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An Update on the Epidemiology of Schizophrenia with a Special Reference to Clinically Important Risk Factors

Ahmed El-Missiry · Ahmed Sayed Aboraya · Hader Manseur · Johnna Manchester · Cheryl France · Katherine Border

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Abstract Schizophrenia is a chronic mental illness which poses a tremendous burden on the families, caregivers and the society. The purpose of this paper is to provide an updated review of the epidemiology of schizophrenia with a special attention to the clinically important risk factors such as drug abuse, hormonal factors and the new advances in genetic research. The authors reviewed the literature with a special focus to the recent papers published from January 1970 to present. The prevalence of schizophrenia varied by ten-fold and the incidence of schizophrenia varied by five-fold among different studies. Significant advances in genetic research and DNA technology have been achieved over the past two decades and suggested substantial genetic etiology of schizophrenia. Extensive studies have been done with many variations in the prevalence, incidence and risk factors of schizophrenia among different studies.

Keywords Schizophrenia · Dementia praecox · Prevalence · Incidence · Epidemiology

Psychoses are major and prevalent mental illnesses with a heterogeneous nature that are associated with high morbidity and mortality. From the time the term "psychosis" was coined in 1845 (Beer 1996) to the present day it has posed an epidemiological enigma. Any epidemiological research depends on a stable concept and a consensual operational definition. Unfortunately this is not the case when it comes to psychosis. On one hand, the core concept of psychosis has never been static and has changed in the context in which it has been employed according to different social, philosophical, and ideological influences (Beer 1995; Heinimaa 2000; Janzarik 2003). Moreover, there is no consensus on the extent of the concept (Janzarik 2003). It ranges from a dimensional unitary approach to a multiple categorical approach (Crow 1995; Peralta and Cuesta 2003; Peralta et al. 2002; van Os et al. 1999). On the other hand, the term "psychosis" in itself is exceedingly hard to define and the different attempts at its definitions never achieved universal acceptance (American Psychiatric Association 2000; WHO 1993). Operational definitions themselves can be

A. El-Missiry · A. S. Aboraya (✉) · H. Manseur · J. Manchester · C. France · K. Border
West Virginia University School of Medicine, Morgantown, WV, USA
e-mail: aaboraya@hsc.wvu.edu

narrowed to encompass only delusions and hallucinations, slightly broadened to include insight and a loss of contact with reality and disorganization syndrome, even extended to include functional impairment and prognosis (American Psychiatric Association 2000). Hence, it appears that the concept and definition of psychosis is like a concertina expanding and retracting to include or exclude psychopathological phenomena as well as mental disorders themselves. The instability of the concept and variance in definitions can paint an unclear and hazy picture for the epidemiology of psychosis, and hence a step-down approach to concentrate on a major psychotic disorder such as schizophrenia can be more effective in highlighting some of the most important epidemiological aspects in psychosis.

Historical Perspective and Assessment of Schizophrenia

Schizophrenia and other psychotic disorders have been recognized in almost all cultures and described throughout much of recorded time (Andreasen and Black 2001). Emil Kraepelin, a famous German psychiatrist at the turn of the 20th century, observed patients with psychosis and mood symptoms over many years. Kraepelin observed a group of patients who developed the illness early in life (praecox) and had a chronic and deteriorating course (dementia), and he used the term dementia praecox for this illness (now called schizophrenia). Kraepelin also observed another group of patients who developed the illness later and had a more episodic course, and used the term manic-depression for this illness (now called bipolar). Dementia praecox was eventually renamed schizophrenia by Eugene Bleuler, which means a splitting of the psychic processes (thought, emotion and behavior). Bleuler described primary symptoms of schizophrenia (the four A's): affective blunting, disturbance of association (i.e., fragmented thinking), ambivalence (i.e. fragmented emotional responses) and autism. Bleuler described delusions and hallucination as secondary symptoms of schizophrenia. The current diagnosis of schizophrenia according to the DSM-IV and DSM-IV-TR requires two or more of psychotic symptoms (delusions, hallucinations, disorganized thoughts, disorganized behavior, catatonia or negative symptoms), deterioration in social, occupational, or interpersonal relationship, and continuous signs of the disturbance for at least 6 months. In addition, for a diagnosis of schizophrenia, schizoaffective disorder and mood disorder with psychosis must be ruled out, and the disturbance must not be due to the direct physiological effects of a substance or a general medical condition (American Psychiatric Association 1994; American Psychiatric Association 2000).

During the first half of the twentieth century and due to the influence of psychoanalysis, many psychiatrists were not very interested in making diagnoses and did not have the adequate tools to do so had they had the interest. Beginning in the 1950s, clinicians started to diagnose psychiatric disorders more often. However, the unreliability of psychiatrists' diagnoses was a serious problem (Spitzer and Fleiss 1974; Star 1950). Psychiatrists in the U.S. diagnosed schizophrenia among hospitalized patients almost twice as frequently as their counterparts in the U.K. This prompted the United States-United Kingdom (US-UK) diagnostic study to investigate the differences in the rates between schizophrenia and manic depressive disorder in the United States and United Kingdom (Cooper et al. 1972). In this study, psychiatrists from both countries had similar training in a structured interview, the Present State Examination (PSE) and applied the same diagnostic criteria. The results showed that the rates of US and UK patients with schizophrenia and manic depression were the same. The study concluded that the differences in the rate were due to the differences in the diagnostic practices between the psychiatrists across the Atlantic rather than of true differences in morbidity patterns between both countries.

