconclusive nature of the 2 pharmacologic studies. At best, these studies showed only marginal benefits in the primary outcome of preventing or delaying patients' conversion to schizophrenia. Results are open to interpretation, but it appeared that there was no dramatic effect of pharmacologic treatment compared to patient monitoring and support. Moreover, there is some question about the applicability of these data to patient groups outside the specialty clinical care setting. Patients in the general community treated with antipsychotic medications may have a lower risk of converting than those who participated in the 3 studies presented here.

Another possible explanation for the discrepancy between the voting of the faculty members and survey respondents is that the use of the term *prodromal phase* may imply that the patients in question are expected to convert to schizophrenia. Because the faculty members strongly agreed that early intervention in patients with first-episode psychosis is indicated as soon as possible after the psychosis occurs, it may be that this is how the statement was interpreted by many of the survey respondents. If so, the discrepancy between the faculty members and survey respondents supports the opinion that the term *prodromal phase* is misleading and should be replaced by another term, such as *ultra high risk*.

Although the primary interventions differed in these studies, all 3 of them found that conversion to full psychosis was not inevitable. Therefore, even when attenuated psychotic symptoms are present, it does not mean that a person will inevitably develop schizophrenia or another severe psychotic disorder. This issue is covered in greater detail in the review of Statement 1, "Identification of the earliest prodromal phase of schizophrenia is feasible."

A hopeful clinical finding in the 3 studies was that the individuals who did convert to schizophrenia seemed to do better by being treated in a structured outpatient environment in which clinicians could act quickly once acute psychotic symptoms appeared. It seems that symptomatic, high-risk individuals benefit when they receive close monitoring and support, and the consequences of the initial psychotic episode are thereby minimized. This contrasts with the typical course of routine clinical care for a first-episode patient who may experience a long duration of untreated psychosis, resulting in adverse effects on the patient's long-term prognosis.[182,183]

Future Directions

These 3 studies represent an important advance in understanding the risk profiles of young adults who are at high risk of developing psychosis and the diagnosis of schizophrenia. With the encouraging preliminary results of CBT in preventing or delaying conversion to full psychosis, CBT is currently the subject of an ongoing, prospective, multicenter study in the United Kingdom.

Unanswered questions at this point include whether other pharmacologic treatments aside from antipsychotic medications (e.g., antidepressants) might be useful in delaying the onset of psychosis[168] and whether the effectiveness of substance abuse interventions, especially interventions for users of cannabis, may reduce a patient's risk of conversion.[184,185] Finally, there is an important question of whether any effective intervention given to patients in specialized, high-risk programs during the patients' "prodromal phase" can be generalized to real-world clinical settings to improve treatment for a broader spectrum of patient symptoms and diagnoses.[171]

STATEMENT 8: PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA REQUIRE COMBINATION ANTIPSYCHOTIC TREATMENT

John M. Kane, M.D., and Christoph U. Correll, M.D., were the contributors of this section.

Rationale and Definition of Statement

A substantial proportion of patients with schizophrenia, as high as 31% in some studies, receive more than 1 antipsychotic medication.[241] Precise estimates of the percentage of patients who are receiving multiple medications due to "treatment resistance" (TR) are not available, but it is likely that a substantial number of patients fall into this category.

Although epidemiologic data are limited, it is thought that approximately 50% of patients with schizophrenia continue to have at least 1 positive or negative symptom of moderate or greater severity after an adequate treatment trial.[242] Whether these patients should be considered to have TR is unclear, as there is no universally accepted definition of this patient subtype.

Defining TR really begins with the question of what medications are included. Historically, and probably still most frequently, TR refers to a lack of adequate response to first-generation as well as second-generation (i.e., atypical), non-clozapine antipsychotic medications. This label is frequently used to classify those patients who have failed first-line treatments and who might be considered for treatment with clozapine. Since the U.S. Food and Drug Administration labeling of clozapine specifies that it should be reserved for use in those patients who are otherwise treatment resistant, this label represents an important landmark in patient management. The meaning of TR also can be extended to include that group of patients who have shown inadequate response to any antipsychotic medication, including clozapine. Both categories of TR will be discussed here, but for the sake of clarity, the latter type

will be referred to as clozapine TR and will, by definition, imply that the patient was considered resistant to other antipsychotic medications prior to undergoing a trial of clozapine.

Regardless of the type of TR, all suboptimal responses warrant an assessment of compliance. Measurement of blood medication concentrations is done infrequently, yet this could help identify those patients in whom therapeutic blood levels were not achieved due to noncompliance, problems in absorption, or rapid metabolism.

The definition of either TR type also involves the identification of what criteria need to be met before declaring resistance. These criteria, which include the required number and duration of trials, are far from uniform. The lack of widely accepted criteria causes difficulty not only in enrolling consistent patient groups in clinical trials used to evaluate treatments but also in making therapeutic management decisions.

A commonly used definition of TR is the one that was applied in a large study of clozapine.[186] In this study, patients were included if they had, in the 5 years preceding enrollment, at least 3 periods of treatment with antipsychotic medications from at least 2 different chemical classes at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for a period of 6 weeks without significant improvement and with no period of adequate functioning during those 5 years. The study patients also were required to score at least 45 on the BPRS (18-item version), be classified as "moderately ill" on the Clinical Global Impressions scale, and score at least "moderate" in 2 of the following 4 BPRS items:

- conceptual disorganization,
- suspiciousness,
- hallucinatory behavior, or
- unusual thought content.

