Highlights from The Twelfth Biennial International Congress on Schizophrenia Research, San Diego, CA March 28–April 1, 2009

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Abstract

The Twelfth Biennial International Congress on Schizophrenia Research (ICOSR) was held in San Diego, California from March 28 to April 1, 2009. This was the largest Congress meeting to date, with 289 presentations, 825 posters, and 11 workshops that covered all aspects of schizophrenia research. This biennial meeting included approximately 1,140 attendees from approximately 29 countries. This article provides a selected account of the Congress proceedings with a focus on genetics, treatment, cognition, and prevention. Presentations included in the current manuscript were selected based on their apparent relevance and anticipated interest to clinical practitioners. The next ICOSR meeting, occurring in 2011, will be held in Colorado Springs, Colorado.

Introduction

This article provides a selected account of the International Congress on Schizophrenia Research (ICOSR) proceedings with a focus on genetics, treatment, cognition, and prevention. Presentations included in the current manuscript were selected based on their apparent relevance and anticipated interest to clinical practitioners.

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Genetics

Schizophrenia is a complex trait, with complex genetic underpinnings. One guiding genetic hypothesis, the "common disease-common variant" (CDCV) hypothesis, proposes that genetic influences on common complex diseases are due to common polymorphisms in the population. The CDCV hypothesis has guided much of genetic research in complex illness, but has mixed support in the literature (1). The CDCV hypothesis is also the framework for genome-wide association studies. An alternative to the CDCV hypothesis is the multiple rare variant (MRV) hypothesis. The MRV hypothesis posits that there are multiple rare variants that are responsible for the common complex diseases. There are proponents and opponents of both of these hypotheses, and which is the most dominant is study dependent.

Plenary speaker Eichler (2) initiated the ICOSR, raising questions concerning the limits of the CDCV hypothesis. This hypothesis may be somewhat limiting in our quest for the genetic underpinnings of schizophrenia. He suggested

A message from the ICOSR co-founders …

We are delighted that Ms. Trotman and Dr. Miller have provided for readers of ***Clinical Schizophrenia & Related Psychoses*** this detailed synthesis of many of the key research findings from the Twelfth Biennial International Congress on Schizophrenia Research held in San Diego, California, March 28–April 1, 2009. Scientists representing the broad range of disciplines involved with discovery in schizophrenia gathered at the Congress to exchange data, techniques and ideas. Their cutting-edge experimental work stimulated lively discussion and open exchange of ideas toward a better understanding of the neurobiology and treatment of schizophrenia. We were particularly pleased that the Congress also provided a special opportunity for introducing young investigators to the colleagueship of the schizophrenia scientific community. Several of these outstanding researchers, including Dr. Miller, were recipients of Young Investigator Travel Awards sponsored by the National Institute of Mental Health.

Understanding schizophrenia is a leading challenge for medical research today. We are delighted that the Congress plays a formative role in advancing new knowledge concerning this disabling condition. As you read this excellent report, we hope that you share the same excitement that we have concerning our field's development.

Carol Tamminga, MD and Charles Schulz, MD
Co-Founders and Co-Organizers
International Congress on Schizophrenia Research

that genetic mutations (deletions and insertions) that predispose one to schizophrenia are rare, highly penetrant, of recent origin, and likely specific to single cases or families. Other proponents of the MRV hypothesis (3) found new deletions and duplications in only 5% of control participants, but in 15% of individuals with schizophrenia and in 20% of individuals with early-onset schizophrenia. Eichler (2) proposed that recurrent de novo mutations (mutations found in offspring that were not present in either parent) are interspersed across "hotspots" in the genome. In other words, large scale de novo mutations occur disproportionately across regions of the genome (2). De novo mutations were proposed as a potential explanation for unexplained mental retardation. Because these structural variations are rare, much larger study samples, perhaps around 50,000, will likely be necessary to identify additional variants (2).

Other studies in the literature also find increased structural variation among schizophrenia patients. For example, Kirov et al. (4) found that individuals with schizophrenia have 4.53 times more deletions than control subjects. They also have slightly more duplications than controls (OR=1.71). In addition, rare Copy Number Variations (CNVs) not present in control participants were found in schizophrenia patients (4). CNVs are segments of DNA that have been duplicated or deleted. These duplications and deletions vary within the population and can range in size from one kilobase to several megabases. Data from these studies on structural variation do not fit the CDCV hypothesis and, as Eichler (2) emphasized, detecting this variation in the genome will require new techniques with larger samples.