The unreliability of psychiatrists' diagnoses resulted in two important developments in psychiatric epidemiology; first the development of diagnostic criteria and second the development of structured interviews (Aboraya et al. 2006). Efforts to develop diagnostic criteria are attributed to the World Health Organization (WHO) and the American Psychiatric Association (APA). The World Health Organization (WHO) published the sixth revision of the International Classification of Diseases (ICD-6) in 1948, which included a mental disorders section (WHO 1948). Several publications of the International Classification of Diseases (ICD) followed and the latest is the tenth edition published in 1992 (WHO 1992). In the USA, the American Psychiatric Association Committee on Nomenclature and Statistics developed and published in 1952 the first edition of the Diagnostic and Statistical Manual: Mental Disorders (DSM-I) (American Psychiatric Association 1952). Several publications followed and the latest is the fourth edition of the DSM, Textbook Revision, published in 2000 (American Psychiatric Association 2000). The use of diagnostic criteria of mental disorders removes an important source of unreliability (Grove et al. 1981).

Structured interviews were developed to provide explicit rules in psychiatric assessment and to avoid ambiguity. Structured interviews standardize how to ask questions, how to skip or follow on different areas of psychopathology and how to rate the severity and the causes of symptoms. Structured interviews minimize the variability among the interviewers, prevent unexplained decisions and consequently improve the reliability of the diagnosis. Two structured interviews are widely used: the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (Spitzer et al. 1992; Wing et al. 1990).

Community surveys of psychiatric disorders in the community usually require a large sample size to meet the adequate power of the study. In addition, community surveys involve interviewing a large number of normal individuals. The use of psychiatrists in community interviewing is very expensive and impractical. To overcome this problem, investigators developed structured interviews designed to be used by lay interviewers who are not clinicians or psychiatrists. Typically, a lay interviewer is college level undergraduate who receives few days of training with the specific instrument. The Diagnostic Interview Schedule (DIS) was developed and used in the Epidemiological Catchment Area (ECA) survey in the U.S. in 1980–1982 (Robins et al. 1981). The Composite International Diagnostic Interview (CIDI) is another structured interview based on the DIS and is designed to be used by trained lay interviewers (Robins et al. 1988; World Health Organization (WHO) 1990). Other screening instruments were developed and are available such as the psychiatric epidemiology research interview (PERI) (Dohrenwend et al. 1986) and General Health Questionnaire (GHQ) (Goldberg and Williams 1991; Goldberg 1972). Typically, lay interviewers screen patients in the first phase of the study. Respondents who score positively in the first phase are re-interviewed again in the second phase of the study by clinicians using the clinical skills and more detailed structured interviews.

Materials and Methods

Computerized literature searches were conducted using MEDLINE and PsychINFO. Searches were conducted using entries from January, 1970 to December 2008 that were published in English. Table 1 summarizes the results of searches.

Additionally, relevant references attached to published papers were also reviewed while the authors identified more papers and books through consultations with colleagues and

Table 1 Literature Search Results from January 1970 to December 2008 Published in English Using Medline and PsychINFO Databases

Database	Search words	Number of citations
Medline	Incidence of schizophrenia	117
PsychINFO	Incidence of schizophrenia	111
Medline	Prevalence of schizophrenia	153
PsychINFO	Prevalence of schizophrenia	156
Medline	Cannabis and schizophrenia	83
PsychINFO	Cannabis and schizophrenia	65
Medline	Amphetamine and schizophrenia	52
PsychINFO	Amphetamine and schizophrenia	39
Medline	Estrogen and schizophrenia	20
PsychINFO	Estrogen and schizophrenia	28
Medline	Genetics and schizophrenia	164
PsychINFO	Genetics and schizophrenia	523

experts in the field. The authors were looking for updated information on the prevalence and incidence of schizophrenia. The authors were also looking for clinically important risk factors such as drug abuse, hormonal factors and the new discoveries in genetic research.

Results

Prevalence of Schizophrenia

The prevalence of schizophrenia varies by ten-fold among different studies world-wide (Eaton 1985). The reasons for the variation include the study design, the measuring instruments, the type and training of interviewers, the sampling method and the population under study. Table 2 compares the design, the measuring instrument and the resulting prevalence rates of four important studies on schizophrenia.