In clinical practice, there is considerable divergence of expert opinion in terms of how long to wait before considering a trial of treatment to be ineffective. One survey of schizophrenia experts indicated that a period of 2.6 to 5.5 weeks was required.[187] However, in many hospitals, a patient's length of stay is substantially shorter than 3 to 4 weeks, and clinicians may feel pressured to combine multiple medications before an adequate trial has taken place with the hope that patient response might be enhanced. On the other hand, there are emerging data suggesting that a lack of minimal response after 1 or 2 weeks is a powerful predictor of subsequent poor response.[188,189]

In addition, there is no consensus as to what antipsychotic medication combinations are most appropriate or what differing pharmacologic profiles should be combined to enhance therapeutic effects. Although adding quetiapine to other antipsychotic medications appears to be the most prevalent form of combination treatment, it is likely that quetiapine is used for its sedative, hypnotic, and anxiolytic properties rather than for its augmentation of an antipsychotic medication.

Existing guidelines do not specifically recommend the use of combinations of antipsychotic medications when 1 agent alone has failed. Despite this, the practice of polypharmacy appears to be widespread. In routine clinical practice, it is likely that physicians use less-consistent and less-stringent criteria to define and treat TR.

Because these concepts are not well defined in routine practice and there are relatively few studies to inform this decision, the aim of this section is to assess the strength of evidence supporting or refuting the assertion that patients with treatment-resistant schizophrenia require combination treatment. Evaluation of available evidence is complicated further by the fact that some of the published studies investigate the use of an adjunct antipsychotic treatment in patients who are clozapine TR. This patient population is a very different and substantially smaller subgroup of individuals than those who are resistant to first-line antipsychotic medications used to treat acute episodes.

Literature Search

The register of the Cochrane Schizophrenia Group was searched in January 2008 for published and unpublished randomized controlled trials (RCTs) that compared antipsychotic medication monotherapy with the combination of the same antipsychotic medication with another medication. Only English-language studies meeting the Cochrane handbook quality criteria A (i.e., adequate randomization) and B (i.e., studies stated to be randomized without giving further details) were included. In addition, the reference sections of the identified studies were screened, and the lead authors were queried to determine whether they were aware of additional relevant trials.

An original search was conducted in 2008 by Correll et al.[190] that yielded 1483 potentially relevant studies. Fifty-one of these were RCTs, but 27 were excluded because they did not meet the inclusion criteria. Two more were excluded because they had fewer than 20 subjects, as well as 3 others that did not have relevant data. Of the remaining 19 studies, 15 involved clozapine and 4 studies did not.

Evidence

Chien and Cole[191] reported on a heterogeneous sample of 46 patients, 76% of whom were diagnosed as having schizophrenia. The remaining 11 patients in this study had psychotic depression and substance-induced psychosis. The researchers did not conduct separate analyses by diagnostic subgroup. The mean age of the study population was 37 years. No diagnostic instruments were utilized in this study, and all medications were costarted at baseline. Out of the total patient population, 15 received chlorpromazine with a mean dose of 388 mg, 16 received

fluphenazine enanthate with a mean dose of 28.5 mg every 11 days, and 15 patients received both medications in combination (i.e., chlorpromazine 350 mg and fluphenazine enanthate 26 mg every 11 days). Data were analyzed after the 10-day point. Patients who received long-acting, injectable fluphenazine alone as well as those receiving it combined with chlorpromazine were more likely to be rated "much improved" after 10 days than those who received chlorpromazine alone. The difference between the 2 groups who did receive the fluphenazine was not significant.

In 1957, Barrett et al.[192] reported on 30 chronically hospitalized patients with a mean age of 25. Similarly, no diagnostic instruments were utilized, and all medications were costarted at baseline. The study was triple blind with a 2-month placebo lead-in phase, and the trial duration was 12 weeks. Of the 30 patients, 10 received chlorpromazine with a mean dose of 520 mg, 10 received reserpine with a mean dose of 2.3 mg, and 10 received chlorpromazine with a mean dose of 230 mg. Although data indicated a trend for patients receiving combined treatment to do better, the differences were not significant, and the sample size was too small to draw any meaningful conclusions.

A study published in 1976[193] by Yagi reported on a double-blind trial conducted in Japan involving 233 patients with chronic schizophrenia. No diagnostic instruments were utilized, and the patients' mean age was not reported. In this double-blind study, patients were randomly assigned to receive chlorpromazine alone (mean doses were not provided) or chlorpromazine plus perphenazine. Medication combination was costarted at baseline, and patients were followed for 8 weeks. A third group of patients (N = 118) received chlorpromazine plus an antidepressant, but they were excluded from this analysis. The researchers concluded that there was no significant advantage for the patients in the combination treatment group.

In 1964, Talbot[194] published a report on 77 patients with chronic schizophrenia who were hospitalized and considered to be severely ill. No diagnostic instruments were used, and the patients' mean age and gender distribution were not reported. This was a double-blind study as well, and patients were randomly assigned to 1 of 3 groups. Group I received chlorpromazine 150 mg/day plus trifluoperazine 10 mg/day for 2 months. This was followed by 300 mg of chlorpromazine and 10 mg of trifluoperazine per day for 6 months. Group II received chlorpromazine alone at the same dose as Group I, whereas Group III received trifluoperazine alone at the same dose as Group I. Results showed that 67% of the patients receiving combined treatment (i.e., Group I) had high levels of global improvement after 8 months, compared to 48% of the patients receiving chlorpromazine alone (i.e., Group II) and 16% of the patients receiving trifluoperazine alone (i.e., Group III).

In 2007, Paton et al.[195] conducted a meta-analysis of 4 RCTs in which clozapine was augmented with another antipsychotic agent for patients with schizophrenia who had experienced a partial response to clozapine. A total of 166 patients participated in the 4 RCTs. By pooling the effect sizes across the 4 studies, a clinically important heterogeneity was revealed, which was largely accounted for by trial duration. Analysis of the 2 studies that lasted 10 weeks or longer yielded an odds ratio of response to treatment of 4.41 (95% CI = 1.38 to 14.07).

