Project ice storm: A prospective study of the effects of prenatal maternal stress on other risk factors for schizophrenia

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MORTALITY IN SCHIZOPHRENIA PATIENTS TREATED WITH SECOND-GENERATION ANTIPSYCHOTICS

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The increased mortality rate of persons with schizophrenia has been of concern for several decades and is known to be 2-3 times higher than the general population. The relative risk of developing cardiovascular disease may be approximately 5 times higher than the general population. This risk may be rising, possibly due to newer medications. While second-generation antipsychotics (SGAs) offer many advantages over conventional antipsychotics, some may have serious long-term health consequences associated with use. All patients with medical or pharmacy assistance treated with clozapine in the State of Maryland (inpatients and outpatients) and all patients treated with risperidone as inpatients prior to December 31, 2000 were examined for date and cause of death by the Social Security Death Index and death record acquisition. During this time period 3,095 people with schizophrenia were included of which 152 (~5%) were found to be deceased. The mean age of death was significantly younger in patients who have been treated with clozapine vs. risperidone (59.2 vs. 72.9 years; $p<0.001$). Rates of suicide reported were very low (<1%) and did not differ between clozapine and risperidone treated patients. Death by a cardiac event was reported in 51% and 44% of clozapine and risperidone treated schizophrenia patients, respectively. The mean age at death for cardiac causes was 61.7 years for clozapine-treated patients and 80.3 years for those without clozapine treatment ($p=0.0008$). While long-term follow-up is needed, treatment with clozapine may be associated with premature death, particularly due to cardiac-related events.

THE NUMBER OF PRESCRIPTION DRUGS USED BY PATIENTS TREATED FOR SCHIZOPHRENIC OR BIPOLAR DISORDERS

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Background: Individuals with schizophrenic or bipolar disorders are often treated with multiple prescription drugs for their psychiatric conditions, for co-occurring medical conditions, and to counteract treatment-emergent drug side effects. The complexity of these individuals' medication regimen is apt to increase their risk for adverse drug interactions. The objective of this study was to assess the number of prescription drugs used for any purpose by individuals with schizophrenic or bipolar disorders. Methods: An administrative claims database from a managed care organization was used to identify adults who in 1999 were diagnosed with schizophrenic (N=1717) or bipolar disorders (N=3153), and received at least one drug for their psychiatric condition (an antipsychotic for schizophrenia; a mood stabilizer or an antipsychotic for bipolar disorders). Primary meausres were (a) the annual average number of unique prescription drugs received per patient; and (b) the annual average number of filled prescriptions of any kind per patient. Primary measures were calculated for all patients, and were broken down by diagnostic group, by diagnostic subtype within each diagnostic group, by age, and by gender. Descriptive statistics employed Chi-square tests for categorical variables, and one-way analysis of variance, with post tests (Tukey) for continuous variables. Results: The annual average number of different drugs was 9.3; 8.9; and 9.8 per patient, for all patients, for schizophrenia, and for bipolar patients, respectively. The annual average number of filled prescriptions was 34.5; 35.0; 33.9 per patient, for all patients, for schizophrenia, and bipolar patients, respectively. A significantly lower number of prescription drugs was used by men, by patients aged 18-41 compared with three older age groups, by those diagnosed with schizophrenia as compared with schizoaffective disorder, and by individuals diagnosed with bipolar manic, as compared with bipolar depressed or mixed subtype. Conclusions: The medication regimen of individuals treated for schizophrenic or bipolar disorders appear to be characterized by extensive multi-pharmacy, which may increase the risk of adverse drug interactions. On the average, each patient used 9 different prescription drugs, and filled 35 prescriptions on an annual basis. There is a need to study the potential impact of this poly-drug prescription practice on patients' health and on total drug cost.

PROJECT ICE STORM: A PROSPECTIVE STUDY OF THE EFFECTS OF PRENATAL MATERNAL STRESS ON OTHER RISK FACTORS FOR SCHIZOPHRENIA

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The purpose of this study is to determine the role played by the severity and timing of prenatal maternal stress in increasing risk for other putative risk factors for schizophrenia, such as obstetric complications, preterm birth, and delayed cognitive and language development. Following the January 1998 Quebec Ice Storm, which left 3 million people without electricity for several weeks, we recruited 224 women who had been pregnant during the crisis. Initial questionnaires queried about psychiatric symptoms (GHQ), objective events due to the storm, subjective reactions (IES-R), and included 24-hour salivary cortisol sampling kits. A second questionnaire obtained outcome information 6 months after the due date. Cognitive (Bayley) and language development (MacArthur) were assessed in a subsample of 72 children at age 2 years. Results suggest that both the timing and severity of the objective stress exposure, the subjective stress reaction, and pre-existing psychiatric symptoms, predict various outcomes relevant to schizophrenia risk. Ice storm exposure during the 2nd trimester resulted in a significant increase in preterm birth ($p<.05$) and low birth weight ($p<.05$). Subjective reactions to the storm (PTSD symptoms) and the mother's anxiety and depression during pregnancy predicted obstetric complications (all $p<.01$). Moderate-severe objective exposure to the ice storm was associated with IQ scores at age 2 years that averaged .5 standard deviations below the mean IQ of the low exposure group ($p<.01$). The IQ findings using the Bayley Scales were supported by a second approach to cognitive development that evaluates behaviour during free play. The effect of prenatal stress on cognitive development was greatest in those exposed during the second trimester. Moderate-high stress was also associated with significantly lower scores on productive ($p<.01$) and receptive vocabulary ($p<.05$) at this age. We conclude that both timing and severity of prenatal maternal stress produce outcomes

analogous to those associated with risk for schizophrenia (obstetric complications, prematurity, lower IQ, delayed language). Retrospective studies have shown that prenatal maternal stress significantly increases risk for schizophrenia (e.g., Huttunen & Niskanen, 1978; van Os et al., 1998). Our prospective study of an "independent" stressor will help elucidate the mechanisms underlying this effect.

