Schizophrenia Research: A Progress Report, Summarizing Proceedings of the 1999 International Congress on Schizophrenia Research

by Peter F. Buckley, Robert W. Buchanan, Carol A. Tamminga, and S. Charles Schulz

Abstract

The Seventh International Congress on Schizophrenia Research was held in Santa Fe, New Mexico, in April 1999. This was the largest Congress meeting to date, with almost 1,000 presentations that covered all aspects of schizophrenia research. This article provides an account of the Congress proceedings. Several research areas received extensive coverage, including early detection of illness through the use of cognitive and behavioral precursors of schizophrenia and the etiology and treatment of childhood-onset and first episode schizophrenia. The etiopathophysiological hypothesis of schizophrenia as a disorder of neural dysconnectivity was promoted across cognitive, neurochemical, neuroimaging, and postmortem domains. The importance of cognition as a major outcome measure and the impact of new antipsychotics on the treatment and conceptualization of schizophrenia were also major topics. Overall, the conference was noteworthy for the convergence of findings across research domains.

Keywords: Schizophrenia, epidemiology, etiology, treatment, pathophysiology.


Over 1,500 national and international researchers attended the Seventh International Congress on Schizophrenia Research (ICOSR) from April 17 to 21, 1999, in Santa Fe, New Mexico. The organizers, Dr. Carol A. Tamminga and Dr. S. Charles Schulz, were ably assisted by the ICOSR coordinators Susan Basham and Deborah Hudson (Maryland Psychiatric Research Center) and by the program planning committee, chaired by Professor Jeffrey Lieberman, University of North Carolina, Chapel Hill. The Maryland Psychiatric Research Center, Case Western Reserve University, and the William K. Warren Foundation sponsored the ICOSR. The National Institute of Mental Health (NIMH) and several pharmaceutical companies also supported the conference. Forty-one junior researchers (named at the end of this article) received ICOSR Young Investigator Awards, supported by NIMH and the ICOSR, which provided support for the junior researchers’ attendance at the meeting. The majority of Young Investigators participated in a daily review of presentations that was designed to provide an opportunity for discussion and clarification. They also assisted with coverage of the conference proceedings for this article.

Two other prestigious awards were given at the meeting. Robert Freedman, M.D., Professor of Psychiatry at the University of Colorado Health Science Center, Denver, Colorado, received the 1999 William K. Warren Research Award in recognition of his contributions to the identification of genetic markers and phenotypes for schizophrenia. During a plenary lecture, he described work from his laboratory demonstrating alterations on the human chromosome 15q14 in the gene that codes for the nicotinic receptor and also his related work on P50 auditory evoked potentials. He articulated a vulnerability model for schizophrenia that involved a pathogenic role for environmental factors in synergy with an already established genetic liability to schizophrenia.

E. Fuller Torrey, M.D., Director, Stanley Foundation Research Programs, Bethesda, Maryland, received the 1999 ICOSR Lifetime Achievement in Schizophrenia Research Award. Dr. Torrey recounted the real progress over the last two decades in the understanding of major mental illness. While he expressed optimism that the next millennium would soon bring a cure for schizophrenia, he stressed the current need for advocacy in collaboration with family members to destigmatize mental illness and to achieve broader parity for mental illness. In a plenary lecture on the epidemiology of schizophrenia, Dr. Torrey suggested that the robust worldwide variations in incidence and prevalence, as well as the urban/rural and seasonal differences, are important areas to pursue further.

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Other experts delivered plenary lectures. Charles Nemeroff, M.D., Emory University, Atlanta, Georgia, gave a comprehensive overview of neuropeptides, an endogenous neurotransmitter in schizophrenia, showing different effects on neuropeptide expression when rats receive either conventional or atypical antipsychotic medications. Dr. Steven Grossberg, Department of Cognitive Neuroscience and Neurosystems, Boston University, Boston, Massachusetts, explained how an imbalance in neural networks may, through compensatory mechanisms, result in the expression of some of the core features of schizophrenia, such as thought disorder or inattention. He pointed out that key areas in these complex circuits included the prefrontal cortex (PFC) and the amygdala. He postulated that the imbalance in these circuits was consistent with the observations of hypofrontality and of abnormal social perception in schizophrenia. Dr. Marion DiFiglia, Laboratory of Cellular Neurobiology, Massachusetts General Hospital, Boston, MA, described the work from her laboratory on the genetics of Huntington’s disease and provided insight into the potential of research on the genetic basis of schizophrenia.