Subsequently, Chang et al.[196] reported an additional trial involving 62 patients who had not responded adequately to 1 year's treatment with clozapine with at least 8 weeks at a stable dose of 400 mg/day or more (unless the patient experienced adverse effects). Patients were randomly assigned, double-blind, to either aripiprazole (5–30 mg) or placebo augmentation. There was no significant difference in the primary outcome (i.e., change in BPRS total measurement) between the 2 groups. In secondary analyses, negative symptoms improved significantly, and prolactin and triglyceride levels were significantly lower in the aripiprazole-treated group.

Correll et al.[190] conducted a meta-analysis involving 19 studies, which includes those reviewed above as well as the studies involving clozapine. This meta-analysis did not exclude any trials on the basis of sample size. The results of the analysis showed that antipsychotic medication cotreatment was superior to monotherapy in 2 a priori–defined, co-primary outcomes: efficacy and all-cause discontinuation. However, sensitivity analyses were also conducted, which identified 6 efficacy moderators, including

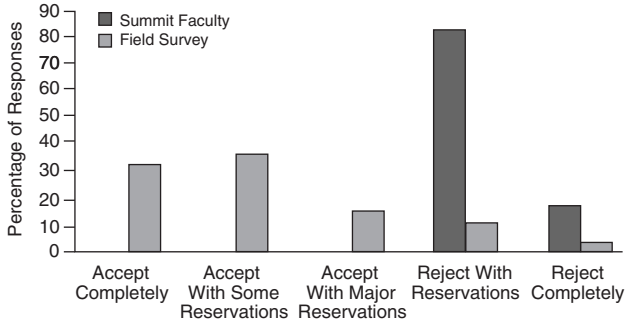
- acute exacerbation,
- concurrent polypharmacy initiation,
- clozapine combinations,
- trial duration greater than 10 weeks,
- trials conducted in China, and
- second-generation plus first-generation antipsychotics.

This meta-analysis supported the value of combining other antipsychotic medications with clozapine for acute exacerbations when the combination was initiated concomitantly. Except for studies that included clozapine, none were found that used modern-day diagnostic criteria to identify treatment-resistant patients or in which patients were randomized to monotherapy or combination treatments. The critical question for routine clinical practice, therefore, is whether antipsychotic polypharmacy is helpful for treatment-resistant patients prior to a trial of clozapine.

Grading of Evidence

Based on a review of the data presented above, 5 of the 6 Summit faculty workshop members (83%) agreed that the

Figure 11. Level of Support for Statement 8, "Patients With Treatment-Resistant Schizophrenia Require Combination Antipsychotic Treatment"



evidence to support this statement was Level V (insufficient evidence to form an opinion). One faculty member (17%) considered the evidence to be Level III (evidence obtained from case series, case reports, or flawed clinical trials).

Level of Support

Regarding the level of support for the statement, 82% of the Summit faculty members voted to reject the statement with reservations, and 18% voted to reject the statement completely. In comparison, the field survey found that 33% of respondents accepted the statement completely, 37% accepted it with some reservations, 15% accepted it with major reservations, 12% rejected the statement with reservations, and only 3% rejected the statement completely (Figure 11).

Discussion

Given the substantial proportion of patients who continue to experience clinically and functionally significant symptoms after an adequate trial of an antipsychotic medication, the management of TR is of key importance. Furthermore, despite the lack of supporting evidence, the practice of combining antipsychotics is widespread, as the field survey results suggest.

It is important to consider a number of key issues when reviewing the existing evidence. Essentially, there are no studies that address the relative merits of combination antipsychotic therapy in patients with treatment-resistant schizophrenia. Even the data with clozapine are far from clear. In some studies, the concomitant medication was started simultaneously with clozapine, while in others it was added to clozapine after the patients had failed an adequate trial of the latter. There were other studies that reported on combination treatment in patients who had acute exacerbation of symptoms, but not necessarily those who were resistant to treatment.

It also is important to recognize that modern-day diagnostic criteria were not always applied in these studies, and many studies did not utilize a measurement-based categorization of TR. Furthermore, in most trials, patients' therapeutic blood levels were not measured to determine the adequacy of treatment, which is a factor that should be considered in future research.

In clinical practice, there is tremendous variability in the length of treatment and the treatment approach before a patient is considered to have TR. Although existing data suggest that clozapine may have better efficacy compared with both first- and second-generation antipsychotic medications in the treatment of refractory patients, this medication is not recommended for use until a patient has undergone and failed trials with other antipsychotics.

Future Directions

Clearly, appropriate research in this area should have a high priority. This is an important clinical issue, and there is considerable disparity between the existing evidence base and clinical beliefs and practice. Studies need to be conducted with prospective establishment of an operational definition of "treatment resistance," as well as patient randomization to antipsychotic combination therapy versus monotherapy. Attention should be given to the rationale for combining specific medications, the dosages employed, and the duration of the trials. Ideally, a monotherapy clozapine arm would be an appropriate third trial arm in order to identify antipsychotic medication combinations within an appropriate continuum of all available treatment options.

STATEMENT 9: IMPROVEMENT IN COGNITIVE FUNCTION IS AN ESSENTIAL TREATMENT TARGET IN PATIENTS WITH SCHIZOPHRENIA

Raquel E. Gur, M.D., Ph.D.,
was the contributor of this section.

Rationale and Definition of Statement

The observation that impaired cognition is core to schizophrenia was reflected in its initial introduction as "dementia praecox" (i.e., premature dementia). However, the focus of clinical characterization and management subsequently has been on the positive manifestations of the disease (e.g., hallucinations, delusions), which were more glaringly disruptive and generally could be treated by antipsychotic medications. With the introduction of neuropsychological testing to the diagnosis of schizophrenia, it became evident that cognitive deficits are a common and pervasive feature of the disorder, and they exist at the onset of the illness and persist throughout its course. Impairments in executive functions (e.g., attention, working memory, reasoning, abstraction, mental flexibility),

language, and episodic memory (e.g., verbal, visual, facial) have been well documented.

