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Review article

The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies

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ABSTRACT

Background: The role of environmental risk factors in the development of bipolar disorder (BD) is not well characterized. We evaluate the prevalence, duration, and predictive value of environmental exposures for BD in longitudinal studies.

Methods: We conducted a systematic search of PubMed, Scopus and PsychINFO databases until April 01, 2015, using the following words in combination: prenatal exposure; maternal exposure; trauma; childhood abuse; alcoholism; cannabis; smoking; cocaine; central stimulants; opioids; uv light; pollution; global warming; vitamin d AND bipolar disorder. Additional references were obtained through cross-referencing. We included (1) longitudinal cohort studies or case-control studies nested within longitudinal designs; (2) studies of subjects without lifetime BD diagnoses at initial assessment and a diagnosis of BD at follow-up by clinical or structured assessment. Familial-risk studies were excluded. We tabulated details of study-design, exposure, diagnostic criteria, risk of bipolar disorder expressed as odd ratio (OR), relative risk (RR) or hazard ratio (HR).

Results: Of 2119 studies found, 22 met inclusion criteria. Risk factors identified can be grouped in 3 clusters: neurodevelopment (maternal influenza during pregnancy; indicators of fetal development), substances (cannabis, cocaine, other drugs – opioids, tranquilizers, stimulants, sedatives), physical/psychological stress (parental loss, adversities, abuses, brain injury).

Limitations: Heterogeneity of designs and methodology prevented the use of meta-analysis of the findings; studies did not provide sensitivity, specificity and predictive value of the risk factors identified; case-control studies classify cases based on diagnostic membership, but do not control for familial or genetic liability; methods for determining the exposures varied among studies.

Conclusion: Only preliminary evidence exists that exposure to viral infection, substances or trauma increase the likelihood of BD. Given the limited data available, the specificity, sensitivity and predictive value could not be computed. As exposures are sometimes amenable to prevention, further research is needed.

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1. Introduction

Bipolar disorder is a chronic and recurrent mental illness with high rates of morbidity and mortality due to alcohol and substance abuse, psychiatric and medical disorders and suicide (Crump et al., 2013). Bipolar disorder has a lifetime prevalence of 0.8% for bipolar-I, 1.1% for bipolar-II, 2.4% for bipolar-NOS in adults (Merikangas et al., 2007). According to DSM criteria, the symptoms include loss of energy, social withdrawal and melancholia in depressive episodes and elation, irritability, increased energy with hyperactivity, racing thoughts, pressured speech, decreased need for sleep and an increased involvement of pleasured activities in manic episodes. Psychotic symptoms, such as delusions and/or hallucinations, occur in about 50% of bipolar patients, suggesting some symptomatic and even pathophysiological overlap with schizophrenia (Coryell et al., 2001). Furthermore, apart from affective symptoms, bipolar disorder displays impaired cognitive performance, mainly in attention, memory and executive tasks (Torres et al., 2007). Cyclothymic and hypomanic temperament traits are on a continuum and increase both the risk for major depression and hypomania/mania (Akiskal and Mallya, 1987).

Bipolar disorder has a strong genetic background, associated with family psychiatric history and early onset-age (peaking at ages 15–25 years). Twin studies have suggested a monozygotic concordance rate of 0.43 and population-based family risk studies have estimated a heritability rate of about 58% (Kieseppä et al., 2004; Song et al., 2015). Since it has recently become possible to quantify the genetic contribution using molecular genetic data, it became apparent that genetic variants account for a smaller proportion of variance than the twin-based heritability estimates suggested (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). One of the most likely explanations for the heritability gap is that gene-environment interactions involving shared environmental factors are part of the twin heritability estimates but do not contribute to the molecular heritability estimates that are based on unrelated individuals. The impact of environmental factors in the development and course of severe psychiatric disorders has been studied especially for schizophrenia (Schmitt et al., 2014). According to the neurodevelopmental hypothesis, schizophrenia is related to genetic and environmental factors leading to abnormal brain development during the prenatal or postnatal period whereas onset of disease appear in early adulthood during the synaptic pruning and myelination process. Several environmental factors such as antenatal maternal virus infections (influenza, varicella-zoster, measles, rubella, and polio), obstetric complications entailing hypoxia as common factor (preeclampsia, uterine bleeding, uterine atony, emergency Ceasarian section), low birth weight, early gestational age, cannabis abuse in adolescence, migration and urbanicity have been identified to increase significantly the risk of schizophrenia (Schmitt et al., 2014).

Since bipolar disorder presents as a neurodevelopmental illness (Demjaha et al., 2012), the aim of our study is to review available data on environmental exposures as risk factors for bipolar disorder in longitudinal studies and to assess their specificity, sensitivity and predictive value. For the purpose of this review we defined environmental exposure as an exogenous risk factor that comes into direct contact with the mother, the fetus or the adult subject.

2. Methods

2.1. Data sources

We carried out a computerized search of PubMed, Scopus, PsychINFO databases from inception up to April 01, 2015, using the following words in combination: *prenatal exposure; maternal exposure; trauma; childhood abuse; alcoholism; cannabis; smoking; cocaine; central stimulants; opioids; uv light;pollution; vitamin d) AND bipolar disorder.* Hand searching of references in identified reports led to additional relevant articles.

2.2. Study selection and data extraction

The authors screened search results, applied inclusion and exclusion criteria and resolved discrepancies by consensus. Articles selected were published in the English language and met the following inclusion criteria: (1) longitudinal observational cohort studies or case-control studies nested within longitudinal designs; (2) studies of subjects without lifetime bipolar disorder diagnoses at initial assessment and with bipolar disorder diagnoses at follow-up. Diagnosis may be clinical or with structured interviews (meeting DSM-III, IV, ICD-9/10 criteria).

Our review specifically focused on a discrete, substantive behavioral outcome – a new diagnosis of bipolar disorder. Clear, substantive outcomes offer the most robust foundation for evidence-based prediction. Cross sectional studies are not reviewed as their lack of prospective observation following exposures introduces bias. Furthermore, since a causal relationship is not proven by these studies, the conclusions that can be drawn are limited.

We also excluded reviews, case reports, clinical trials, studies on genetic abnormalities, personality disorders, temperaments, neuropsychology and neuroimaging risk factors, and studies where the bipolar outcome was combined with other diagnosis (major depression, schizophrenia, psychosis). Studies of offspring of parents diagnosed with bipolar disorder were excluded due to the co-occurrence of genetic risk and exposure to parental psychopathology.

Studies of antidepressant exposure for anxiety or mood disorders were excluded as they have been recently reviewed elsewhere (Baldessarini et al., 2013; Offidani et al., 2013).

For each of the selected reports, we extracted: author/year, type of exposure, population, duration of follow up, number of exposed and not exposed (for cohort studies), number of cases and controls (for nested case-control studies), diagnostic criteria for bipolar