This article highlights some new findings and gives an overall picture of current schizophrenia research. Similar reports have appeared on previous conferences (Schizophrenia Bulletin, 24:501–518, 1998). The proceedings of the meeting are also published in abstract form (Schizophrenia Research, 36:1–3, 1999).

Etiology

The findings from several genetic linkage and association studies complemented Dr. DiFiglia’s presentation at this meeting. The results of genetic linkage studies of large family pedigrees were described, with linkage being documented on chromosomes 5, 6, 8, 13, and 22. The q14 region of chromosome 13 appears to be the most promising site for genetic linkage. However, the associations overall are modest and thus far only partly replicated, such that evidence for a major gene defect for schizophrenia is presently slim. On the other hand, it is possible that genetic deficits, each individually of small effect, could have an overall large impact if they occur commonly in this disorder. Several genetic association studies at the conference examined candidate genes, and positive associations were described for the dopamine D3 receptor gene but not for the 5-HT2A receptor gene. It was urged that genetic research should be integrated with other aspects of neurobiology, such as brain imaging, and that large epidemiological samples should be sought. These approaches are timely; the Human Gene Project is nearing completion, and more association studies are being undertaken. In this regard, several groups reported structural abnormalities in the brains of relatives of individuals with schizophrenia (see Neuroanatomy below). It was also reported that relatives of persons with schizophrenia exhibit subtle cognitive dysfunction of a pattern similar to that of (and of lesser magnitude than) patients (see Neurocognition below).

The importance of studying clinical phenotypes in schizophrenia was also emphasized at this meeting. Several studies examined the clinical, structural brain imaging, and neurocognitive correlates of adults with chromosome 22q11 deletion syndrome and comorbid schizophrenia. Several groups reported on epidemiological followup studies of individuals who had been exposed to viral infections in utero and who had subsequently developed schizophrenia.

The role of environmental risk factors and markers of abnormal development to the development of schizophrenia was also examined at the conference. Prenatal and perinatal environmental adverse events have been frequently implicated as risk factors for the development of schizophrenia, with obstetric complications (OCs) most frequently implicated. The etiologic significance of the interaction between OCs and genetic and other etiologic/developmental factors and the mechanism by which OCs may cause schizophrenia are major areas of investigation. Mothers with schizophrenia are more likely to have OCs, and their offspring are more likely to experience an adverse effect of these complications than children either of mothers with affective disorders or normal controls. Although the offspring of mothers with affective disorders do exhibit an increase in behavioral abnormalities, the abnormalities are not as severe as those observed in patients with schizophrenia. The mechanism by which OCs are thought to exert their effect is through decreased oxygen supply to the developing brain. In a large case register study, a marker of hypoxia-ischemia was shown to be the most important determinant of the future development of schizophrenia, even after controlling for the presence of other confounding factors, including the presence of other OCs.

The ability to predict which subjects who experience OCs will go on to develop schizophrenia is complicated by the inability to ascertain the severity of the specific OC and whether it produced a sufficient insult to the developing brain. The examination of behavioral and cognitive milestones may lead to the early identification of individuals at increased risk for developing schizophrenia after exposure to an OC. Data from the 1966 North Finland Birth Cohort suggest that a delay in the development of the ability to stand is linearly associated with the development of psychotic disorders. If the delay occurs in conjunction with perinatal brain damage, there is an increased likelihood that the subject will go on to develop schizo-
phrenia. In contrast—although social maladjustment, deviant behavior, and cognitive abnormalities are observed before the diagnosis of schizophrenia—data from the Philadelphia cohort of the National Collaborative Perinatal Project suggest that these abnormalities are no more common in patients who experienced perinatal hypoxia.

The trajectory of neurodevelopmental schizophrenia remains ill-defined. One unifying perspective holds that an early environmental insult occurring in the context of genetic predisposition might result in neurodevelopmental abnormalities. Thereafter, a subsequent (perinatal or childhood/adolescent) environmental insult could cause further brain dysfunction and ultimately lead to the clinical expression of schizophrenia. Delayed, inadequately treated, or persistently active psychosis was also proposed as another important variable that could evoke the trajectory of neurodegeneration and of clinical deterioration, resulting in chronic psychosis. Several studies have examined the clinical sequelae of duration of untreated psychosis (DUP), but as yet there is no direct evidence for neurodegeneration resulting from prolonged DUP. A magnetic resonance imaging (MRI) study showed no relationship between DUP and structural pathomorphology, while another found that reduction in frontal lobe volume was associated with long DUP.