Because cognitive deficits predict functional outcomes and do not improve significantly with current treatments, they represent a challenging treatment focus for novel therapeutics. In recognition of this challenge, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, funded by NIMH, was designed to stimulate the development of medications to treat cognitive deficits in patients with schizophrenia.[240] With a focus similar to that of the MATRICS initiative, this statement aims to evaluate the strength of evidence that improvement in cognitive function is an essential treatment target in patients with schizophrenia by focusing on studies of pharmacologic interventions that have evaluated the effects of these interventions on patient cognition.

Literature Search

A PubMed database search was completed on January 6, 2008, to identify studies related to pharmacologic interventions used to improve cognitive function in patients with schizophrenia. The following search terms were applied:

1. "schizophrenia," yielding 77,531 articles;
2. "cognitive function," yielding 56,620 articles;
3. "cognitive deficits," yielding 12,744 articles; and
4. "treatment target," yielding 84,894 articles.

These search terms were combined with "OR" for a total of 231,789 articles. Searches combining "schizophrenia" and "cognitive function" resulted in 3717 articles. After limiting these to articles written in English, 3428 articles were identified. A search combining the terms "schizophrenia" and "cognitive deficits" yielded 1713 articles. After limiting these results to articles written in the English language, 1610 articles remained. A search of the terms "schizophrenia" and "treatment target" or "treatment" yielded 3480 articles. Limiting the results to articles written in English resulted in 3043 articles. Finally, a search of "schizophrenia" and "cognitive function" or "cognitive deficits" and "treatment" or "treatment target" resulted in 1809 articles. After limiting these results to articles written in English, a total of 1657 articles remained. Of these, 1440 involved human subjects, 262 reported results of clinical trials, and only 12 articles were deemed relevant to the statement.

Evidence

Overall, these studies examined the effects of first-generation versus second-generation antipsychotic agents on cognition. In addition, some studies also examined the effects of second-generation agents alone and second-generation agents with and without adjunctive treatment on cognition.

Effects of first-generation versus second-generation agents. In a study by Lindenmayer et al.,[197] the efficacy of olanzapine (N = 16) was compared to that of haloperidol (N = 19) in a 12-week, double-blind, controlled study that examined negative symptoms and cognitive impairment in stable patients with predominately negative symptoms. The neurocognitive measures that were used evaluated patients' declarative verbal learning memory, attention and processing speed, executive functioning, and simple motor functioning. The authors reported that negative symptoms improved with use of olanzapine, as did declarative verbal memory and motor function.

In an 8-week, double-blind, randomized treatment study by Lee et al.[198] of haloperidol and risperidone, patients in the treatment group (N = 68, 20 drug-naive) were compared with patients in a control group (N = 95) who were evaluated only at baseline. No drug effect was observed on patients' performance of the Wisconsin Card Sorting Test, but maze performance improved on risperidone. Notably, repeated measures, which were only obtained for patients in the treatment group, showed practice effects. This emphasizes the importance of examining such effects in longitudinal design studies.

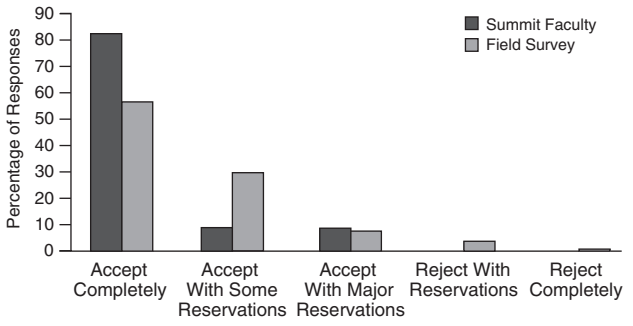
Effects of second-generation agents. A randomized clinical trial by Goldberg et al.[199] compared olanzapine and risperidone and examined practice effects in 104 first-episode patients with schizophrenia compared to 84 control patients. Cognitive assessment was conducted at baseline, at 6 weeks, and at 16 weeks after the initiation of treatment. No differential medication effects on cognitive performance were observed. Improvement was seen in 9 of 16 cognitive measures, but only in 2 measures of logical memory were the performance gains greater than the practice gains evident in the control group. The documented practice effects illustrate the importance of obtaining parallel measures for patients receiving treatment and those in the comparison control group.

In a multicenter, randomized, 52-week, double-blind study by Keefe et al.[200] of olanzapine (N = 133), quetiapine (N = 134), and risperidone (N = 133), baseline assessments were completed and compared for 224 patients with early psychosis. Neurocognitive composite scores were derived using the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the Brief Assessment of Cognition in Schizophrenia (BACS) tools. At week 12 (N = 224) and at week 52 (N = 81), modest improvement in cognitive performance was noted in all treatment groups, and this related to improved functional outcome.

In a study by Harvey et al.,[201] the effects of risperidone and olanzapine on cognition were examined in 176 older adults in an 8-week, randomized with washout, double-blind, switching paradigm. Several cognitive domains improved with both agents.

The effects of aripiprazole (N = 76) and olanzapine (N = 93) on cognition were also compared in a 26-week,

Figure 12. Level of Support for Statement 9, "Improvement in Cognitive Function Is an Essential Treatment Target in Patients With Schizophrenia"



randomized with washout, open-label study by Kern et al.[202] No differential treatment effects in general cognitive function were noted in either group from baseline. The measures applied included the California Verbal Learning, Benton Visual Retention, Wisconsin Card Sorting, Trail Making A and B, verbal fluency, Letter-Number Sequencing, Grooved Pegboard, and Continuous Performance tests. Within the 8 weeks, it was reported that the verbal learning factor improved in patients taking aripiprazole compared to patients taking olanzapine.

Effects of second-generation agents with and without adjunctive treatment. The efficacy of donepezil as an adjunct was examined in a 12-week, double-blind, placebo-controlled, randomized study by Lee et al.[203] with administration of adjunctive donepezil (N = 12) (i.e., an acetylcholinesterase inhibitor) or placebo (N = 12). Patients were evaluated at baseline and at 4, 8, and 12 weeks. Verbal recognition and visual recall improved; however, no effect was found for the executive domain.