Not only are we potentially faced with multiple rare variants, but it is also evident that there are multiple genetic pathways to schizophrenia. That is, the same phenotype can result from multiple underlying genes. One genetic pathway to psychosis is the 22q deletion syndrome (DS) in which 30% of cases develop psychosis (5). 22qDS is likely the best established genetic finding in schizophrenia (5, 6). However, only approximately 2% of people with schizophrenia have this deletion (6); therefore, there are other genetic pathways to psychosis. In addition, the same underlying genetic variant may lead to multiple phenotypes (i.e., transcend diagnostic categories). For example, Eichler (2) reported that large deletions in 16p11.2 were found in both autism and early-onset schizophrenia. In other words, genetic variants are likely more closely related to a developmental process (e.g., brain development) rather than to specific diagnoses. This would explain why the 16p11.2 deletions are shared between disorders related to aberrant brain function.

Challenges in the study of complex genetic disease including multiple genes, environmental effects, epigenetic effects, and poorly defined phenotypes have contributed to few replications (of modest effect) and to many failed replications. Current diagnostic classification systems do not reflect disease as it exists in nature. For instance, as noted above, genetic variants often bridge across disorders (e.g., diseases related to aberrant brain function). Even with the exponential increase in new genetic techniques, only a small portion of the variance is explained from "risk genes." Further, phenotypic expression can differ to varying degrees among individuals with the same genotype. Ayhan (7) illus-

trates this point in a talk on the Disrupted in Schizophrenia 1 (DISC-1) gene and neurodevelopment. The timing of prenatal developmental perturbations influences the observable phenotype of the mutant DISC-1 genotype. That is, the underlying variation in DNA sequence is the same, but the variable phenotype expression may be influenced by the timing of gene expression.

Endophenotypes

Acknowledgment that genes code for functions and not specific disorders has fueled the endophenotype movement. In addition, genes are pleiotropic and code for multiple endophenotypes. An *endophenotype* as conceptualized by Gottesman and Gould (8) is a vulnerability indicator associated with the illness state that is heritable and independent of acute symptoms. The vulnerability or risk marker must also cosegregate with the illness within families and be present in unaffected relatives at a rate greater than within the general population. The term *endophenotype* is often used interchangeably with the term *intermediate phenotype*. The term *intermediate phenotype* is often used to illustrate the level of analysis of the risk marker between the gene and the disease state. An *intermediate phenotype*, like an endophenotype, is a trait or characteristic of the disease state that is closer to the gene. For simplicity, we will used the term *endophenotype* throughout the current paper.

Endophenotypes provide a portal into underlying neurobiology, neuropsychology, and genetics of schizophrenia. Cognitive impairment, such as working memory impairment, is one example of an endophenotype in schizophrenia (9). Gur (10) discussed neurocognition as an endophenotype in multiplex, multigenerational families and proposed that the same liability that accounts for schizophrenia also accounts for neurocognitive deficits in the disorder. Participants were given the Penn computerized neurocognitive battery (CNB) (11) and results demonstrated that the degree of relation affected performance in unaffected relatives. That is, the more removed an individual was from the affected family member, the less impaired their cognitive function. Given these data, Gur (10) has suggested that children in at-risk samples with the greatest cognitive deficits undergo careful monitoring, as they may be at greatest risk for developing a psychotic disorder. Walters (12) pointed out that studying endophenotypes in patients violates the endophenotype concept (i.e., we should see these characteristics in individuals without the disorder). Schork (13) argued for the use of endophenotypes over single nucleotide polymorphisms (SNPs), highlighting that a strong association with a genetic variant (e.g., an SNP) does not indicate that a variant is a good diagnostic predictor. Kleinman (14) emphasized the use of messenger RNA (responsible for gene expression) as the most proximal endophenotype. He presented data on the expression of GRM3Δ4 and demonstrated that this transcript is more pronounced in the fetal brain and, subsequently, declines across the lifespan. Transcripts found in studies of schizophrenia may have little to do with schizophrenia, but instead be important for brain development. Kleinman (14) also raised the issue of whether we have the right genes/SNPs or endophenotypes.

Endophenotypes have most often been identified as risk markers for illness, but Braff (15) advocated for the endophenotype approach for the identification of protective factors. Perhaps protective genes in unaffected relatives contribute to reduced penetrance in these individuals (15). Endophenotype identification, a point that David Braff (15) raised in his William K. Warren Award presentation, may also contribute to new drugs to target markers impaired in patients and family members.