Neuroanatomy

Thalamus. A major focus of the meeting was the thalamus and its potential role in the neuroanatomy of schizophrenia. Thalamic nuclei can be divided into three broad categories: (1) principal nuclei, which are characterized by reciprocal connections to circumscribed cerebral cortical regions; (2) intralaminar nuclei, which project to the basal ganglia and cerebral cortex; and (3) reticular nuclei, which have reciprocal connections with the principal nuclei. The principal nuclei can be further divided into sensory-motor relay and association nuclei. The function of these different nuclei is dependent on their afferent and efferent connections and the intrinsic properties of relay cells—including cell membrane potentials, tonic versus burst firing, and ionotropic versus metabotropic receptors. The physiological properties of the thalamus and the involvement of multiple thalamic nuclei in basal ganglia-thalamocortical neural circuits (BGTC) provide a powerful rationale for hypotheses of the involvement of one or more thalamic nuclei in the pathophysiology of schizophrenia.

A number of structural and functional imaging and postmortem studies have examined whether patients with schizophrenia are characterized by abnormalities of the thalamus. Structural MRI studies have repeatedly documented decreased thalamic volume in schizophrenia. The results of structural imaging studies are replicated and extended by the results of postmortem studies, which have documented decreased neuron count in the medial dorsal (MD) association nucleus. The decreased MD neuron cell count may be specific for the parvocellular region, which projects to the dorsolateral PFC. There is also preliminary postmortem evidence that other thalamic nuclei may be involved in schizophrenia. Positron emission tomography (PET) studies have noted abnormal thalamic and cerebellar metabolism during the performance of various cognitive tasks. Taken together, these results support a disturbance in the connections in the BGTC and between the BGTC and the cerebellum—a disturbance that may underlie the diverse symptom and cognitive manifestations of the disorder.

Animal Models. Although there is currently no single animal model or preparation that models all aspects of schizophrenia, animal models are available that can enhance our understanding of specific aspects of the pathophysiology of schizophrenia. In a neurodevelopmental model of OCs, uterine artery ligation is used to produce placental insufficiency and hypoxia. The procedure results in a number of morphological changes in the brain, including decreased cortical, basal ganglia, and hippocampal volume and increased ventricular volume.

Previous animal models have examined the effect of neonatal hippocampal lesions, but other limbic areas may be involved in the pathophysiology of schizophrenia. Neonatal lesions of the amygdala and/or hippocampus provide an approach for examining the unique contribution of different limbic structures. These lesions result in behavioral and anatomical abnormalities in adult rats that are analogous to those seen in patients with schizophrenia. There were other models that were presented at the ICOSR:

1. Intraventricular kainic acid administration results in a number of changes in the hippocampus, including nerve cell loss, decreased glutamate receptors, and diminished glutamate release in the nucleus accumbens.
2. Picrotoxin infusion of the basolateral nucleus of the amygdala results in changes in the hippocampal GABAergic system and provides an alternative model for understanding hippocampal GABAergic abnormalities in patients with schizophrenia.
3. Rats reared in social isolation exhibit sensory-gating deficits, which are transiently reversed with a nicotine receptor agonist.
4. Neurotrophic factors regulate the development and plasticity of the nervous system. Blockade of the p75 neurotrophic factor receptor results in amphetamine-
induced alterations of dopaminergic activity in the nucleus accumbens.

5. Dopamine transporter knockout mice demonstrate a number of abnormalities in dopamine regulation and may help to understand the impact of chronic dopamine dysregulation in schizophrenia.

Postmortem Studies. There is an emerging consensus that the PFC of patients with schizophrenia has pathological changes. Although the exact nature of the underlying process is unclear, many findings are consistent with a decrease in the neuropil rather than an alteration in the number of nerve cells. In BA10, in male patients with schizophrenia there is evidence of a decreased neuron to neuropil ratio, which is associated with an increase in presynaptic protein. The increase in presynaptic protein has not reliably replicated. The observation of increased neuronal density may be restricted to specific regions or cell types of the PFC. The total density of parvalbumin containing cells (i.e., GABAergic interneurons) is decreased in BA9 and BA46. The decrease in GABAergic interneurons may be associated with a compensatory increase in GABAA receptors. Investigation of the orbitofrontal PFC (BA10/47) suggests that there is decreased, rather than increased, neuronal and glial density, whereas there appear to be increased density and decreased number of kainate-stained pyramidal cells in BA11.

