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Jérôme Endrass · Stefan Vetter · Alex Gamma · William T. Gallo · Astrid Rossegger · Frank Urbaniok
Jules Angst

Are behavioral problems in childhood and adolescence associated with bipolar disorder in early adulthood?

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Abstract Several recent studies have found an association between conduct problems and bipolar disorder in adolescents. However, prospective studies are rare and most do not apply multivariable analysis strategies to control for important variables (e.g. socio-demographics). The aim of this study was to test the association between certain conduct problems and bipolar disorders. The sample consisted of 591 adolescents (male and female) representative for 2,600 persons from the Canton of Zurich in Switzerland. Data were prospectively collected through an interviewing procedure, with the first screening taking place at the age of 19–20. The incidence rate was computed using sampling weights, and risk factors of bipolar II disorder were estimated using a multivariable logistic regression model. The 9-year incidence rate of bipolar II disorder in the canton of Zurich was 8.4% ($n = 65$). Adolescents and children showing behavior such as repeated running away from home and physical fighting were 2.6–3.5 times more likely to experience a bipolar II disorder than those with no indication of conduct problems. Sensitivity analysis showed that the conduct problems were not the result of low socio-economic status.

Key words bipolar II disorder · adolescents · conduct problems · Zurich study

Introduction

“Childhood-onset bipolar disorder is commonly associated with or preceded by conduct disorder (CD), attention-deficit disorder (ADHD), and/or oppositional defiant disorder (ODD)” concluded Chang et al. [7], summarizing the literature. Kutcher et al. [16] found that 42% of 19 bipolar adolescents had conduct disorder, and Kovacs and Pollok [15] found a very high lifetime comorbidity with conduct disorder (69%) and a 54% within-episode comorbidity among 26 bipolar youths. Prepubertal bipolar disorder was found to be associated with sustained conduct and impulse-control problems [28].

High risk studies of children of bipolar parents are of great interest in this context. Reviews have been made by Lapalme et al. [17], and DelBello and Geller [8]: in BP offspring attentional and behavioral problems [6], disruptive problems [23], and hyperactivity were found [18]. Chang et al. [7] found ADHD as well as mood disorders to be associated with parental bipolar disorders in BP offspring.

In the Amish high risk study among children of bipolar parents, bipolar disorders were not clearly associated with ADHD and discipline problems. This negative finding may be explained by the markedly different cultural background [11] of the subjects. A prospective high risk study of adolescents over 5 years found an association of anxiety disorders in 46% of bipolars [24].

Prospective studies on risk factors for bipolar disorders are needed. Only limited epidemiological data exist concerning the longitudinal course of bipolar disorders in adolescence. Carlson and Weintraub [6] found attentional and behavioral

J. Endrass, PhD (✉)
Psychiatric/Psychological Service
Crime Prevention Research Unit
Feldstrasse 42
8090 Zürich
Switzerland
E-Mail: jerome.endrass@ji.zh.ch

J. Endrass, PhD · S. Vetter · A. Gamma · J. Angst
Zurich University Psychiatric Hospital
Zürich, Switzerland

A. Rossegger · F. Urbaniok · J. Endrass
Criminal Justice System
Psychiatric/Psychological Service
Zürich, Switzerland

W.T. Gallo
Yale University
New Haven, CT, USA

problems to be predictive of mood disorders. In a longitudinal study, Lewinsohn et al. [20] investigated both the course of and the co-morbid factors associated with bipolar disorder in a representative community sample of 1,709 adolescents. Although the prevalence rate for bipolar disorder (1% at age 18) was very low in this sample [19], the authors found that juvenile bipolar subjects experienced impaired functioning in social situations, with family and at school [20]. Significantly fewer bipolar subjects in this sample earned a bachelor's degree [19]. Using data from the NIMH Epidemiologic Catchment Area Project, Robins and Price [25] found that in their sample of 19,482 subjects conduct problems were strongly associated with a wide range of psychiatric disorders. In a later re-analysis of data from wave 1 of the Epidemiologic Catchment Area Study, Carlson [5] found multiple conduct disorder symptoms to be significantly associated with bipolar I disorder in younger adults (ages 18–29). Especially interesting was the fact that serious rule violations were of greater significance than more “typical” conduct disorder symptoms such as stealing, vandalism and fighting.

In a study analyzing differences between children with dysphoric and those with non-dysphoric types of conduct disorders, Biederman et al. [4] found that children with conduct disorders and symptoms of mania had an elevated risk of mood disorders.