Two recent methodologically sound systematic reviews were published about the prevalence of schizophrenia across different countries. Goldner et al. reviewed 18 prevalence studies and reported estimated pooled rates of 0.34% for 1-year and 0.55% for lifetime prevalence (Goldner et al. 2002). The same study also confirmed that prevalence may vary greatly from country to country and the Asian populations may have lower prevalence rates of schizophrenia. More recently, Saha et al. analyzed a total of 1,721 prevalence estimates from 188 studies drawn from 46 countries. They reported point, period, lifetime, and lifetime morbid risk per 1,000 persons to be 4.6 (1.9–10.0), 3.3 (1.3–8.2), 4.0 (1.6–12.1), and 7.2 (3.1–27.1), respectively (Saha et al. 2005). They noted by analyzing 15 migrant studies that the prevalence of schizophrenia in migrants was higher compared to native-born individuals: the migrant-to-native-born ratio was 1.8 (0.9–6.4). Interestingly, when they grouped countries by economic status, prevalence estimates from "least developed" countries were significantly lower than those from both "emerging" and "developed" sites ($p = 0.04$). This finding should be interpreted with caution because of different factors. First as the authors quoted it is difficult to use of a single economic variable to assess a complex and multidimensional concept. Second, there is a cross cultural difference in features of schizophrenia and the perception of recovery and other factors that

Table 2 Prevalence Studies of Schizophrenia

Study Reference	Design of the Study	Measurement Instrument	Prevalence %
(Myers and Weissman 1986)	Community study of treated and untreated persons	-RDC criteria and SADS structured interview were used -College and graduate-level interviewers with 3 month training on SADS and RDC	Point Prevalence=0.4
(Myers et al. 1984)	Epidemiological Catchment Area (ECA) survey	Lay interviewers using DIS	Six-month prevalence: New Haven, Conn. =1.1 Baltimore=1.2 St. Louis=0.6
(Levav et al. 1993)	-Survey of a ten-year birth cohort born in Israel between 1949–1958 -Two phase study with screening phase followed by psychiatrist evaluation phase	Psychiatric Epidemiology Research Interview (PERI) for phase one and SADS for phase two	Six-month prevalence=0.69
(Kessler et al. 1994)	Community survey of a national probability sample in USA	-Lay interviewers using CIDI -Respondents with psychotic symptoms were reinterviewed by clinician using SCID	12 month prevalence of Psychosis=0.5 Lifetime rate for schizophrenia=0.14

can shape the course of illness which can in turn influence prevalence rates. Third, there were only 19 estimates from least developed countries as compared to 22 from emerging countries, and 96 from developed countries, which may skew the data especially with report of the authors that higher quality score studies, which are more likely to be found in developed countries' studies, had significantly higher prevalence estimates ($p = 0.02$). Therefore, the findings can be only interpreted as a statistical variation rather that an evidence to reinforce that prevalence rates are directly related to the economic status of the countries.

Incidence of Schizophrenia

Studies on the incidence of schizophrenia also show different rates depending upon the study design, the measuring instruments, the type and training of interviewers, the sampling method and the population under study. Table 3 shows the incidence rate of schizophrenia from several studies across the globe. Overall, the incidence rate is, at least, less than one-tenth that of the prevalence rate (i.e., less than 1 per 1,000) (Eaton 1985).

The landmark study on incidence of schizophrenia was the WHO ten-country study (Jablensky 2000; Jablensky et al. 1992; Sartorius et al. 1986) which employed both narrow and broad diagnostic criteria uniformly across sites. The incidence ranged from 2 to 14 per 100,000 when narrow criteria for schizophrenia were used (CATEGO S+), and 9 to 42 per 100,000 when the ICD9 criteria for schizophrenia were used. The study results suggested

Table 3 Incidence Studies of Schizophrenia

Place	Study Reference	Year	Crude annual rate / 1,000
England (London)	(Castle et al. 1991)	1965–1984	0.25 (ICD criteria)
England (Nottingham)	(Brewin et al. 1997)	1978–1980	0.14 (ICD criteria)
		1992–1994	0.09 (ICD criteria)
Canada	(Nicole et al. 1992)	1983–1987	0.31 (ICD criteria)
England (Salford)	(Bamrah et al. 1991)	1984	0.11
India (Madras)	(Rajkumar et al. 1993)	1987–1988	0.41
Canada	(Bray et al. 2006)	1989	0.77 for females
		1998	0.90 for females
		1989	0.67 for males
		1998	1.2 for males
Taiwan	(Chien et al. 2004)	1997	0.95
		2001	0.45

that the incidence of schizophrenia is very similar in the different populations. In a recent systematic review of incidence studies from 33 countries by McGrath (2004), the median value of incidence rates was 15.2 (7.7–43.0) per 100,000. The distribution of rates in this review was asymmetric and interpreted as a possible variation in the incidence of schizophrenia. Finally, while some recent studies have suggested that the incidence rates of schizophrenia across time are in decline (Chien et al. 2004; Nicole et al. 1992; Suvisaari et al. 1999; Takei et al. 1996), more recent studies in London and Canada have shown an increase in the incidence rates of schizophrenia across time (Boydell et al. 2003; Bray et al. 2006).

Risk Factors of Schizophrenia

Age, Gender and Estrogen Hypothesis

Schizophrenia affects males and females with equal incidence and prevalence (Saha et al. 2005; Seeman 1982). This consensus has been challenged by some authors suggesting higher incidence risk in males. Aleman et al (2003) reported in a systematic review that males tended to have a higher incidence risk ratio that ranged between 1.42 (95%CI, 1.30–1.56) and 1.31 (95% CI, 1.13–1.51). They noted that the sex difference was less in studies before 1980 and in studies from developing countries. McGrath et al (2004) in another systematic review also reported higher male: female risk ratio of 1.40 (1.1–1.8). Recently published Data by Thorup et al using the Danish register suggested that incidence rates for males exceeded those for females (Thorup et al. 2007).