Medication Adherence and Functional Disability

Antipsychotic medication is central in the treatment of schizophrenia, yet individuals with schizophrenia do not adhere to medication regimens. Functional impairment, one of the most debilitating aspects of schizophrenia, is not improved by antipsychotic medications. In fact, the functional disabilities in schizophrenia further complicate adherence. Researchers have tried various methods for increasing medication adherence (self-report, pill counts, provider reports, blood draws) with limited success. Some methods slightly increase compliance (e.g., blood draws, pill counts), but are cumbersome and not practical for community providers or are prone to bias (e.g., self-report, provider report).

Cognition also plays a role in medication adherence. In fact, there is an association between neurocognitive performance and patient attitudes toward medication adherence (16). Medication adherence is also likely impacted by functional disability and, according to Keefe (17), global cognitive measures are correlated with real-world functioning in schizophrenia patients. Nonetheless, the ecological validity of neuropsychological tests is often questioned. Harvey (18) presented data that suggested that the Wisconsin Card Sorting Task separated employed from unemployed individuals with schizophrenia. Patients also have little insight into their actual ability. For example, data from Harvey (18) illustrated only 4% shared variance between patient self-reported functioning and actual neuropsychological performance. In addition, self-report disability ratings are also not related to real world outcome; thus, Harvey (18) proposes the use of the UCSD performance-based skills assessment (UPSA), an assessment of residential independence.

Prevention

It is now recognized that brain development occurs well into the third decade of life, including the traditional "risk period" for schizophrenia. To target those at greatest risk, researchers have attempted to identify the most relevant risk factors with modest success. In addition to genetic predisposition, researchers have examined cognitive impairment, social adjustment/functioning (19), role functioning, neurohormonal abnormalities, and neurobiological aberrations. Until recently, retrospective investigation has dominated the field, but prospective approaches for identifying individuals at the greatest risk for schizophrenia are increasing. This shift follows the NIMH initiative to target the presymptomatic stage of illness over the next decade.

Social and role functioning as a risk factor for schizophrenia was examined at length during the ICOSR. Addington (20) presented data on premorbid functioning in clinical high-risk (CHR) and first-episode schizophrenia (FES) patients. Similar patterns of premorbid functioning were found in both the CHR and FES samples. As expected, CHR participants with poorer premorbid functioning had poorer cognition and increased prodromal symptoms, but, interestingly, the rate of conversion was not higher among CHR participants with poor premorbid functioning compared to those with good premorbid functioning (20). Also, as expected, CHR and FES participants had better role functioning when compared to a chronic patient group. Addington suggested that perhaps social functioning in CHR participants does not follow the "attenuated" symptom pattern as do other prodromal symptoms in at-risk individuals. Unfortunately, a trial of Cognitive Behavior Therapy (CBT) had no effect on social functioning or negative symptoms.

Two presentations examined the relation between social/role functioning and other risk factors (i.e., cognition and neurohormonal abnormalities). Cadenhead (21) presented data on social/role functioning and neurocognition in the prodrome. Individuals with impaired executive function and elevated disorganized symptoms had greater impairment in social functioning. With regard to work functioning, those with poorer processing speed demonstrated the most impairment. Walker (22) discussed the impact of cortisol on conversion to psychosis and role functioning. There is normal activation of the HPA/HPG axis during adolescence, but data indicated that there were even greater elevations for individuals who converted to psychosis compared to those that did not. Converters also had more impaired role functioning.

Data from high-risk samples indicated a positive association between stressful life events, daily stressors, and plasma cortisol. Garner (23) found that participants closer to conversion had increased pituitary volume. Baseline pituitary volume predicted treatment response in this high-risk sample, as larger pituitary volume was associated with less subsequent symptom improvement. Authors also measured DHEA (a neurosteroid released in response to acute stress) and found symptom improvement related to the change in the cortisol/DHEA ratio. These data support a role for early intervention aimed at stress reduction.

Other well-replicated environmental risk factors include obstetric complications (24), lower premorbid intelligence (25), urban residence (26), and cannabis use (27). Research into relevant risk factors has important implications for understanding the etiopathophysiology of schizophrenia, as well as for prevention through decreased exposure to specific risk factors.

Clarke et al. (28) presented on the relationship between obstetric complications and developmental deficits in patients with schizophrenia, their unaffected siblings, and matched controls. They found that patients with schizophrenia were significantly slower to reach developmental motor milestones in the first year of life compared to their unaffected siblings. Unaffected siblings were slower to reach these milestones than healthy controls. These data support delayed motor development as an endophenotype for schizophrenia. Patients with schizophrenia also had significantly lower Apgar scores than unaffected siblings and controls. There was an additive effect of delayed motor development and low Apgar score on schizophrenia risk.