A multisite, 16-week, double-blind, double-dummy, randomized study by Buchanan et al.[204] evaluated the effect of adjunctive glycine (N = 52), D-cycloserine (N = 53), and placebo (N = 52) on negative symptoms and cognitive performance. The neuropsychological battery included measures of processing speed, motor speed, verbal fluency, verbal memory, visual memory, auditory working memory, visual spatial working memory, attention, and executive function. This study showed that these agents, which modulate NMDA receptor function, demonstrated no effect on negative symptoms or on any cognitive measure. Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms.

In an 8-week, randomized, double-blind study by Schubert et al.,[205] stable patients treated with risperidone received either adjunctive galantamine (N = 8) (i.e., a cholinesterase inhibitor with putative, nicotinic-like effects) or placebo (N = 8). Improved performance in attention and delayed memory tests was reported in patients treated with adjunctive galantamine.

In a 24-week, randomized, double-blind, placebo-controlled study by Sharma et al.,[206] researchers evaluated patients who were stable on treatment with antipsychotics and who were treated with adjunctive rivastigmine (N = 11) (i.e., an acetyl cholinesterase inhibitor) versus patients given a placebo (N = 10). No improvement was reported in cognitive variables in the rivastigmine group compared to the placebo group. Additionally, practice effects were observed in both groups.

Notable throughout most of these studies, however, were relatively small sample sizes. This may affect the conclusions drawn from the studies and generalizing from these reports to the impact of these interventions on cognition.

Grading of Evidence

Based on a review of the studies cited above, all 6 of the faculty members of the Summit workgroup (100%) agreed that the evidence available to support this statement was Category II (evidence was obtained from well-designed cohort or case-controlled studies).

Level of Support

When voting on the support for this statement, 82% of the Summit faculty members voted to accept the statement completely, 9% voted to accept the statement with some reservations, and 9% voted to accept the statement with major reservations. Thus, in general, there was agreement that improvement in cognitive function is an essential treatment target for patients with schizophrenia. Similarly, of the 1064 clinical psychiatrists who participated in the online survey, 57% voted to accept the statement completely, 30% voted to accept it with some reservations, 8% voted to accept it with major reservations, 4% voted to reject the recommendation with reservations, and 1% voted to reject it completely (Figure 12).

Discussion

This statement is of key importance in the development of new treatments for patients with schizophrenia. The extent and magnitude of cognitive deficits in this patient population, the presence of these deficits throughout the course of illness, and the impact the deficits have on functional outcomes make them a legitimate target for intervention.

Inferences that can be derived from the literature on the effectiveness of the pharmacologic interventions on cognition are limited. Overall, the literature is relatively limited because the incorporation of cognitive measurement in treatment studies is a more recent addition to pharmacologic intervention research. In addition, first-generation antipsychotic and anticholinergic medications may have deleterious effects on patient cognition. Second-generation agents generally did not show

differential effects when compared with one another. However, second-generation agents were clinically associated with some cognitive and functional improvement. The current literature on adjunctive treatment does not indicate enhancement in cognition with these treatments.

As indicated by this review, several methodological considerations need to be addressed. These include sample characteristics, inclusion of controls, cognitive measures, and paradigms applied.

Sample characteristics. Sample sizes vary from well-designed studies with adequate power to small, underpowered samples that render study results inconclusive. Even in studies with large samples, attrition during the follow-up period created endpoint samples that were reduced in size. The participants' stage of illness is another variable requiring attention. Some studies included only patients with first-episode schizophrenia who were more likely to respond to treatment. Other studies included patients with more chronic conditions who had variable treatment histories.

Inclusion of controls. Because a repeated-measures design was the standard in these studies, the availability of a healthy comparison group to assess practice effects was required. Most studies did not include such a control group.

Cognitive measures. Diverse tests were applied to the assessment of patients. While similar cognitive domains were evaluated (i.e., attention, abstraction and mental flexibility, verbal memory), different measures were used. This renders direct comparison of study results difficult. Additionally, the number of measures, burden on participants, ease of administration, scoring, and database interface varied among the studies. The cross-cultural applicability of cognitive measurement tools also needs to be established. This is a particularly important consideration, as international, multisite trials are common.

Paradigms applied. Paradigms differed between the various studies listed here. This included such things as switching from one agent to another or stabilization of patients on their current regimen.

Future Directions

The understanding that cognition is a pervasive deficit in patients with schizophrenia and that cognition relates to functional outcome has sparked an interest and increased efforts in treatment research. This has resulted in the inclusion of cognitive measures in research studies as well as a move toward standardization of measures. While this is an important step, most studies published to date have examined medications that were not developed to target cognition. Novel approaches are needed to advance research in this field. As research continues, it will be necessary to rethink issues of study design, measures, targeted populations, and scope of intervention, such as the integration of cognitive remediation and pharmacologic intervention.

STATEMENT 10: MANAGING SUBSTANCE ABUSE IS A KEY TARGET OF TREATMENT

Alan I. Green, M.D.,
was the contributor of this section.

Rationale and Definition of Statement

Substance abuse and substance use disorder (SUD), a more inclusive term that refers to either substance abuse or substance dependence, are common in patients with schizophrenia. Moreover, clinical experience suggests that patients with schizophrenia who have an SUD tend to have poorer outcomes when compared to patients who do not have an SUD. Despite this, many treatment programs for patients with schizophrenia do not adequately address substance abuse, so it often goes unrecognized and is undertreated. In part, this stems from the separation of mental illness and addiction treatment systems and the philosophies of treatment within those systems.

Providing adequate treatment for substance abuse in a "dual diagnosis" patient (i.e., one who has both schizophrenia and SUD) often requires the addition of new therapies to an existing mental illness treatment program to address the SUD. This statement aims to assess the evidence underlying this practice and specifically to assess the importance of managing SUDs when providing treatment to patients with schizophrenia.

