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Developing bipolar disorder

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chapter 4

Five year follow-up of effects of stressful life events on the onset of mood disorders among offspring of patients with bipolar disorder.

In preparation for submission

Five year follow-up of effects of stressful life events on the onset of mood disorders among offspring of patients with bipolar disorder.

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INTRODUCTION

The temporal process of onset of mood disorders following stressful life events (SLEs) is an intriguing field of research. In a previous study (Hillegers et al., 2004) our aim was to understand the temporal relationship between SLEs and the onset of mood disorders and interactions with family load (FL) for mood disorders in a high-risk cohort of adolescent offspring of bipolar patients. We therefore constructed four models with different levels of progressive decay, and found a best fit for the model in which the effect of SLEs on the onset of the first mood disorder episode was described as an accumulating effect of SLEs and at the same time a 25 % decay per time interval (year).

The time span in which these SLEs were retrospectively measured was between 7 and 16 years. After this study we did a follow-up involving two subsequent measurements approximately one and five years after the first measurement (Reichart et al., 2004, Hillegers et al., 2005). The aim of the current study is to extend our prior data by collecting five year follow-up data on our cohort of adolescent offspring of patients with bipolar disorder.

METHODS

This study presented here is part of an ongoing prospective study of a high-risk cohort of 140 adolescent offspring of 86 parents with a bipolar disorder in The Netherlands. The study design, recruitment procedure and study population have been described in detail previously (Wals et al., 2001).

The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study. After a complete description of the study was given to all participants, a written informed consent from was obtained.

Sample

All subjects were enrolled into the study between November 1997 and March 1999. A second assessment took place fourteen months after the first assessment and included 132 subjects (13-23 years) (Reichart et al., 2004).

The third measurement took place 41 months (SD=5.2) after the second measurement. The cohort still consisted of 129 respondents and included 60 females and 69 males. The mean age was 20.8 years (SD=2.7) with a range of 16-26 years. The lifetime prevalence of bipolar disorder in this sample was 10% (n=13), the lifetime prevalence of mood disorders was 40% (n=38) and the prevalence of psychopathology in general was 59% (Hillegers et al., 2005). The mean ages of the subjects did not differ significantly. The subjects with a bipolar disorder were 21.5 years (SD=3.5); those with an unipolar mood disorder had a mean age of 21.2 years (SD= 2.5), and those without a mood disorder had a mean age of 20.5 years (SD=2.7).

MATERIALS

Diagnoses

Lifetime DSM-IV diagnoses at third measurement were based on the psychiatric interviews that took place during all three measurements adding up the incidence of psychopathology between second and third measurement to the incidence of psychopathology between first and second measurement and the lifetime diagnoses at first measurement. At the same time the hierarchal rules of DSM-IV were taken into account (Hillegers et al., 2005).

During the first two interviews, diagnoses were assessed using the Schedule for Affective Disorders and Schizophrenia for school-age children - Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL is an interviewer-oriented diagnostic interview designed to assess current and past DSM-IV symptoms resulting in diagnoses in children and adolescents and consist of interviews of the parent(s) and child separately. Because of increasing age of our sample, we could not use the K-SADS-PL for the third measurement. Therefore we used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) (First et al., 1999) to determine current (last month) and past (as of second measurement) diagnoses. All interviewers were intensively trained, and all interview outcomes were evaluated with a child- and adolescent psychiatrist (CR).

Family load

Using the Family History - Research Diagnostic Criteria (FH-RDC), (Andreasen et al., 1977) the family load (FL) for unipolar mood disorders was constructed for all participating subjects, taking the first and second degree relatives into account (Wals et al., 2003, Hillegers et al., 2004). In our analyses, we used the familial loading for unipolar mood disorders, because all subjects had a first degree family member with a bipolar disorder and consequently the FL for bipolar disorder did not differentiate between groups with and without onset of mood disorders.

Stressful life events (SLEs)

The investigator-based Bedford College Life Event and Difficulty Schedule (LEDS) (Brown and Harris, 1978, 1989) is a semi-structured interview for assessing life events and long term difficulties in adults. The LEDS collects detailed information about the event itself, the timing of its occurrence (date) and relevant contextual information for each event. Based on the contextual information, the threat for each event is rated via standardized rating procedures. Monck and Dobbs (1985) originally adapted the Bedford College LEDS methodology for use with adolescents. The LEDS interviews were conducted by psychologists who received a LEDS training prior to interviewing. The events were rated from written transcriptions of the interview by three independent raters, who had not been involved in the interviews and blind to the respondents' mental health status. A panel consisting of the three raters and the first two authors (MH, MW) reached consensus on the events that raised rating problems. Since the LEDS interview initially covered the life cycle (childhood, early and late adolescence), all events were dated on a yearly basis. Subsequently, we evaluated whether and when (which year) each subject had experienced an event and the total number of severe events.