Studies on the peak age of onset reveal a peak for men is between age 15 and 25 followed by a steady decline and for women there is a broader peak between 25 and 35 (Hafner et al. 1998a, b; Kaplan and Sadock 1991). Although schizophrenia appears to start later in females, there is a second smaller peak of increased incidence between the age 45–49 in females (Hafner et al. 1989, 1998a, b). Castle and Murray (1993) had similar results, but suggested another peak in females over-65 years.

Many of the studies on gender differences investigated the age at first hospitalization. However, the time of first hospitalization for schizophrenia overlaps with the relatives'

perception of the time of onset of symptoms (Kramer 1978). Hafner found a mean difference of 5–6 years in age at first hospitalization between males and females in Danish and German populations with males hospitalized earlier (Hafner et al. 1989). Similarly, data on first admission rates for schizophrenia in England in 1984 showed that male to female ratio peaks at 2.1:1 in the 20–24-year age group, reaches unity at around the age of 40, and declines to 0.6:1 at around 65 years (Castle and Murray 1993). In Canada, male: female ratio in the over-40 group is 3:5 (Bland 1977). Overall, the incidence of schizophrenia in the 40–60 age group is about double in women compared with men (Riecher-Rossler 2002).

In addition to the late onset of schizophrenia in females, the severity of symptoms and the course of illness are milder in females. They consistently show better functioning over time, more frequent periods of good functioning and periods of recovery, less likelihood of uniformly poor outcome, and fewer and shorter rehospitalizations (Grossman et al. 2006). Goldstein followed 90 patients for 10 years and found that females have fewer rehospitalizations and shorter stays than men (Goldstein 1988). Moreover, female patients respond better to neuroleptic treatment. Female patients between ages 20–40 require lower doses of neuroleptics than older females and males of the same age group (Seeman 1983). In a comprehensive review of the literature on gender differences in schizophrenia between 1966–1999, Leung found that male patients have earlier onset, more negative symptoms, more cognitive deficits, poorer premorbid functioning and poorer response to antipsychotic medications (Leung and Chue 2000). There is extensive evidence that males display more negative symptoms (Goldstein and Link 1988; Ring et al. 1991; Schultz et al. 1997). However, in general, the positive symptoms appear to be of equal distribution between the two genders (Shtasel et al. 1992).

Riecher-Rossler and Hafner proposed the estrogen protection hypothesis that estrogens exert a protective effect in schizophrenia (Riecher-Rossler and Hafner 1993). Other studies have shown the protective effect of estrogens (Cho et al. 2003; Garcia-Segura et al. 2001; Grigoriadis and Seeman 2002; Hochman and Lewine 2004; Kolsch and Rao 2002). Estrogen has an antidopaminergic effect (Di Paolo et al. 1979; Dufy et al. 1979; Schaeffer and Hsueh 1979). The estrogen hypothesis provides an excellent explanation for epidemiological and clinical research findings. The estrogen hypothesis can explain why females have delayed onset, less severe symptoms, better treatment response and better course of illness. The estrogen deficiency after age of 40–45 can also explain why females have second peri- menopausal peak onset (Hafner et al. 1989) and that symptoms severity increase with age only in females (Seeman 1998). Psychotic symptoms ameliorate during pregnancy when estrogen blood concentrations are high, but worsen during physiological states such as the postpartum period, the perimenstrual period, or menopause, when estrogen blood concentrations are low (Hallonquist et al. 1993; Riecher-Rossler 2002). Exacerbation of psychotic symptoms have been noted for female schizophrenic patients during the low-estrogen phases of menstrual cycle (Endo et al. 1978; Hallonquist et al. 1993). Estrogen supplementation have been shown to ameliorate psychotic symptoms in some female patients (Korhonen et al. 1995; Kulkarni et al. 2001). Some patients with postpartum psychosis were successfully treated with estrogen (Ahokas et al. 2000). Riecher-Rossler studied the relationship between estradiol levels and psychopathology in 32 patients and found that psychopathology as measured by BPRS improves as estradiol level increases (Riecher-Rossler et al. 1994).

Pregnancy and birth complications Abnormalities of pregnancy, delivery and neonatal period can cause brain structural changes and increase the risk of neurological and psychiatric disorders. For schizophrenia, there is ample of evidence that pregnancy and

birth complications (PBC) increase the risk of schizophrenia. In a meta-analysis of 18 studies, Geddes and Lawrie found that subjects exposed to obstetric complications of any kind are twice as likely to develop schizophrenia (Geddes and Lawrie 1995). Jones et al. followed 1966 birth cohort in North Finland and identified individuals who later developed schizophrenia by the age of 28. Compared to the control group, low birth weight (<2500 g) and the combination of low birth weight and short gestation (<37 weeks) were more common among schizophrenic subjects. In addition, severe perinatal brain damage increase the risk of schizophrenia (odds ratio 6.9 and 95% confidence interval is 2.9–16.3) (Jones et al. 1998). Another birth cohort study in Sweden supports the theory of an association between three obstetric complications (malnutrition during fetal life, prematurity and hypoxia) and schizophrenia. Although preeclampsia was the only significant risk factor, there was evidence of increased risk associated with all three etiologic mechanisms (Dalman et al. 1999). Another study by Kendell et al. showed that pregnancy and birth complications (PBC), especially pre-eclampsia and infants detained for neonatal care, were common among schizophrenic patients compared to controls (Kendell et al. 1996). An interesting link was found between prenatal nutritional deficiency and increased risk for schizophrenia (Susser et al. 1996).