Literature Search

Epidemiology and complications of substance abuse in schizophrenia. A PubMed search was conducted on February 8, 2008, to identify articles related to the epidemiology and complications of substance abuse in patients with schizophrenia. The search terms used were "substance-related disorders/epidemiology" OR "substance-related disorders/complications" AND "schizophrenia/epidemiology" OR "schizophrenia/complications." This search resulted in 1137 articles in English.

A second search was conducted using the terms "substance-related disorders/epidemiology" OR "substance-related disorders/complications" and "schizophrenia/epidemiology" OR "schizophrenia/complications" AND "comorbidity" OR "dual diagnosis." This search revealed 476 articles in English. A third search was undertaken using the terms "substance-related disorders" AND "schizophrenia" AND "comorbidity" OR "dual diagnosis," limited to RCTs, meta-analyses, or systematic reviews written in English. This search yielded 32 articles.

Therapy of patients with substance abuse and schizophrenia. The search terms used were "substance-related disorders/therapy," "drug therapy," "complications," AND

"schizophrenia/drug therapy," "therapy," "prevention," and "control." Results were limited to RCTs, meta-analyses, and systematic reviews written in English. This search yielded 45 articles.

Recent articles not available on MEDLINE. A search using the terms "substance abuse" OR "drug abuse" AND "schizophrenia," NOT "MEDLINE" revealed 82 articles in English. The combined searches revealed 32 articles and 4 reviews that were related to the statement.

Evidence

Epidemiology. The most cited paper, the Epidemiological Catchment Area Study by Regier et al.,[207] suggested that a lifetime history of co-occurring SUD occurs in 47% of patients with schizophrenia, a rate approximately 3 times that of the general population. According to the study data, alcohol is the most commonly abused substance in patients with schizophrenia. This high rate of use occurs in patients with chronic schizophrenia as well as in first-episode patients.

However, data reported by Green et al.[208] indicate that in the subgroup of first-episode patients, the most commonly abused substance is reported to be cannabis. Importantly, cannabis use is now considered an important risk factor for triggering schizophrenia in patients at risk for psychosis, and strategies to limit cannabis use are becoming increasingly important in this patient population.[209]

Complications. It is clear that SUDs can complicate and worsen a patient's schizophrenia. Studies have shown decreased compliance with treatment in substance abusers, more frequent discontinuations and relapses, and increased costs of treatment in patients with both schizophrenia and SUD compared with patients with schizophrenia who were not substance abusers. In a longitudinal 6-month study of 161 patients with schizophrenia by Owen et al.,[210] substance abuse at the 6-month follow-up was associated with a substantial increase in medication noncompliance. Another study by Smelson et al.[211] of 632 patients randomized to olanzapine, risperidone, or typical antipsychotics, the patients who had a diagnosis of substance abuse at follow-up were found to discontinue their treatment sooner ($p < .001$). In a second report of first-episode patients randomized to olanzapine, risperidone, or quetiapine by Perkins et al.,[212] ongoing substance abuse was shown to be associated with the patient's discontinuation of treatment against medical advice.

Two reports have addressed the issue of increased relapses in patients with schizophrenia who have an SUD. In a study of neuroleptic dose reduction by Swofford et al.,[213] relapses were much more common among patients with a history of substance abuse (i.e., 7 out of 9 vs. 9 out of 37). The presence of a history of substance abuse was found to be a more likely determinant of relapse than neuroleptic dose reduction. Gupta et al.[214] reported on a retrospective analysis of 22 patients with schizophrenia (i.e., 11 substance abusers and 11 nonabusers) who were followed and treated with fluphenazine decanoate or haloperidol decanoate for at least 2 years. Those in the substance abuse group had a mean of 2.5 symptom recurrence–related hospital admissions during the 2-year period, compared with a mean of 0.5 symptom recurrence–related admissions in the non–substance abuse group ($p < .001$).

In a study by Swartz et al.[215] of 331 patients with severe mental illness who were involuntarily hospitalized, a review of the number of episodes of violence over the preceding 4 months revealed that the rate of violence in those who abused substances was greater than the rate in those who were not substance abusers (i.e., ~27% vs. ~13%). Lastly, a study by Dickey and Azeni[216] of more than 16,000 individuals based on information obtained from a combination of Medicaid claims as well as inpatient and community mental health center files in Massachusetts revealed that those with severe mental illness and substance abuse were 4 times more likely to be admitted to the hospital. Additionally, the patients with SUDs in this study were dramatically more costly to treat than were those with severe mental illness without a history of substance abuse (i.e., $22,917 vs. $13,930 in annual costs).

Management: psychosocial approaches. Management of patients with schizophrenia and co-occurring SUD is challenging, in part because many treatment programs for patients with schizophrenia are not configured to provide adequate management of SUDs. Additionally, there are few studies that focus on the optimal approach for treating these patients.[217–219] The most important aspect of providing treatment to patients with both diagnoses may be in the configuration of the treatment center to ensure that it is structured to recognize and provide treatment for both schizophrenia and substance abuse.

In general, clinical wisdom suggests that an understanding of the patient's readiness to change his or her substance use is a key component to the timing and success of treatment. Treatment approaches must be tailored to the patient's readiness to change.[217,220] In addition, there are several aspects of successful treatment programs, including working with the patient in shared decision making; providing support for housing, medical, and employment needs; and recognizing that relapses tend to occur.[217,220] A number of psychosocial approaches have been advocated for those who treat these patients; however, evidence suggesting the superiority of any one approach is minimal.