Statistical Model

To explore the impact of adverse life events on onsets of mood disorders, a discrete time survival method was used with combinations of time dependent co-variates.To study the impact of life events on the onset of mood disorder, the life event load at a particular point in time (year y) was calculated as the sum of the threat scores of the life events in year Y and all preceding years. The sum was subjected to an exponential decay function of 25 % loss per year. This reflects the hypothesis that the impact of life

events principally accumulates but at the same time gradually decays as time goes by (Hillegers et al., 2004).

Data analysis

The relationship between life events and the occurrence of mood disorder was studied using Cox regression with time-varying covariates (Cox, 1972), a statistical model relating determinants whose status change over time to survival type (censored) outcome data. Because the 140 subjects originated from 86 families, these data must be considered correlated through family. Therefore we used a "frailty" model, which consisted of a Cox model, with a cluster variable indicating family. Time-varying influences of life events were permitted by including the time dependent life event load, as a continuous time-varying covariate in the model. In this model, the dependent variable was the time from the age five to first mood disorder or, if no mood disorder occurred, the time from age five to the third measurement. The results are expressed as hazard ratios, indicating the instant relative risk of mood disorder, per unit life event load; thus representing the strength of the association. Hazard ratios were presented with 95% confidence intervals (95% CI). The level of significance in all analyses was P< 0.05 (two-sided).

RESULTS

Descriptive

Table 1: Relative risk of onset of a mood disorder after stressful life events (SLEs) using a model of 25% event effect decay over three follow-up periods.

	Time period	LE load	P	LE load adjusted for FL	P
A	From 5 years of age to T1*	1.100 (1.064 – 1.137) *	.000*	1.091 (1.053-1.130)*	.000*
B	From 5 years of age to T3	1.108 (1.067 - 1.151)	.000	1.100 (1.060 – 1.142)	.000
C	From T1 to T3	1.157 (1.081 - 1.239)	.000	1.159 (1.079 – 1.244)	.000

***: Hillegers et al., 2004**
LE: Life event, BP: Bipolar disorder, FL: Family load
T1: first measurement, T2: second measurement, T3: third measurement
Values are hazard ratios for mood disorder per unit life event load with 95% confidence intervals between brackets.

The relationship between life event load and mood disorder onset over different time periods is depicted in table 1. As described in an earlier paper (Hillegers et al., 2004) the life event load form the age of 5 years until T1 (period A) was significantly associated with an approximately 10% increased risk (hazard ratio 1.1) of mood disorder per unit life event load. This increased risk remained significantly present when the time period was extended with the follow-up period of almost five years until T3 (period B).

Moreover the risk was also significant if we only take into account the time period from T1 until T3 (period C). During this follow-up period 15 subject developed a first mood episode. When focussing on only the thirteen subjects with a bipolar disorder we also find an increased impact of SLEs on their first mood episode during period B (results not shown). Adjusting for Family Loading (FL), dichotomised at the median, does not significantly change the impact of SLEs on the onset of the first mood disorder in any of time periods. This means there is no statistically significant interaction or confounding by FL in this study. Both SLEs and FL have independent effects on risk of mood disorders onset.

DISCUSSION

This study replicates the earlier found impact of SLEs on the onset of first mood episodes in adolescent and young adult bipolar offspring (Hillegers et al., 2004) by now using the five year follow-up data of two subsequent measurements. The life event load remained significantly associated with an approximately 10% increased risk of mood disorder per unit life event load during the additional follow-up period (period B). To rule out the possibility that these results are explained mainly by events that occurred before T1 (period A) we also analyzed separately the effect of SLEs during the follow up period (period C). Even then, and with only 15 subjects developing a first mood episode, the same significant hazard ratio of 1.1 was found. Moreover, we found that the effect was significant for the offspring who had developed a bipolar disorder. As in the previous study, familial loading for mood disorders did not modify the association of SLEs and onset of mood episodes. Possibly that is because of the lack of power. However, this study suggests that there is no evidence of gene-environment interaction concerning familial loading and SLEs.

In the present study a strong relationship between life events and the risk of mood disorder in the offspring of patients with bipolar mood disorder was demonstrated. It

is therefore that clinicians should extend their interventions beyond mere treatment of mood symptoms. They should also pay attention to prevention and rehabilitative interventions, especially in people at high risk to develop the disorder, such as the offspring of patients with bipolar disorder. Altering or improving coping strategies could be a target for selective prevention in this population who are at high risk of developing a bipolar disorder. By intervening before the onset of full-blown bipolar disorder, the disorder may be prevented or at least ameliorated in its severity, preventing poor social and vocational functioning. A possible way might be to help patients to identify their prodromal symptoms and/or individual maladaptive coping strategies in stressful situations and try to change these coping strategies (Wong & Lam, 1999; Lam et al., 2001).

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