Altered neuronal count or density may be related to disruptions in the cortico-thalamic pathways. In the superior medial PFC (BA9), evidence shows that the number of axon terminals from neurons originating from the medial dorsal nucleus of the thalamus is decreased. There may also be abnormalities in the neurotransmitter systems that project to both of these regions. The mRNA for gluta
tate receptors, but not dopamine or serotonin receptors, may be decreased in selected thalamic nuclei, whereas 5HT2a receptors, but not glutamate receptors, were reported to be decreased in BA9.

MRI. Structural MRI may address three different questions. First, what brain regions are involved in schizophrenia, and do they exhibit progressive changes? Second, what is the relative contribution of different etiological risk factors to observable brain abnormalities? Third, do certain patterns of structural abnormalities define a phenotype?

Widespread gray matter reductions in the frontal, parietal, temporal, and occipital cortices are observed in first episode patients. First episode patients also exhibit increased cerebrospinal and ventricular volumes. The extent of changes in the frontal cortex may be related to different types of onset (i.e., insidious, acute), duration of untreated psychosis, or duration of illness. In support of the latter hypothesis is the observation that the superior and orbitofrontal PFC regions are more affected in chronic than in first episode patients. However, in longitudinal studies, only the posterior superior temporal gyrus and the ventricular system have demonstrated a progressive loss of volume.

The relative contribution of genetic versus environmental factors was examined in several studies. In sibling and twin studies, a variety of cortical changes, particularly in the frontal and temporal gray matter, may be observed in affected probands and their siblings, which suggests that genetic factors affect the expression of these changes. Reductions in amygdala/hippocampus and thalamus volumes have also been observed in both patients and their siblings. The amygdala/hippocampus is also reduced in the nonpsychotic offspring of patients with schizophrenia. Thus, cortical, limbic, and thalamic changes may serve as potential phenotypes of the underlying genetic abnormalities. In contrast, patient/normal control total brain and ventricular volume differences were observed to be unrelated to genetic factors, with ventricular enlargement associated with a history of perinatal hypoxia.

Structural MRI studies of the neuroanatomy of comorbid schizophrenia were also presented at the meeting. Studies examined the brain structure in persons with comorbid schizophrenia and learning disability, persons with comorbid schizophrenia and substance abuse, and individuals with schizophrenia who exhibit persistent violence. These studies provided preliminary evidence of more prominent brain abnormalities in these comorbid patient groups. It is premature yet to conclude that these comorbid conditions show any distinct pattern of dysmorphology. However, these presentations provide a clear indication of the evolution of MRI methodology and its thoughtful application to examine the heterogeneity of schizophrenia and its comorbid manifestations.

Neurochemistry and Electrophysiology

Converging data suggest that interactions between the glutamergic and dopaminergic systems are important in the pathophysiology of schizophrenia. Several magnetic resonance spectroscopy studies pointed to decrements in glutamate in patients with schizophrenia. Neurochemical studies examined the clinical and neurotransmitter effects of pharmacological probes on the glutamergic N-methyl-D-aspartate (NMDA) system. Phencyclidine (PCP) induces psychotomimetic changes in normal volunteers and its cogener ketamine, an agonist at the NMDA receptor, provokes a transient worsening of psychotic symptoms (especially thought disorder) in patients with schizophrenia. These clinical effects are also associated with
release of striatal dopamine in volunteers and with more pronounced dopamine release in the striatum of patients. It was shown that the extent of dopamine release correlated with measures of increased thought disorder. The amelioration of ketamine effects by new mood stabilizing and antipsychotic drugs was also reported on at this meeting. Lamotrigine, an anticonvulsant drug that reduces glutamate release, was noted to ameliorate the psychotic and cognitive effects of ketamine in normal volunteers. In other studies using animal subjects, ketamine-induced metabolic activation was fully attenuated by clozapine and partially attenuated by risperidone and by olanzapine. Failure of typical antipsychotics to attenuate ketamine psychosis and the differential effect of the newer antipsychotics suggests that complex glutamatergic-dopaminergic interactions may be occurring in schizophrenia. Such imbalances may be relevant to the therapeutic effects of these newer antipsychotics.