According to Wozniak et al. [27], the significant group with both conduct disorder and bipolar disorder should be viewed as a distinct nosological entity. Biederman et al. [3] suggest that if children with conduct disorders display symptoms of mania, a diagnosis of bipolar disorder should be considered. However, CD symptoms should not be viewed as a direct consequence of bipolar disorder, nor is there evidence for the opposite [3]. Akiskal [1] hypothesized that adolescent conduct disorder can often be referred to an unrecognized underlying bipolar disorder.

According to Dilsaver [10], pre-pubescent subjects with conduct problems often experience phases of euphoria oscillating with phases of psychic pain. However, in this study the sample size was too limited to apply multi-variable analysis strategies to control for socio-demographic (or other) variables. The inclusion of socio-economic variables is important, since factors such as gender, age of onset, and marital status have been shown to be important risk factors for the course of affective disorder, especially in younger patients [14].

The aim of this paper was to investigate the association between conduct problems (but not conduct disorder) and bipolar disorders, as well as testing possible associations for confounding factors such as socio-economic status. First, the question of whether conduct problems in childhood present a risk factor for bipolar II disorder in (early) adulthood was addressed, focusing especially on the temporal aspect of

this question, as the comorbidity between the two have been extensively researched, in regards to their temporal association however, there is a somewhat limited body of literature. If such an association were found, then the question would have to be raised of whether conduct problems are not simply a reflection of an unfortunate socio-economic status—which has been shown to be a risk factor for a number of mental health disorders—or whether conduct problems represent an independent risk factor that can be understood as a symptom of a prodromal stage of bipolar II disorder.

The data of the Zurich study are suited to testing these questions. Most of the data are prospective, include an extensive array of socio-demographic factors, and are representative for 2,600 persons of the Canton, allowing investigators to generalize their findings for the population of the Canton of Zurich, where one sixth of the population of Switzerland live. In an earlier paper on hypomania [26], high rates (compared to the control group) of disciplinary problems at school (30% vs. 12%), and more frequent thefts during childhood and adolescence (21% vs. 10%) were found.

Method

■ The sample

The Zurich Study is composed of a cohort of 591 subjects (292 males, 299 females) drawn from a larger sample screened in 1978 with the Symptom Checklist 90-R (SCL-90-R) [9]. The cohort is a stratified sub-sample of the screening sample, with two thirds scoring high (≥ 85 th percentile) on the SCL-90-R Global Severity Index, and a random selection of subjects scoring below the 85th percentile. This stratification ensured an enrichment of the cohort by including cases with a high risk of psychiatric morbidity. After reversing the weighting of the sample stratification, the cohort is representative for 2,600 persons of the Canton of Zurich in Switzerland. The screening took place at ages 19 (males) and 20 (females). Interviews were conducted in 1979, 1981, 1986, 1988, 1993, and 1999, for a total of six interviews. In every interview wave, an average of 10% of the subjects was lost due to non-compliance. In order to have a sufficient sample size, only data from 1978 to 1988 were used for analysis. Of the 292 male subjects in 1978, 200 remained in 1988; the number of female subjects was reduced from 299 in 1978 to 224 in 1988. Thus the attrition rate for the entire sample was 28%.

■ Diagnostic interview

Clinical psychologists and some psychiatric residents administered a semi-structured diagnostic interview developed for the Zurich study (“Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology”). This instrument investigates psychiatric/psychological and functional/somatic syndromes, of both the subjects and their family. It also collects information on socio-economic and demographic variables, childhood characteristics, and attitudes to work and leisure time.

Symptoms, their duration and frequency, the degree of suffering, treatment, and possible social consequences were assessed for each syndrome. The interviews covered symptoms within the twelve months prior to assessment.

■ Dependent variable

The 9-year incidence rate of bipolar II disorder was examined as a dependent variable. The disorder was diagnosed according to a Zurich definition: it required the presence of a DSM-III-R major depressive episode plus at least two of the seven criterial symptoms for hypomania of DSM-IV [2].

■ Independent variables

All independent variables examined had been reported by subjects during interviews as having occurred prior to the start of the study and prior to the diagnosis of bipolar II disorder, thus meeting the necessary temporal criterion required to interpret them as risk factors.