Contingency management techniques (i.e., providing reinforcement for clinic attendance or for biological evidence of substance non-use) were shown to be helpful in several studies.[221–223] In a randomized study by Bellack et al.[221] ($N = 129$), the active treatment program (i.e., the Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness) showed superiority over a more traditional, supportive approach. In a randomized study by

Haddock et al.[222] (N = 36), a combination of motivational interviewing, cognitive behavioral treatment, and family intervention was compared to treatment as usual. The combined treatment produced significant improvement in global functioning ($p < .05$), and the overall increased costs for delivering this type of treatment were shown to be offset by the savings in hospitalization costs. In a small study by Graeber et al.[223] (N = 30), therapy involving motivational interviewing was shown to be more effective than educational therapy for alcohol drinking outcomes in patients with schizophrenia ($p < .05$).

Management: medication approaches. Medication strategies for dual-diagnosis patients are just beginning to be assessed. Most existing data focus on the effects of antipsychotic medications. There is general consensus that the typical antipsychotic medications used to treat schizophrenia do not cause a reduction in alcohol or other substance abuse in this patient population.[208] However, recently published nonrandomized studies strongly suggest that clozapine may effectively limit patients' substance abuse. A naturalistic study by Drake et al.[224] of 151 patients with schizophrenia or schizoaffective disorder, all of whom had a co-occurring SUD, demonstrated that patients treated with clozapine during the course of the study were dramatically more likely to decrease alcohol or cannabis abuse than if they continued to be treated with their typical antipsychotic medication alone ($p < .05$). The follow-up investigation of the patients whose alcohol abuse had remitted during treatment further indicated that patients treated with clozapine were much more likely to maintain their remission than were the patients treated with typical antipsychotic medications ($p = .001$).[224]

The data regarding other atypical antipsychotic medications are less substantial and less consistent than those for clozapine. In an open-label study by Smelson et al.[225] (N = 18), researchers suggested that risperidone use was associated with a decrease in cue craving when compared to use of typical antipsychotic medications. However, in a retrospective study by Green et al.[226] (N = 41), data indicated that risperidone was less likely to be associated with cessation of substance use than clozapine. In a randomized study of long-acting, injectable risperidone by Rubio et al.[227] (N = 115), researchers reported that risperidone demonstrated superiority as measured by clean urine samples when compared to zuclopenthixol-depot (a medication not currently available in the United States).

Two small-sample, randomized studies compared olanzapine use in patients with schizophrenia and cocaine abuse.[228,229] The study by Smelson et al.[228] (N = 31) compared use of olanzapine to the use of haloperidol. The other study by Akerele and Levin[229] (N = 28) compared use of olanzapine to the use of risperidone. In the study of olanzapine and haloperidol, researchers found that olanzapine use was associated with decreased craving for cocaine.[228] Both studies noted a trend level of improvement in the olanzapine groups regarding clean urine samples. In contrast, a large, naturalistic study by Noordsy et al.[230] (N = 153) showed that improvement of substance abuse was no greater in patients treated with olanzapine than in those treated with typical antipsychotic medications.

Another study by Potvin et al.[231] addressed the use of quetiapine in this patient population. In this open-label study (N = 24), quetiapine use was associated with a decrease in craving for cannabis, decreased dollars spent on alcohol or cannabis, and decreased overall SUD severity. Lastly, 2 small, open-label studies by Brown et al.[232] (N = 10) and Beresford et al.[233] (N = 20) found that aripiprazole use may be associated with a decrease in urine tests positive for cocaine as well as a reduction of alcohol use.

A few studies have addressed the possible use of other medications for patients with schizophrenia and co-occurring alcohol use disorder or cocaine use disorder. One randomized study by Petrakis et al.[234] of 31 patients with schizophrenia and alcohol dependence reported an improvement in days of heavy drinking for patients who were given adjunctive naltrexone versus placebo. A second randomized study by Petrakis et al.[235] of 66 patients with a psychotic spectrum disorder and co-occurring alcohol use disorder reported that both naltrexone and disulfiram, whether used separately or together, resulted in more days of abstinence and fewer heavy drinking days than reported by the patients given a placebo. Contrary to these findings, some clinicians have voiced concerns that disulfiram could increase psychosis.[236]

Lastly, in a study by Ziedonis et al.[237] of an open-label, adjunctive treatment of 27 patients with schizophrenia or schizoaffective disorder and cocaine dependence, the researchers suggested that adjunctive desipramine resulted in fewer cocaine-positive urine tests, greater abstinence, and fewer psychiatric hospitalizations than in patients given adjunctive placebo.

Grading of Evidence

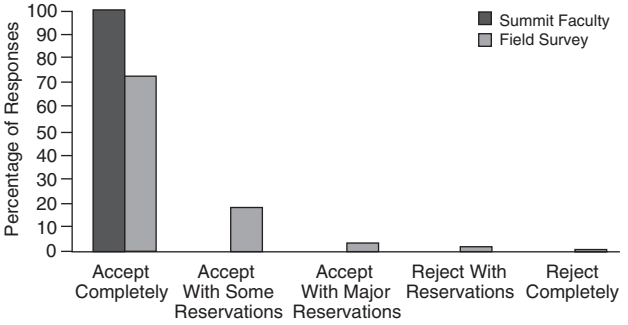
Based on a review of the 32 studies and 4 review articles, 2 of the 5 workgroup members (40%) considered the evidence available to support this statement to be Category I (evidence obtained from at least 1 well-designed, randomized, controlled trial). The remaining 3 faculty members (60%) considered the evidence to be Category II (evidence obtained from well-designed cohort or case-controlled studies).

Level of Support

When voting on the support for this statement, all 10 (100%) of those attending the Summit completely agreed with the statement. For those completing the field survey, 72% completely agreed with the statement, 19% accepted the statement with some reservations, 4% accepted the statement with major reservations, 3% rejected the

statement with reservations, and 1% rejected the statement completely (Figure 13).

Figure 13. Level of Support for Statement 10, "Managing Substance Abuse Is a Key Target of Treatment"



Discussion

The discussion at the Summit focused on a number of issues. First, the question of the role of cannabis use and the onset of schizophrenia was raised. There are accumulating data suggesting that cannabis use is a risk factor for the development of schizophrenia.[209] There was a consensus among the Summit faculty members that ultra-high-risk individuals (i.e., those with quasi-psychosis) should be encouraged not to use cannabis.