Neurotropins are known to affect neuronal viability, growth, and synaptic plasticity. Several studies examined the expression of neurotropic factors in schizophrenia. Brain-derived neurotropic factor infusion was shown to enhance c-fos (an immediate early gene) expression in the rat striatum following treatment with haloperidol. In another study, clozapine-induced elevation of striatal neurotropins was not observed in response to other atypical or typical antipsychotic medications.

Abnormalities of event-related potentials and eye movements have been widely investigated in patients with schizophrenia as potential biological trait markers. Event-related potentials were shown to be abnormal in clinically unaffected relatives who may be carriers of a genetic liability for schizophrenia. Deficits in sensory gating were also observed in patients with schizotypal personality disorder. P300 abnormalities in the left temporal lobe were observed in first episode schizophrenia patients but not in first episode affective disorder patients. These abnormalities were shown to be present over the course of the illness. In a similar manner, smooth eye movements were found in first episode patients and in patients with spectrum personality disorders. These abnormalities also appear to be stable over the course of illness.

Neurocognition

Functional imaging studies of cognition may provide insight into the normal functional neuroanatomy involved in the performance of these tasks, the extent of involvement of these regions during patient task performance, and potential compensatory mechanisms. Normal controls activate the superior and middle PFC and parietal cortex and suppress temporal lobe activation during the performance of the N-Back working memory task. Patients with schizophrenia exhibit decreased activation, as measured by either the peak activation or the average cluster size of activation, and show marked variability in the location of maximal activation in the dorsolateral PFC during the performance of this task. These differences are not related to level of performance. In addition, they also fail to suppress temporal lobe activation, which may indicate impaired coordination of cortical activity.

The anterior cingulate and inferior PFC may be involved in the normal inhibition of inappropriate behavioral responses. These regions appear to be insufficiently activated in patients with schizophrenia, which may explain the problem patients have with selective attention tasks and monitoring and responding to errors. In response to the oddball stimulus task normal controls activate various brain regions, including the left superior temporal gyrus, bilateral inferior parietal cortex, anterior cingulate, and thalamus. In the same task, patients do not demonstrate similar activation of the thalamus but show activation of multiple PFC regions, and, more important, they appear not to respond to the oddball stimulus. Rather, patients appear to respond only to the standard tone, which may help to explain the differences in the observed patterns of activation and raises the general question of whether patients are actually performing the same behavioral task as normal controls.

Early in the course of illness, patients may show increased and bilateral activation of the middle PFC during accurate performance of working memory tasks. In contrast, normal controls exhibit unilateral activation of this region. However, even first episode patients will not show normal activation when they are performing an attention or working memory task at suboptimal levels.

Course of Illness. The relationship of cognitive impairments to other clinical variables was highlighted at the conference. Increasing evidence shows an important relationship between disorganized behavior and impairments on neuropsychological test performance, with the level of disorganization inversely related to the level of performance. Patients with persistent functional impairments and symptoms of disorganization perform more poorly on cognitive tasks. There were no differences in severity of disorganization symptoms between patients with intermittent and persistent functional impairments. However, the predictive utility of cognitive impairments is not a consistent finding. In a group of stable outpatients, disorganization symptoms were more predictive of community function than cognitive impairment. The discrepancy in study results may be due to different measures of outcome or to the fact that it appears that outcome, cognitive impairments, and disorganization symptoms are not independent constructs (i.e., there are significant interrelationships among the three constructs).
In first episode patients, the extent of neurocognitive impairment predicts significantly work outcome. Patients who remain cognitively intact after the onset of illness are more likely to have exhibited intact premorbid cognitive function and exhibit persistently intact performance on followup examinations.

Gender appears to have a significant effect on cognitive impairment in patients with schizophrenia, with female patients exhibiting less memory impairment than male patients. It was reported at the meeting that estrogen may play a protective role and mitigate the effects of the disease process in women.

Relationship to Etiopathophiology. Cognitive impairments can be used as a tool for investigating the etiology, pathophysiology, and treatment of schizophrenia. A major area of investigation is the potential of specific cognitive impairments to serve as phenotypic markers. The results of studies of patients with schizophrenia, first degree family members, and normal comparison groups suggest that measures of attention, nonverbal concept formation and reasoning, and working memory may be useful in this regard. Studies of adolescent subjects manifesting prodromal symptoms of schizophrenia found that these subjects exhibited attention, working memory, and verbal memory impairments—results that are similar to those from family studies. Subjects at high risk who go on to develop schizophrenia also exhibit olfactory impairments. Olfactory abnormalities have previously been shown to be related to executive functions.