1. *Symptoms of behavior problems in childhood/adolescence:* truancy, running away from home, frequent physical fights, theft, and frequent disciplinary problems at school. These symptoms were assessed using an item-checklist during the interview in 1986. A formal diagnosis for conduct disorder could not be obtained from this item-checklist; therefore, we have not intended to make inferences about conduct disorders, but rather about conduct problems.
2. *Family history of mania, anxiety states, and depression:* A detailed family history was taken at the interview in 1986 (age 27/28). A formal diagnosis was not made; only the occurrence of the syndrome in first degree relatives was identified.
3. *Socio-demographic variables and gender:* A large number of social variables were assessed at the screening for the Zurich study in 1978. The following variables were chosen for the analysis: Highest level of education achieved, monthly income of parents, profession of father, family atmosphere in childhood and adolescence, and gender. All socio-demographic variables referred to the years prior to 1978 and were ordinal scaled.

■ Statistics

Three different analysis strategies were pursued:

1. Since the data used for this investigation are representative of the Canton of Zurich, the cumulative incidence rate was computed using sampling weights. The models of this analysis were performed using the "svymean" command in STATA SE Release 8.0.
2. The outcome variable of this analysis is sufficiently rare for it to meet a condition allowing it to be interpreted as a relative risk. Therefore, all models were fitted with logistic regression analysis. The model building strategy for the logistic regression analysis followed recommendations made by Hosmer and Lemeshow [13]. In order to make the results more interpretable, all variables not dichotomized were divided by their standard deviation. Some variables had to be reversely coded in order to make the results clearer. Continuously scaled variables were tested for their linearity in the logit using the 'fractional polynomial' procedure in STATA. All significant predictors were tested for confounding and effect modification. In the final model, no effect modifier was used. All models were estimated using STATA SE Release 8.0.
3. In a sensitivity analysis, the question of whether 'low parental financial status' was statistically associated with conduct problems was addressed. It is well known from previous research that a family history of bipolar disorder is a strong predictor for developing bipolar II disorder. If 'low parental financial status' was found to be predictive for bipolar II disorder, it could be assumed that subjects with a family history of bipolar disease simply have a socio-economic burden that leads to conduct problems such as theft and running away from home. If this was the case, conduct problems could not be interpreted as inde-

Table 1 Rates of bipolar II disorder and selected risk factors for mood disorders in the Zurich population (age: men, 20–29; women 21–30, $n = 591$)

	<i>n</i>	Rates (in %)
Bipolar II disorder	65	8.4
Family history of generalized anxiety	150	24.6
Family history of bipolarity	37	7.8
Low parental financial status	233	42.2
Repeated running away from home during childhood/adolescence	17	3.0
Truancy during childhood/adolescence	38	4.1
Repeated physical fights during childhood/adolescence	34	5.5

pendent predictors for bipolar II disorder, but rather as the result of an unfortunate socio-economic status. Since this analysis was not intended to develop a predictive model for low parental financial status, bivariate logistic models, rather than multi-variable logistic models, were used to address this question—additionally, bivariate models are more sensitive than multivariable models. All bivariate logistic regression models were estimated using STATA SE Release 8.0.

Results

■ Cumulative incidence of bipolar II disorder and prevalence of socio-economic variables

The 9-year cumulative incidence rate of bipolar II disorder in the Canton of Zurich was 8.4% ($n = 65$). The family history of generalized anxiety disorder was considerably higher than the family history of bipolar disorder (24.6% and 7.8%). More than 40% of subjects reported 'low parental financial status'. 'Truancy', 'running away from home', and 'physical fights' were infrequent in the study population (3–5.5%) (Table 1).

■ Risk factors of bipolar II disorder: a multi-variable model

In the multi-variable logistic model, both 'family history of generalized anxiety disorder' and 'family history of bipolar disorder' were predictive for bipolar II disorder. Although 'family history of bipolar disorder' was only marginally significant at the 5% level, it was retained in the model for two reasons: it proved to be a confounder and it was determined to be a clinically plausible predictor. Each of the family history variables contributed independently to an increased risk of bipolar II disorder. Family history of generalized anxiety disorder and bipolar disorder increased the risk of bipolar II disorder by 100% and 130%, respectively.