Obstetric complications can also decrease the age at first presentation of schizophrenia (Verdoux et al. 1997a). Another study showed that obstetric complications decrease age at first presentation of schizophrenia in a dose response relationship (Kelly et al. 2004). Other studies did not find this relationship (Nicolson et al. 1999).

Socioeconomic Position (SEP)

Measures of socioeconomic position (SEP), including education and income, have shown consistent inverse relationship between SEP and schizophrenia for decades (Dohrenwend and Dohrenwend 1969; Hollingshead and Redlich 1958). Eaton had two reviews which showed a higher risk of schizophrenia for those with lower SEP (Eaton and Harrison 2001; Eaton 1974). A recent Danish national register based study showed that the risk of schizophrenia was associated with unemployment, low educational attainment, being single, lower wealth status and lower income (Byrne et al. 2004).

Two hypotheses can explain this consistent phenomenon. The first hypothesis is that environmental hazards, stress, infection and poor obstetric care associated with lower SEP increase the risk of schizophrenia. The second hypothesis is selection-drift hypothesis. The selection component (intergenerational) refers to the patients' inability to attain their parents' social class. This is because the insidious onset of schizophrenia in adolescence prevents patients from learning social and educational skills they need to achieve their parents' social class. The drift component (intra-generational) refers to the patients' drift to lower class after symptoms appear. Given that schizophrenia is heterogeneous disorder; both hypotheses play parts in explaining this phenomenon.

Viral Hypothesis

The hypothesis that schizophrenia is caused by an infectious agent, probably a virus, occurring either in utero or at any time up to the age of onset has been the focus of research over many decades (Torrey 1988). Several studies were conducted to prove the viral etiology of schizophrenia using direct measures (e.g. detection of viral antigen or antibodies) or indirect measures (seasonality or schizophrenic births or prevalent studies). Following the influenza pandemic and subsequent outbreak of Von Economo's encephalitis

after World War I, many post encephalitic patients were observed with signs and symptoms of schizophrenia. Another similar link was found between 1957 pandemic of A2 influenza in England and an increase in births of individuals who have been subsequently diagnosed with schizophrenia (O'Callaghan et al. 1991). However, the results of these studies are inconclusive.

Season of Birth

A robust finding in epidemiology of schizophrenia is that people who later have schizophrenia are more likely to have been born in the winter and early spring (Kaplan and Sadock 1998). The excess in winter-spring births of those who are later diagnosed with schizophrenia has been clearly established in many studies in the Northern Hemisphere (Torrey et al. 1988). In the Southern Hemisphere, this finding is variable and weaker compared to the Northern Hemisphere (McGrath and Welham 1999). Several factors have been suggested to explain this finding such as viruses, perinatal trauma, toxins, malnutrition or a combination of these factors. In a large cohort of Swedish males and females born between 1973 and 1980, Fouskakis et al found modest non-significant increased risk of schizophrenia among winter births (Fouskakis et al. 2004). This modest increase of winter births of schizophrenia did not appear to be confounded by birth-related exposures. Another study by Verdoux et al found that 20% excess of winter births (January–March) was found among patients born in highly densely populated areas (>136 inhabitant/km2) (Verdoux et al. 1997b). These results suggest that seasonal early environmental risk factor(s) linked to schizophrenia predominantly operate in urban areas.

Substance Abuse

Alcohol and drug abuse are common problems among individuals with schizophrenia. The prevalence of illicit drug use in persons with schizophrenia is greater than in the general population. The Epidemiological Catchment Area (ECA) study found that 47% of individuals with schizophrenia have or have had an alcohol or illicit drug use disorder during their lifetime (Regier et al. 1990), which is about four times higher than the prevalence of such disorders in a non-schizophrenic population (Mueser et al. 1992). There are various accounts for why individuals with schizophrenia have such high rates of substance abuse, but the topic remains controversial and largely unresolved due to the retrospective nature of the preponderance of such research.

The controversy about the high prevalence of substance abuse disorders in schizophrenic individuals stems from researchers having difficulty determining whether the substance use increases the risk for developing schizophrenia or if those who have schizophrenia are more likely to abuse substances (Bowers et al. 2001). While some research indicates that substance abuse increases the risk of developing schizophrenia (Buhler et al. 2002; Weiser et al. 2003), other researchers posit that individuals use illicit substances to self-medicate symptoms that precede early symptoms of impending psychosis (e.g., depression) or that both the substance abuse and schizophrenia can be explained by some premorbid common factor (Mueser et al. 1992). Despite the heuristic appeal of such interpretations, no conclusive evidence has been established to either confirm or refute these ideas. The majority of the literature addressing the link between schizophrenia and substance abuse concerns the use of marijuana and stimulants such as amphetamine and methamphetamine. The literature regarding the use of these substances in relation to schizophrenia will be reviewed in the following sections.