In vivo and naturalistic studies of early brain insults provide an approach for examining the effects of disturbances in normal brain development on cognitive function. The in utero application of the mitosis inhibitor methylazoxymethanol results in spatial learning and memory and object memory impairments. The nature of the impairment is dependent on which in utero day the drug is administered. In a followup study of adults exposed to in utero rubella infections, subjects who exhibited cognitive abnormalities as children were more likely to develop psychotic disorders.

Relatively little is known about the neuropharmacology of cognitive impairments. An increase in the understanding of the neurotransmitters and receptors that regulate cognitive functions may provide an empirical basis for developing more effective treatments. The dopamine D1 receptor has been shown to regulate working memory performance. Intermittent D1 agonist treatment reverses working memory impairments produced by the chronic administration of haloperidol. In vivo animal models may be used to evaluate the comparative effect of different antipsychotic agents on behavioral/cognitive responses. Risperidone-treated rats produced more errors on a putative measure of working memory than those treated with either clozapine or haloperidol. These types of studies serve to provide a framework for interpreting the results of studies that compare the efficacy of different types of antipsychotics for cognitive impairments in patients with schizophrenia.

Symptoms

The relationship among symptoms, course, and etiologic factors was examined in several studies. The relationship of symptoms to etiologic factors was examined through the use of factor analysis to define different symptom dimensions in the populations of patients under study. Family history of psychosis or level of genetic risk of schizophrenia and related disorders was found to predict positive and negative symptoms. Disorganization and paranoia were not associated with familial transmission of schizophrenia, with paranoia related to nonfamilial etiologic factors. Symptom dimensions also differ in their relationship to outcome. Patients with schizophrenia who have passed through an acute episode and continue to exhibit either negative or depressive symptoms have a poorer outcome than those without these symptoms. Increased neurological signs are also associated with poor outcome. Outcome does not appear to be related to adolescent versus adult onset of illness or other symptom dimensions. The results of these studies are consistent with a multidimensional framework for schizophrenia symptoms and the etiologic and prognostic significance of negative symptoms.

Treatment

Medications. The strategy of examining the neurobiology of schizophrenia by way of comparing the differential effects of typical and atypical antipsychotics was evident throughout the conference (see previous sections). In the area of clinical psychopharmacology, relatively little information was available at this conference on the role of newer antipsychotics in treatment-refractory schizophrenia. The majority of treatment studies focused on the care of first episode or partially responsive patient groups. Some longer duration studies (over 20 weeks) reported comparable efficacy between haloperidol and the newer antipsychotics and comparable outcome between clozapine and risperidone. The new drugs showed clear advantages for low extrapyramidal symptoms (EPS). Moreover, studies showed that patients' subjective response was more favorable with the medications. It was also noteworthy that studies confirmed that the rate of tardive dyskinesia during treatment with these newer agents is substantially less than with the older antipsychotics. Overall,
these studies suggest that advantages of newer over older antipsychotics were most apparent at the extreme ages of illness (i.e., in young adolescents who are sensitive to EPS and in older patients who are at high risk to develop tardive dyskinesia). Findings also were encouraging on the use of newer antipsychotics in specific patient subgroups. For example, clozapine-treated patients with comorbid substance abuse and schizophrenia were noted to have a sustained cessation of substance abuse and lower long-term (one-year) rates of rehospitalization. There was also some evidence of differential rehospitalization rates between antipsychotic medications, with the older antipsychotics (even when given in long-acting intramuscular form) being associated with the highest rates of relapse and rehospitalization.

The adverse effects of newer antipsychotics were also examined. Weight gain has emerged as a major concern with the new medications. It was shown that clozapine and olanzapine were the most likely of the newer drugs to cause weight gain, with perhaps sertindole (available only in Europe) and ziprasidone (currently under Food and Drug Administration review) being the least likely. However, most data were from short-term trials. Moreover, there was an absence of studies on the management or the long-term consequences of weight gain with new antipsychotics. It was noteworthy that some studies showed substantial polypharmacy that may be relevant to weight gain. The continued practice of polypharmacy, particularly for long-stay (State hospital) patients, may be an attempt to augment the efficacy of the newer antipsychotics in treatment-refractory patients, since these new drugs have not thus far showed comparable efficacy to clozapine in this patient subgroup.