Khandaker et al. (29) reported data from a population study based meta-analysis of premorbid intelligence and risk for schizophrenia. Data suggest that full-scale, verbal, and performance IQs were significantly lower in cases that later developed schizophrenia. There was no significant difference between premorbid verbal and performance IQ. Risk for schizophrenia increased by 3.7% with each 1-point decrease in IQ. McGrath et al. (30) reported that advanced paternal age, a well-replicated risk factor for schizophrenia, was associated with poorer scores on neurocognitive measures in infancy and childhood in a large birth cohort. Taken together, the study of developmental risk factors continues to be an important area of research, as patients with schizophrenia also have an increased prevalence of other developmental risk factors such as minor physical anomalies and neurological soft signs.

Urban (versus rural) residence has been documented as a risk factor for schizophrenia, but how urbanicity contributes to schizophrenia risk has been less clear. Veling et al. (31) presented data on neighborhood characteristics and the incidence of psychotic disorders. They found a dose-response relationship between neighborhood social disadvantage (composite measure of neighborhood socio-

economic level, residential mobility, population density, voter turnout for local elections, and crime) and risk for psychosis.

Cannabis use is also associated with psychosis. It is unknown whether the association is causal, an effort at "self-medication" in the early phase of illness, or the result of similar underlying mechanisms. Kuepper et al. (32) presented data from an eight-year, prospective, longitudinal, population-based study that demonstrated that cannabis use at the four-year follow-up was associated with increased risk for psychotic symptoms at the eight-year follow-up. These findings remained even when the sample was restricted to baseline cannabis-naive individuals with no previous psychotic experiences. By contrast, four-year follow-up psychotic symptoms did not predict eight-year follow-up cannabis use, challenging a self-medication hypothesis for the association between cannabis and psychosis. Another presentation, from this same cohort, indicated that the effect of cannabis use on risk of psychosis was stronger in participants who grew up in an urban area compared to those who grew up in a rural area, suggesting an interaction between cannabis use and urbanicity (33).

Another presentation examined cannabis and alcohol use using an experienced-sampling method (34). Patients were given personal digital assistants (PDAs) that provided time-stamped, interval reminders. Cannabis use predicted later increases in psychotic symptoms and sadness. Increased anxiety predicted alcohol use, but not cannabis use; and, interestingly, increases in psychotic symptoms predicted decreases in both alcohol and cannabis use. Alcohol use did not predict future mood or psychotic symptoms. Increased anxiety did appear to support a self-medication hypothesis, but these data, like in Kuepper et al. (32), do not suggest a self-medication hypothesis for the association between cannabis and psychotic symptoms.

The pre-schizophrenia/prodromal state is receiving increased attention in recent years, so much so that a new diagnosis is being considered for *DSM-V* (35). McGlashan (35) argued that variables such as current symptoms, risk for getting worse, cognitive impairment, and functional impairment should be considered in a prodromal diagnosis. The data he presented suggested a 40% conversion rate by 2½ years in patients diagnosed as "prodromal" for psychosis. Nonetheless, there continues to be concern about the inclusion of a prodromal category in *DSM-V*. For instance, Yung raised ethical concerns regarding patient care, questioning the reliability and validity of the prodromal diagnosis.

Treatment

Pharmacological

Commonly prescribed antipsychotic medications block dopamine receptors, but dysfunction in the glutamate neurotransmitter system is also linked to schizophrenia. A successful clinical trial in the literature examined the antipsychotic effect of a metabotropic glutamate 2/3 (mGlu2/3) receptor agonist, LY2140023 (36). Kinon (37) presented a replication study and found no significant differences between the four doses of the experimental drug and placebo on any Positive and Negative Symptoms Scale (PANSS) measures. This failed replication was perhaps the most notable finding of the ICOSR. In this trial, the agent LY2140023 was not an effective antipsychotic treatment alone; however, this does not preclude the use of this novel class as an adjunctive agent to first- or second-generation (dopamine receptor antagonist) antipsychotic medications.

Nicotinic acetylcholine receptors are another possible therapeutic target for schizophrenia. Freedman et al. (38) presented data on a Phase 2 clinical trial of DMXB-A, a partial alpha 7-nicotinic agonist, in thirty-one patients. There were no changes in the cognitive performance assessed by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) cognitive battery; however, they reported significant improvement (at the higher dose) on the Scale for the Assessment of Negative Symptoms (SANS) total score, and a trend toward improvement on the Brief Psychiatric Rating Scale (BPRS) total score. According to the authors, the clinical utility of this treatment is not yet determined.