Marijuana

Marijuana is one of the most commonly cited drugs of abuse for individuals with a diagnosis of schizophrenia (Hambrecht and Hafner 2000). The onset of marijuana use may precede, follow, or co-occur with the onset of schizophrenia (Bowers et al. 2001), thus creating controversy among the several theories regarding the relation between marijuana use and schizophrenia. Three explanatory theories that have been identified in the research are: 1) Marijuana use increases the likelihood of later development of schizophrenia (Leweke et al. 2004; Smit et al. 2004; Zammit et al. 2002), 2) Marijuana use is a stress factor that can cause schizophrenia only in an individual who is vulnerable to develop it (Leweke et al. 2004; Mueser et al. 1992) and 3) Marijuana is used to self-medicate the prodromal and/or negative symptoms of schizophrenia (Green 2000; Hambrecht and Hafner 2000).

Theory 1: Data from a Swedish study have shown a dose-dependent relative risk for developing schizophrenia in healthy individuals who used marijuana more than 50 times (Leweke et al. 2004; Zammit et al. 2002). A New Zealand study revealed that using marijuana prior to age 15 increased the likelihood of experiencing symptoms of schizophrenia in adulthood. Based on these findings, authors conclude that cannabis use increases the risk of the incidence of psychosis in individuals who were previously psychosis-free (Arseneault et al. 2002; van Os et al. 2002). After reviewing the literature, Smit, Bolier, and Cuijpers (Smit et al. 2004) similarly conclude that cannabis use doubles the risk of becoming schizophrenic and that the risk is increased when greater amounts of marijuana are used.

Theory 2: Some researchers have suggested that rather than causing schizophrenia, marijuana use may trigger schizophrenia in individuals who were already destined or prone to develop a psychotic illness. This is difficult to illustrate, however, as one cannot determine which individuals are destined to become psychotic in their later lives. This 'vulnerability theory' is supported by newer neurobiological findings (Leweke et al. 2004). Other support for this theory comes from studies illustrating that marijuana use is associated with a more abrupt onset of psychiatric symptoms and an earlier age of onset of psychosis (Bowers et al. 2001; Veen et al. 2004). One significant conclusion from a recent literature review on the topic is that marijuana use more than doubles the risk of becoming schizophrenia in vulnerable populations (Smit et al. 2004).

Theory 3: The self-medication theory posits that individuals experiencing prodromal signs of schizophrenia (prior to the first psychotic break) may use marijuana in attempt to alleviate those symptoms. This "reversed causality" hypothesis suggests that it is the schizophrenia that causes the marijuana abuse rather than the other way around (Smit et al. 2004). It has also been suggested that some individuals with active symptoms of schizophrenia may use marijuana to alleviate distressing negative symptoms (Hambrecht and Hafner 2000) or to cope with side effects related to treatment with antipsychotic medications (Green 2000).

Amphetamine/Methamphetamine

Amphetamine use has been established to produce psychotic symptoms associated with paranoid schizophrenia (i.e., delusions of a persecutory nature and hallucinations) in people

without history of mental illness (Bowers et al. 2001). These psychotic symptoms generally clear within several days to a week of cessation of amphetamine use, however, some evidence from animal studies suggests that methamphetamine psychosis may lead to a chronic syndrome that more closely resembles schizophrenia (Bowers et al. 2001; Yui et al. 2000). One study reported that the paranoid-hallucinatory state persists after the drug wears off, is indistinguishable from paranoid schizophrenia, and that individuals with a history of methamphetamine psychosis undergo spontaneous recurrence of their paranoid-hallucinatory states in response to stress (Yui et al. 2000). There is evidence that chronic relapsing psychosis may result from methamphetamine abuse in some healthy humans, yet the psychosis is characterized by persistent positive symptoms and significantly fewer negative symptoms than typically seen in a schizophrenic individual. It remains unclear whether this persistent psychosis represents an activation of underlying schizophrenia or if it should be classified as a separate disorder, similar to schizophrenia, that is induced by amphetamine use. Although there is no direct evidence from studies that amphetamine use leads to schizophrenia, some researchers have asserted that there is compelling evidence that stimulant abuse can precipitate the onset of schizophrenia at an earlier age in biologically vulnerable people (Mueser et al. 1992).

In conclusion, a review of the research indicates that substance use can clearly alter the course of schizophrenia by increasing the severity of symptoms and eliciting relapse in individuals with psychotic disorders (Leweke et al. 2004; Swofford et al. 2000). Schizophrenic patients with a history of marijuana abuse are generally younger when they are first admitted to hospitals and tend to have more admissions to hospitals than schizophrenic patients who are not marijuana users (Isaac et al. 2005). Poorer prognosis, higher reality distortion and more positive symptomatology are also characteristic of substance-using patients with schizophrenia (Baker et al. 2005; Hambrecht and Hafner 2000). In a study comparing substance-using patients with schizophrenia to their non-substance using counterparts, Swofford et al. (Swofford et al. 2000) found that the substance users had significantly higher severity of illness scores on the Brief Psychiatric Rating Scale (BPRS), reported twice as many hospitalizations, and had a greater rate of missed appointments.