Several studies showed how PET and single photon emission tomography may help further researchers’ understanding of the effects of typical and atypical antipsychotics on the dopaminergic and serotonergic systems. It was shown that, in general, the newer antipsychotics have a profile of low dopamine (D2) receptor binding and high rates of serotonin (5-HT2A) binding, although this appears to differ substantially between these drugs. Clozapine and quetiapine show the lowest D2 binding, with D2 occupancy rates below 50 percent during treatment with therapeutic doses. This low D2 occupancy may be particularly relevant to the observations that neither clozapine nor quetiapine cause motor side effects or prolactin elevation. These are important clinical distinctions. With regard to 5-HT2A receptor occupancy, olanzapine, risperidone, sertindole, and clozapine all appear to have substantial 5-HT2A receptor occupancy. In one study, the in vivo 5-HT2A occupancy with quetiapine was reported as ranging from 20 to 95 percent. Evidence also was presented that showed the motor side effects of typical antipsychotics are likely to occur when D2 occupancy is at or above 78 percent. While there is some evidence for relationships between plasma haloperidol levels, in vivo D2 receptor occupancy, and clinical response, it is presently unclear whether such relationships exist for any or all of the newer antipsychotics. In this regard, there was an absence of studies on the utility of plasma levels for the newer drugs in clinical practice.

A significant number of patients develop schizophrenia and go on to have a chronic course of illness, with marked functional impairments. Available pharmacological and psychosocial treatments have limited benefits for these patients. The ability to develop systems of care able to identify prepsychotic patients has raised the hope that early intervention may decrease the overall morbidity associated with schizophrenia. In light of the adverse predictive value of prolonged duration of untreated psychosis for treatment response, the development of sensitive and specific approaches for the early detection of preschizophrenia individuals is of utmost importance. Patients with schizophrenia are commonly characterized by poor premorbid social adjustment and function. The use of these measures—along with family history, maternal age, negative symptoms, substance use, and the presence of stress—may be useful in predicting which subjects who present with emotional/behavioral problems will go on to develop schizophrenia. Biobehavioral markers offer an alternative approach to prodromal symptoms for the identification of these individuals. Biobehavioral markers are a stable trait, present in the relatives of patients with schizophrenia, and are independent from clinical state. In this regard, a biobehavioral marker that may be of particular utility is attentional impairment, which fulfills the definition of a biobehavioral marker and is observed in high-risk children by 12 years old.

In addition to intensive psychosocial treatments, the use of low-dose antipsychotics may also be beneficial in preventing the progression of prodromal symptoms to psychosis. The advent of the new generation of antipsychotics, with their decreased incidence of adverse motor effects, makes this a more viable strategy. In patients who have progressed to a first episode of psychosis, intensive intervention appears to be most beneficial for patients who have been psychotic between 1 and 6 months. Patients who have been ill less than 1 month or greater than 6 months do not receive as much benefit from intensive interventions. The use of low-dose antipsychotics is also indicated in first episode patients, as they tend to be more responsive to lower doses of antipsychotics than more chronic patients. The use of low doses of conventional and new-generation antipsychotics is supported by plasma level studies and more directly by PET studies of dopamine receptor occupancy.
Given the recent attention paid to the issues of placebo-controlled trials and of psychotomimetic challenge studies in patients with schizophrenia, it was noteworthy that several studies at this meeting provided new data to guide this debate and to inform the field of the relative risks and benefits of these approaches. These studies showed that, in general, drug withdrawal or placebo/medication-free periods did not diminish future drug response. Moreover, it was not possible to predict later treatment response from the level or pattern of symptoms during the placebo phase. Data were also presented on the capacity and process for obtaining informed consent for persons with schizophrenia who participate in clinical trials. The capacity to give informed consent to treatment was enhanced when patients went through an education program before questioning about study participation. This is an important consideration in future discussions on conducting clinical trials.