DIFFERENT BIRTH-MONTH PATTERNS IN AUTISM AND SCHIZOPHRENIA

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Birth-month patterns that differ significantly from those in the general population have been found in numerous studies of both schizophrenia and childhood autism. For autism, several studies have reported a significant excess of births in March and/or April, compared with general population births at the respective sites. Most investigators have assumed this pattern in autism reflects a season-of-birth effect, as appears to be true for schizophrenia, but this has never been directly tested. We conducted the first Southern Hemisphere study of this issue in autism, comparing birth dates of 214 males who were diagnosed with DSM-IV at a large autism clinic in greater Melbourne, and were born in Australia from 1975-1997. Male autistics were significantly more likely (with a 73% higher rate) than people in the general population to be born in March and April ($p < 0.005$), suggesting the intriguing hypothesis that environmental teratogens associated with certain calendar birth months may be etiologic factors in autism. In the case of schizophrenia, by contrast, several types of data suggest that there is a significant birth-season (rather than calendar birth-month) effect, and that this effect may be stronger for sporadic than for familial cases. To test this hypothesis further, we conducted a meta-analysis of studies that provided separate birth-season distributions for familial vs. sporadic cases of schizophrenia. Overall, the proportion of births in intemperate months was in fact higher for sporadic than familial cases. Of greater interest, however, was the fact that this proportion tended to be strongest for sites with the most intemperate weather. This pattern provides further evidence for the hypothesis that environmental factors associated with birth in months with intemperate weather may be etiologically significant in schizophrenia, and that these factors may be especially important for sporadic cases.

SUICIDE ATTEMPTS IN AN AFRICAN SCHIZOPHRENIA POPULATION: AN EVALUATION OF RISK FACTORS AND AFFECTED SIBPAIR STATUS

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Suicide and suicide attempts contribute significantly to the morbidity and mortality associated with schizophrenia. This study investigated 449 African (Xhosa) schizophrenia patients for the lifetime presence of suicide attempts. Participants were interviewed with the diagnostic interview for genetic studies and then stratified into those with and without previous suicide attempts. A subgroup of 99 sibpairs was then analyzed separately. Demographic and clinical parameters (SANS/SAPS) were evaluated for their discriminatory value. 91 suicide attempts (20.3% of total) were reported; 30 (14.6% of total) from the sibpair group, significantly less ($p=0.016$). No significant difference was found in gender distribution for either group. Subjects only attempting suicide once were responsible for 78.7% of attempts and in the sibpair group this figure was 75.9%. Poisoning was the most common attempted suicide method. Of the 99 sibpairs only 3 showed concordance for suicide attempts. While suicide attempts were present in a substantial proportion of the Xhosa schizophrenia sample and therefore in line with current literature; this study demonstrated that the affected status of the sib may be protective in nature.

HALLUCINATORY EXPERIENCES AND ONSET OF PSYCHOTIC DISORDER: THE ROLE OF COGNITIVE APPRAISALS

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This study examined the hypothesis that the risk for onset of psychotic disorder in individuals with self-reported hallucinatory experiences would be higher in those who subsequently developed delusional ideation and/or depressed mood than in those who did not. A general population sample of 4672 individuals with no lifetime evidence of any psychotic disorder was interviewed with the Composite International Diagnostic Interview Schedule (CIDI, WHO, 1990) at baseline and 1 and 3 years later. At year 3, individuals with CIDI evidence of psychotic symptoms were interviewed by clinicians to identify onset of psychotic disorder. Psychotic disorder was defined as evidence for a pathological intensity of the positive symptoms of psychosis as assessed with the Brief Psychiatric Rating Scale (Lukoff et al., Schizophr Bull 1986, 12, 594-602) and need for mental health care in relation to these symptoms. An interaction was fitted between presence of hallucinatory experience at baseline (absence versus presence) and presence of delusional ideation 1 year later (absence versus presence). In order to calculate the statistical interaction under an additive model, the BINREG procedure in the STATA statistical programme (StataCorp, Release 7.0, 2001), which fits generalized linear models for the binomial family estimating risk differences, was used. Given the presence of hallucinatory experiences, the increase in risk on the additive scale of having the psychosis outcome at year 3 was much higher in those with delusional ideation at year 1 than in those without delusional ideation (risk difference 18.7%, 95% CI 2.2, 35.2). Similarly, development of depressed mood at year 1 increased the risk for the psychosis outcome at year 3 in those with hallucinatory experiences at baseline (risk difference between those who did and did not develop depressed mood: 16.8%, 95% CI 0.4, 33.3). Adjustment for the presence of delusional ideation at year 1 slightly reduced this effect (risk difference 14.18%, 95% CI -1.34, 29.71). Individuals with hallucinatory experiences who become deluded or depressed have a greatly increased risk of becoming a clinical case for treatment than those who do not. The results provide support for current psychological models of psychosis that emphasize the role of secondary appraisals of psychotic or psychosis-like experiences in the onset of clinical disorder.