Many questions remain unanswered about the nature of the relation between substance use and schizophrenia, but this is an area of concern due to the high incidence of substance use disorders in this population. Use of marijuana and stimulants can induce transient psychotic reactions lasting the duration of and sometimes longer than the intoxication period of the substance. These psychoses tend to mimic the positive symptoms of paranoid schizophrenia such as paranoia, delusions, and hallucinations, and are not generally associated with the negative symptoms. A look at the research reveals controversy regarding the possibility that substance use can induce schizophrenia in an otherwise healthy individual. A commonly cited notion is that drug abuse may precipitate schizophrenia in vulnerable individuals or create a separate substance-specific psychosis, but there is currently little evidence supporting the idea that drug use actually causes schizophrenia (Swofford et al. 2000). There is, however, little question that substance use is associated with a more malignant course of the illness (Mueser et al. 1992), and is therefore a significant concern given the increasing number of dually-diagnosed individuals.

Genetics

The past two decades have witnessed scientific advances in genetic research and DNA technology. First, through a large number of twin, family and adoption studies, it has been demonstrated conclusively that genetic factors play a significant etiologic role in

schizophrenia (Kety et al. 1994). Compared to ~1% lifetime risk of developing schizophrenia in the general population, first cousins of schizophrenics have ~2% risk whereas siblings of patients have ~9% risk. Individuals with both an affected sibling and parent have ~16% risk (Gottesman and Shields 1982). The heritability, defined as the proportion of population variance in a trait that can be ascribed to genetic factors, of schizophrenia is relatively high (~80%) suggesting a substantial genetic etiology (Cardno and Gottesman 2000; Sullivan et al. 2003).

However, identifying susceptibility genes has proven to be difficult primarily because schizophrenia is not inherited in a simple Mendelian manner (McGue et al. 1983). Moreover, the presence of non-genetic risk factors is also difficult to unravel. Another obstacle is that schizophrenia is diagnosed based on history and clinical examination in the absence of investigations to confirm diagnosis or to aid in sub-classifying the disorder (McGuffin et al. 1987). The mode of inheritance is complex like cancer, diabetes and heart diseases and it involves interaction among multiple genes and environmental factors (Risch 1990). In this polygenic model, multiple risk genes of small effect are acting additively or multiplicatively (Gottesman and Shields 1967). Because non-genetic etiological factors are obscure, genetic investigations may hold the key to understanding etiology.

Linkage Studies

Recently, several positive linkages to several chromosomal locations have been reported (Blouin et al. 1998; Brzustowicz et al. 2000; Cao et al. 1997; Gurling et al. 2001; Lindholm et al. 2001; Schwab et al. 2000; Stefansson et al. 2002; Straub et al. 1995). In this kind of analysis, the co-segregation of genetic polymorphisms with the disease state in families with multiple affected members is investigated. Statistically significant evidence for co-segregation is termed 'linkage'. If the chromosomal location of the polymorphism is known, it is then possible to localize the region that harbors the disease gene/s. Through linkage analysis, a judiciously chosen set of polymorphisms can enable coverage of the entire genome. In spite of the extensive research involving linkage studies of schizophrenia, there have been relatively few consistent results (Moldin 1997). This is likely due to inadequate sample size and difficulty recruiting affected families, which are relatively rare (Owen et al. 2000). Meta-analyses may offer a solution to the problems of power and replication (Badner and Gershon 2002; Levinson et al. 2003; Lewis et al. 2003).

Association Studies

Association studies provide a complimentary approach to linkage analysis. In these studies, selected polymorphisms are examined among cases versus unrelated controls. If case-control differences in the distribution of particular alleles (variants) are detected, this suggests that the polymorphism itself confers susceptibility or is located very close to the disease locus. Basically, association studies are employed to investigate genes in regions where linkage has been detected. Association studies used to investigate relatively small genomic regions. Hence, it is difficult to screen the whole genome by association studies. To overcome this issue, most studies examined positional and functional candidate genes.

Owing to lack of consistent evidence for linkage studies, most studies to date have focused on 'functional candidate genes', i.e., genes encoding proteins implicated by biochemical, pharmacological or other factors (Nimgaonkar 1997; O'Donovan and Owen 1999). Development achieved recently in genome analysis (Lander et al. 2001) has extended the list of functional candidate genes to include the glutamatergic, GABAergic,

and genes involved in neuromodulation and neurodevelopment (Williams et al. 2002). Thus, genes involved in dopaminergic and serotonergic neurotransmission have received the greatest interest. To date, several hundreds of candidate gene association studies have been reported with mixed findings. The majority of these studies have only investigated one polymorphism per gene, so failure to detect a significant association cannot be considered as definitive exclusion of that gene. Replication has been attempted for only a minority of loci, and most of these attempts have been inconsistent and under- powered (Baron 2001).