It was also noteworthy that a special symposium on ethics and schizophrenia research, chaired by Dr. William Carpenter, was held at the Congress. New data from a large survey of patients provided insight into the perceptions of patients of the altruistic value and instillation of hope that comes from participating in research studies. The role of family members in research and the leadership of the National Alliance for the Mentally Ill was also represented and advocated. Dr. David Shore described the fundamental guidance of NIMH and stressed the importance of a balanced viewpoint. These issues are particularly important for the development and testing of newer antipsychotics for which comparative efficacy and tolerability has traditionally been established against both placebo and an active comparator. It was clear that these issues will require ongoing consideration by the psychiatric community and also by the general public.

Cognitive and Social Skills Therapies. Cognitive-behavioral techniques have been shown to be efficacious in the care of patients with chronic psychotic illnesses. New data were presented on the use of cognitive-oriented psychotherapy as a strategy in early intervention and the management of first episode schizophrenia. This approach was noted to be effective for the management of suicidality in young people with first episode schizophrenia. Evidence also showed that use of a technique called “cognitive adaptation training,” which minimizes functional disabilities through attention to environmental cues and by maximizing social supports, may be of benefit to patients with persistent cognitive and skills impairments. It was reported that when social skills training occurs in the patient’s own environment (as opposed to the clinic setting), then generalization and perpetuation of effect beyond the treatment period may occur. However, despite the therapeutic optimism and the intuitive appeal of combining psychological and medication treatments to optimize outcome, results of long-term (one- to two-year) studies where patients received both medication and psychosocial treatments (either family intervention or community skills training) failed to show any interaction or synergy across these combined modalities. It is important to note that these studies typically involved patients who were responders to antipsychotic medications, so that the hypothesis of additive effects of psychosocial interventions may have been less readily testable in these patient samples.

Services Research. The transitioning of institutionalized Department of Veterans Affairs (VA) patients into community services, in the wake of the reorganization of VA services nationally, was reported. These VA programs were cost-effective and showed preliminary evidence of improvements in social and vocational outcomes. Studies also reported on the cost-effectiveness of assertive community treatment (ACT) programs, including a modified ACT program that has been successful in preventing jail recidivism among outpatients with schizophrenia. It was also noted that mental health services differed in their availability and complexity across different cultures. For example, the majority of care for persons with severe mental illness in China was provided in an inpatient setting. Patients are hospitalized for 3 months on average. It was also noted that in this system, only 30 percent of patients with schizophrenia are actually receiving any psychiatric treatment. This may in part explain the reported high rates of suicide among Chinese patients with schizophrenia.

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Appendix. Young Investigator Awards

The following people received Young Investigator Awards at the 1999 ICOSR. Their assistance in reviewing paper presentations at the conference is acknowledged with gratitude.

- Dr. Caleb M. Adler, Department of Psychiatry, University of Cincinnati, Cincinnati, OH
- Dr. Silke J. Bachmann, Psychiatric Hospital/Department of Psychiatry, University of Heidelberg, Heidelberg, Germany
- Dr. Thomas A. Bayer, Department of Psychiatry, University Bonn Medical Center, Bonn, Germany
- Dr. Sabina Berretta, McLean Hospital, Belmont, MA
- Dr. Yue Chen, Psychology Research Laboratory, McLean Hospital/Harvard Medical School, Cambridge, MA
- Dr. Eva W.C. Chow, Schizophrenia Research Program, University of Toronto, Toronto, Ontario, Canada
- Dr. Vivienne A. Curtis, Institute of Psychiatry, Department of Psychological Medicine, London, U.K.
- Dr. Gillian A. Doody, Department of Psychological Medicine, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, U.K.
- Dr. Sharon L. Eastwood, Department of Neuropathology, Radcliffe Infirmary, Oxford, U.K.
- Dr. Igor Elman, Department of Psychiatry, Massachusetts General Hospital, Boston, MA
- Dr. Jennifer R.J. Finkelstein, University of Pennsylvania, Department of Psychology, Pittsburgh, PA
- Dr. Sean W. Flynn, University of British Columbia, Vancouver, British Columbia, Canada
- Dr. Jackie Foong, Institute of Neurology, London, U.K.
- Dr. Fabio Fumagalli, Center of Neupharmacology, Institute of Pharmacological Sciences, Milan, Italy
- Dr. Diane C. Gooding, Department of Psychology, University of Wisconsin–Madison, Madison, WI
- Dr. Leigh A. Holcomb, Central Texas Veterans Health Care System, Neuropsychiatry Research, Temple, TX
- Dr. Louise C. Johns, Department of Clinical Psychology, Research and Teaching Block, West Disbury, Manchester, U.K.
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