Secondarily, although not directly part of the statement under consideration, a question was raised about the nature of substance-induced psychosis. It is uncertain whether substance-induced psychosis invariably leads to schizophrenia or whether some individuals who develop psychosis from substance use do not progress on to a more chronic state. The available data suggest that, at least for some patients, a time-limited psychosis can occur.[238,239] Additionally, the duration of psychosis beyond cessation of substance use most likely can be used to help identify those patients whose psychosis is in the schizophrenia spectrum.

Another issue raised during the Summit was whether limiting alcohol or other substance use in abusers would improve the course of schizophrenia. There was general consensus that improvement was likely to occur for these patients. However, it may be that those who are able to limit or contain their substance use are also those who would otherwise have the best prognosis in their schizophrenia.

There was considerable discussion regarding the importance of including comorbid patients, particularly first-episode comorbid patients, in clinical trials, considering that this subgroup comprises nearly 50% of patients with first-episode schizophrenia. To make SUD an exclusion criterion in studies that include first-episode schizophrenia patients likely would limit the generalizability of data obtained from such studies. This concern applies to both pharmacologic and psychosocial studies. Whether patients had chronic schizophrenia or were early in the course of the disorder, there was overall consensus among the Summit faculty that there is a need to ensure that treatment programs are structured to manage and treat both the psychosis as well as any SUD components in patients with this dual diagnosis.

The beneficial effects of clozapine in this patient population appeared to be clear. Even with the promising data regarding clozapine, however, there is a lack of adequate, well-powered, randomized trials, which limits the conclusions that can be drawn and the clinical recommendations that can be made.[208,218] Nonetheless, the relatively infrequent use of clozapine in patients with schizophrenia was noted, and it was agreed that further studies of its use in patients with co-occurring SUDs should be undertaken.

The Summit faculty members discussed several other pharmacologic considerations, including the potential role of other atypical antipsychotics. There is an obvious need for more complete trials of all of these medications. In addition, the interesting data for co-occurring alcohol use disorder treated with either naltrexone or disulfiram were noted, and once again it was suggested that there is a need for further studies into the potential benefits of these medications in this patient population.[234,235] The faculty members acknowledged that there is a need for caution when using disulfiram to treat patients with psychosis because of the possibility of an exacerbation of psychosis.[236]

Although all the members of the Summit agreed unanimously that management of substance abuse in schizophrenia is a key target of treatment, the field survey showed a more disparate set of opinions. While this may reflect the lack of combined treatment approaches available in the field, it seemed to indicate an important area for education and treatment change.

Future Directions

This review reveals the importance of identifying SUDs in patients with schizophrenia. Data show that SUDs are common in this patient population and predispose patients to poorer outcomes. However, it also is notable that the body of evidence supporting any particular treatment is still developing. There is clear consensus in the medical field that an integrated treatment program that addresses both schizophrenia and SUD is best provided by a single team of health care providers. The choice of the optimal pharmacologic approach for these patients will require further study, using carefully controlled, randomized clinical trials.

SUMMARY

Henry A. Nasrallah, M.D., was the contributor of this section.

The discussion of each of these 10 statements demonstrates that the actual strength of the evidence is not always

commensurate with the degree of confidence that clinical psychiatrists perceive regarding the veracity of the statements. Except for Statement 10, "Managing substance abuse is a key target of treatment," on which there was considerable concordance between clinicians and researchers, and Statement 9, "Improvement in cognitive function is an essential treatment target in patients with schizophrenia," for which the overlap was also good, there were many striking disparities between clinicians and researchers. There was a general trend for the researchers' ratings to cluster together more closely, while clinicians' ratings were more diverse and variable.

Several important questions emerged from this project and deserve additional follow-up. First, are clinicians more easily swayed by Level IV or Level V evidence (i.e., opinions, clinical vignettes) or Level III evidence (i.e., controlled studies, case reports, poorly designed clinical trials), while researchers typically consider only Level I or Level II evidence? Second, are clinicians overly eager to adopt new biological or treatment findings for schizophrenia and possibly other disorders? If this is true, why? And how can this practice be modified so that clinicians implement changes in their practices based only on Level I or Level II evidence? Last, do existing continuing education programs sufficiently emphasize the highest level of evidence so that when clinicians read published articles, they can quickly distinguish the wheat from the chaff?

One of the problems in schizophrenia research, and actually in all of psychiatry, is that the need for Level I evidence is great but resources for funding Level I or even Level II studies are limited. Thus, the bulk of newly published findings are based on Level III, Level IV, or Level V evidence, and the sheer relative volume of such subpar "evidence" takes on the appearance of legitimacy.

However, it is unfair to sit back and criticize clinicians for not adhering primarily to Level I or Level II evidence, because there are numerous psychiatric conditions for which the biology is completely unknown or evidence-based (i.e., FDA-approved) treatments remain unavailable. Thus, although combination antipsychotic treatments are not yet approved for treating patients with schizophrenia, a substantial number of patients with schizophrenia are currently receiving combinations of antipsychotic medications (i.e., 2 or more, first- and/or second-generation medications) in the United States. When considering the voting results for Statement 8, "Patients with treatment-resistant schizophrenia require combination antipsychotic treatment" (Figure 11), the data indicate that most clinicians accept the statement while the majority of researchers reject it.

In summary, this project describes the wide gap between clinical psychiatrists and researchers as far as adhering to the highest level of evidence in accepting and implementing diagnostic and treatment notions about schizophrenia. Examination of these results also generates questions that need to be addressed in order to increase the rigor of the diagnosis and treatment of patients with schizophrenia and the use of knowledge built solely on a solid foundation of high-level evidence. Our patients deserve no less.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, the combination therapy of clozapine plus risperidone is not approved by the U.S. Food and Drug Administration for the treatment of patients with schizophrenia.

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