Genes of Current Interest for Schizophrenia

Recently, researchers focused on genes considered functional as well as positional candidates i.e., those that have a plausible pathogenic role and are localized to putative linked regions. The family and case-control samples used are larger than in the past. Consequently, these studies have revealed more consistent associations (Harrison and Owen 2003) and associations with a number of candidate genes have been reported. Those genes include: catechol-O-methyl transferase (COMT) (Shifman et al. 2002), neuregulin 1 (NRG1) (Stefansson et al. 2002), dysbindin (DTNBP1) (Straub et al. 2002), regulator of G-protein signaling 4 (RGS4) (Chowdari et al. 2002) and G72 and D-amino-acid oxidase (DAAO) (Chumakov et al. 2002).

In conclusion, important advances have been accomplished in our understanding of the genetics of schizophrenia. The recent findings from genetic association studies are a major step forward in the journey to characterize the molecular genetics of schizophrenia. During the recent few years, a number of polymorphisms in several candidate genes were identified as contributing to schizophrenia susceptibility, albeit with a small effect. Technological advances such as rapid high throughput genotyping, progress in genetic analytic methods as well as collecting large samples of families and unrelated cases will pave the way for identifying more polymorphisms with definitive involvement in the pathophysiology of schizophrenia. However, the effect of these polymorphisms on the gene functions and expression need to be investigated. Finally, with the evidence of contribution of both environmental and genetic factors, new recent studies show that gene-environment interactions (GxE) play very important role in the etiology of schizophrenia (van Os et al. 2008; van Zelst 2008). In the near future, it is hoped that genetic counseling and etiological treatment for schizophrenia will be reachable goals.

Discussion

Schizophrenia is a common, disabling and usually lifelong disorder. Its pathogenesis is unknown and treatment remains palliative. The prevalence and incidence of schizophrenia vary tremendously from one study to another, reflecting differences in the study design, the measuring instruments, the type and training of interviewers, the sampling method and the population under study. It is anticipated that as study design becomes more consistent across research sites, rates will show less variability. This was demonstrated in the WHO collaborative study in 12 research centers and 10 countries where researchers used the same design and methods and have shown that schizophrenic illnesses occur with comparable frequency in different populations (Sartorius et al. 1986).

A hundred years ago, Kraepelin introduced the disease (categorical) model in psychiatry and described two distinct disease entities: dementia precox (schizophrenia) and manic depression (bipolar disorder). The disease model of schizophrenia introduced by Kraepelin served to align psychiatry with other medical specialties and provided a basis for research into the nature and causes of mental disorders (Jablensky 1997). The disease model continues to

have a powerful appeal to clinicians and patients alike; both the DSM and ICD contain specific criteria for the disease entity of schizophrenia, current research in diagnostic procedures and specific treatments rely on categorical diagnosis, and the lay public is able to name the condition that has devastating life consequences for themselves or their loved ones. Unfortunately, the literature indicates that "schizophrenia" is too complex to be placed under one disease model. There is a large body of data suggesting that the extent of phenotypic heterogeneity in schizophrenia is too great to support a simple nosological model of the disorder (Jablensky 1997). What investigators study and call schizophrenia now may actually be a heterogeneous set of disorders (Beiser and Iacono 1990).

The question before us now is what to do for future studies? The disease model, the DSM and ICD are here to stay despite the continual doubts by researchers and clinicians (including Kraepelin himself) about the validity of the disease model of schizophrenia. With the advances in psychiatric epidemiology and analytic techniques, future research including both categorical and dimensional models can overcome some of the limitations of categorical classification alone. Studies that combined categorical and dimensional models simultaneously up to this point have been very few, the best example is the above cited WHO ten-country project (Sartorius et al. 1986). In this study, the ICD and CATEGO criteria for schizophrenia were used in combination with the symptoms measured by the Present State Examination (PSE) (Cooper 1970; WHO 1993; Wing et al. 1974). The complexity and the required training needed to be able to use the ICD, the CATEGO and the PSE limit their applications to major projects in major research centers. However, efforts to develop new research tools that use this combined approach are being made (Aboraya and Zheng 2007; Aboraya and Tien 2004).

In addition to the issues of categorical vs. dimensional aspects of the illness, schizophrenia is a dynamic illness and its symptoms change over time. Clinicians who have practiced over several decades often report that cases of schizophrenia they see now are less severe and are less likely to be hebephrenic or catatonic subtypes (Hare 1988). This phenomenon underscores the importance of studying the longitudinal course of the illness as well. Correlating the changes of symptoms over time with the new advances in genetic, DNA and molecular biology research have the potential to discover the etiology of schizophrenia, find more accurate methods of diagnosis and uncover more effective treatments of the illness.

Psychiatric epidemiology have progressed from descriptive to analytic designs over the past two decades (Messias et al. 2007). More complex models incorporating diagnosis, personal deficits, genetic, and environmental factors are now needed to further our understanding what we call schizophrenia (Beiser and Iacono 1990). Future analytic studies should combine multiple risk factors, aiding in clarifying the relative importance of different factors (i.e. genetic versus personal versus environmental). Finally, in his editorial to the American Journal of Psychiatry, Assen Jablensky best summarized our knowledge about schizophrenia by stating "schizophrenia is a disorder with variable phenotypic expression and a poorly understood complex etiology, involving a major genetic contribution as well as environmental factors interacting with the genetic susceptibility" (Jablensky and Kalaydjieva 2003).

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