Data on several other adjunctive pharmacologic agents were also presented. Weiser et al. (39) reported that the addition of the NMDA agonist D-serine to antipsychotic medication over a sixteen-week trial showed no significant improvement in PANSS, SANS, or MATRICS cognition scores in chronic schizophrenia patients. There were also three studies of modafinil or its R-enantiomer armodafinil. Freudenreich et al. (40) reported that, in an eight-week study of schizophrenia patients on clozapine, modafinil did not improve negative symptoms, cognition, or fatigue. But there was not worsening of psychotic symptoms. In another study, however, modafinil was found to improve working memory and emotional face recognition in first-episode psychosis (41). Scoriels et al. (41) provided no data on positive or negative symptoms in this sample. Armodafinil also showed no improvement in cognition over a four-week trial (42), but 200 mg/day of armodafinil may improve negative symptoms. In addition, this drug was well-tolerated and did not increase positive symptoms. These findings may warrant further investigation in larger, randomized, controlled trials.

Subotnik et al. (43) presented data from a one-year trial of risperidone consta versus oral risperidone for patients with recent-onset psychosis. Patients treated with risperi-

done consta had lower rates of relapse, increased time to the first relapse, and a higher degree of independent living. This long-acting injectable medication was suggested to improve both clinical outcome and functioning.

Psychosocial Intervention

Psychosocial interventions are a cornerstone of the comprehensive treatment of patients with schizophrenia, and combined psychosocial and pharmacological treatment is more effective than antipsychotic medications alone.

The recovery model is currently transforming the delivery of mental health services. Certified peer specialists (CPS) are an integral component of the recovery model. A CPS is a licensed professional who has progressed in his or her own recovery from mental illness and works to assist other mental health consumers in regaining control over their own lives and their own recovery process. A CPS provides peer-support services, serves as a consumer advocate, is a resource for psychoeducation, and offers the unique perspective of his or her individual experiences. Additional information about CPS services can be accessed at websites from the Georgia Certified Peer Specialist Project (www.gacps.org) and the National Alliance on Mental Illness (www.nami.org). A CPS from the Medical College of Georgia (MCG), one of the first academic institutions in the United States with a CPS on staff, presented data from a recovery-based education program at MCG (44). Results from this recovery-based education program indicated significant improvement in clinicians' recovery-based knowledge and their recovery-consistent attitudes (44).

Antipsychotic medications as a class are associated with weight gain and an increased risk of the metabolic syndrome, a risk factor for cardiovascular disease. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, over 40% of patients met the criteria for the metabolic syndrome at baseline (45). De Hert et al. (46) presented data from a European epidemiological study of metabolic disorders in patients on second-generation antipsychotics and found, similar to the CATIE trial, a 34% prevalence of the metabolic syndrome. Even more startling was the high prevalence of *untreated* elevated glucose (26%), dyslipidemia (68%), and hypertension (38%), highlighting the need for better monitoring and treatment of the metabolic syndrome.

Interventions to address obesity and the metabolic syndrome were also examined at the ICOSR. Attux et al. (47) presented data from the Brazilian Wellness Program, a nationwide, twelve-week, one-hour group intervention. Authors reported significant improvements in weight, body mass index (BMI), diastolic blood pressure, and physical activity. Similarly, Erickson et al. (48) presented data from a year-long psychoeducational intervention for obesity. Patients randomized to the intervention *lost* an average of 0.13 lbs. per week, while those randomized to usual care *gained* 0.1 lbs. per week over the course of the study. Ganguli and Brar (49) presented two-year follow-up data from participants who had previously participated in a clinical trial of weight reduction in schizophrenia. Participants who received individual "booster sessions" every other week for two years gained significantly less weight during the follow-up period (4.8 versus 13.9 lbs.). After the intervention, participants weighed 6 lbs. *less* than at study entry, whereas control participants weighed 5.3 lbs. *more*. Taken together, results suggest that psychoeducational interventions can result in sustained improvements in the adverse metabolic side effects of medications.

Conclusions

The current article reviewed selected presentations from the 12th International Congress on Schizophrenia Research. Congress presentations covered schizophrenia genetics, including investigations of rare structural variants, multiple genetic pathways, pleiotropic effects, and endophenotypes in schizophrenia. Studies on risk for schizophrenia have become a new focus and this was evident by the number of presentations in this area at the Congress. Also evident at the Congress was the drive for discovering new drug therapies to treat adjunctive problems in schizophrenia that have not responded to traditional dopamine blocking medications. The importance of psychoeducation for schizophrenia patients was emphasized, particularly as a treatment for medication side effects. Also propelling the field forward is the recovery model, which has made inroads in how both providers and consumers think about severe mental illness.

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