'Low parental financial status' proved to be an important predictor for bipolar II disorder. The results suggest an increase in risk of more than 90%. The most important predictors, in terms of increased risk, were the conduct problems 'truancy' (250%),

Table 2 Risk factors of bipolar II disorder (multi-variable model) estimated with a logistic regression model

	Odds ratio	Std. err.	z	P	95% CI	
Family history of generalized anxiety	2.016	0.617	2.290	0.022	1.106	3.674
Family history of bipolarity	2.310	1.013	1.910	0.056	0.978	5.455
Low parental financial status	1.932	0.599	2.120	0.034	1.052	3.549
Repeated running away from home during childhood/adolescence	3.288	2.048	1.910	0.056	0.970	11.146
Truancy during childhood/adolescence	3.480	1.542	2.810	0.005	1.460	8.294
Repeated physical fights in childhood/adolescence	2.636	1.177	2.170	0.030	1.099	6.324
Gender	1.815	0.568	1.910	0.057	0.983	3.351

Table 3 Bivariate associations between 'low parental financial status' and selected risk factors for bipolar II disorder (estimated by logistic regression models)

Low parental financial status	Odds ratio	Std. err.	z	P	95% CI	
Family history of generalized anxiety	0.654	0.134	-2.070	0.038	0.437	0.977
Family history of bipolarity	0.767	0.275	-0.740	0.461	0.380	1.550
Truancy during childhood/adolescence	1.254	0.433	0.660	0.511	0.638	2.467
Repeated running away from home during childhood/adolescence	0.648	0.355	-0.790	0.429	0.221	1.898
Repeated physical fights in childhood/adolescence	1.931	0.695	1.830	0.067	0.954	3.910

'running away from home' (230%), and 'physical fights' (160%). However, the conduct problems 'theft' and 'disciplinary problems at school' dropped out as significant and/or confounding predictors for bipolar II disorder in the multi-variable model.

Because gender was, in itself, a significant predictor in the multi-variable model (the risk for men was 81% higher), the results can be interpreted as being gender adjusted.

Other socio-economic variables, such as highest level of education achieved, profession of father, family atmosphere in childhood and adolescence, dropped out as significant and/or confounding predictors for bipolar II disorder in the multi-variable model (Table 2).

■ Do conduct problems reflect an unfortunate socio-economic status?

The results of the sensitivity analysis reveal that 'low parental financial status' was not associated with 'a family history of bipolar disorder', 'truancy', 'running away from home', or 'a history of physical fights'.

A family history of generalized anxiety was negatively associated with 'low parental financial status' (OR = 0.654), meaning that a one-unit increase in parental financial status was associated with approximately a 50% increase of the risk for generalized anxiety.

In summary, the results of the sensitivity analysis do not reveal that conduct problems are the result of a low socio-economic status (Table 3).

Discussion

Our results suggest that subjects showing criterial symptoms of conduct problems in childhood or

adolescence are 2.6–3.5 times more likely to experience a bipolar II disorder in (early) adulthood than those who do not. This confirms findings of the longitudinal studies by Carlson and Weintraub [6] and by Lewinsohn et al. [19, 20] on impaired social functioning as a predictor for mood disorders and bipolar disorder in particular.

There is no doubt that problematic social behavior such as 'truancy', 'fights', and 'running away from home' are likely to produce subsequent stressful life events. A vast literature supports the theory that stressful life events experienced in adolescence are predictive for major depression in early adulthood [22]. Similar evidence exists for subjects with a family history of bipolar disorder: their first depressive episode is more frequently triggered by stressful life events; additionally, an earlier onset of the disease can be observed [12].

In our study from a set of different family histories of psychiatric diseases, only 'generalized anxiety disorder' and 'bipolar disorder' were predictive factors for the development of a bipolar II disorder. These findings are congruent with comparable results reported elsewhere [8, 21].

Taking our results into consideration, one could argue that, since a low socio-economic background (represented in the variable 'low parental financial status') is evidently associated with bipolar II disorder, conduct behavior problems should be interpreted as the result of an unfavorable background, rather than as problems triggered by an unrecognized or prodromal stage of an underlying bipolar disorder. If this were the case, the results of this investigation could not be viewed as a validation of Akiskal's [1] hypothesis, which states that conduct problems should be viewed in some instances as prodromal symptomatology of a developing bipolar disorder.

In order to investigate the relationship between low socio-economic background and conduct variables, sets of sensitivity analyses were performed. The results of these analyses suggest that the conduct variables are not significantly associated with 'low parental financial status'. Given these results, and the fact that our analysis used only independent variables that were truly predictive in nature (assessed before the onset of bipolar II disorder), as well as data from a cohort representative for the population of the Canton of Zurich, we view our evidence as a positive validation of the theory of Akiskal.

Limitations: Even though the Zurich Study consists of a longitudinal and prospective set of data which covers a time period of almost 30 years, the data examined in this study are retrospective in nature as conduct problems during childhood and adolescence were determined in an interview when subjects were 27/28 years of age. It should also be pointed out that on the basis of this information it was not possible to make a diagnosis of conduct disorder according to the criteria of diagnostic manuals, and we thus opted to examine conduct problems in general.

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