Substance use disorder during the early stages of bipolar disorder:

A prospective longitudinal study of the offspring of bipolar parents

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ABSTRACT

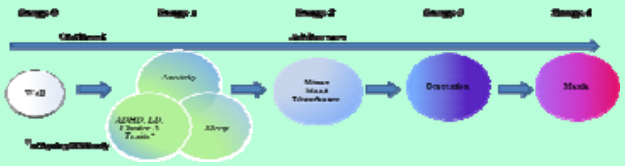
We assessed the relationship between the early stages of bipolar disorder (BD) and the risk of substance use disorders (SUD) in prospectively followed offspring of BD parents. Eligible families had one parent with confirmed BD based on best-estimate procedure. Offspring and a parent completed KSADS-PL interviews by a child psychiatrist at baseline and were then reassessed prospectively. For this analysis, we included 210 offspring of at least 12 years of age and used survival analysis adjusting for sex and SES, with time varying covariates to assess the relationship between the early clinical stages of BD and the risk of SUD. A lifetime SUD was diagnosed in 21% of offspring, cannabis being the most common substance. Male offspring had a 4-fold increased risk of SUD compared to female offspring. The peak period for onset of SUD was between 15-19 years for both sexes. Compared to those offspring well but at risk (stage 0), those in stage 1 (non-specific disorders), stage 3 (major depression) and stage 4 (BD) were at increased risk of SUD; while offspring at stage 2 (minor mood disorders) were at marginally increased risk. SUD is a common comorbidity arising during the early course of emerging BD, even before the first activated episode. Further research is needed to understand the progression of substance use during the early clinical course and to determine effective stage-specific interventions.

INTRODUCTION

Epidemiological and clinical studies have established a strong association between bipolar disorder (BD) and substance use disorder (SUD) with the bulk of evidence favoring onset of mood disorder preceding onset of SUD. Historically, alcohol has been the most frequent substance of misuse; however, in younger community-based and clinical samples cannabis is the most frequently abused substance. There have been reports that particular subtypes of BD have specific risks for certain substances, and that different substances may be used at different phases of the illness. In family members of lithium responsive probands, SUD appears as a complication of mood disorder, rather than an alternative phenotype of BD.

SUD has a devastatingly negative effect on the clinical course and prognosis for patients with BD. With improved understanding of the nature of the association between BD and SUD, targets for early treatment and perhaps prevention could be investigated. Most studies have relied on cross-sectional and retrospective data to investigate this association. New evidence suggests that BD evolves in a predictable sequence of clinical stages (Figure 1). Therefore, prospective studies using a clinical staging framework provide a unique opportunity to study the nature of the evolution of BD and comorbidities such as SUD.

Figure 1. Clinical staging model for bipolar disorder



METHOD

PARTICIPANTS**:** Families in this analysis were identified as part of an ongoing high-risk study. The affected parent had confirmed BD based on best-estimate procedure and the other parent was unaffected for major psychiatric disorder. Parents were subtyped by their response (LiR) or non-response (LiNR) to long-term lithium as per research protocol.

PROCEDURE: 210 consenting offspring (87 males, 123 females) ≥ 12 years of age were included in this analysis. KSADS-PL format interviews of offspring and a parent were completed on average annually by a research psychiatrist. DSM-IV diagnoses were made by blind consensus review which included at least 2 research psychiatrists using all available clinical information.

STATISTICAL METHODS: We used Cox Proportional Hazard model adjusted for sex and SES. Outcome variable (DSM-IV diagnoses) and time variable (age of onset or age of last assessment) was used to calculate the changing numbers at risk over the lifespan and the time order of SUD and psychopathology. Psychopathology and clinical stage were treated as time-varying covariates.

RESULTS

DESCRIPTION OF THE SAMPLE

The average age of HR offspring at recruitment was 16.77 years (sd = 5.05) and at last assessment was 21.49 (sd = 6.25) years. Forty-three (21%) met DSM-IV criteria for a SUD. The drug of choice was cannabis either alone (42%) or in combination with alcohol (40%). The mean age of SUD onset was 16.98 (sd = 2.66) years.

There was no difference in age at recruitment, age at last assessment or SES between the HR offspring with compared to those without SUD. Although not statistically significant, there was a higher proportion of offspring of LiNR with SUD. There was a significantly higher proportion of males with SUD. HR offspring with SUD compared to those without SUD, had a higher rate of major mood disorders, lower global functioning scores and higher rates of lifetime psychotic symptoms. There was no difference between the subgroups in the rate of externalizing disorders (ADHD/LD), anxiety disorders or sleep disorders (see Table 1).

RESULTS

HAZARD MODELS AND FUNCTIONS

Using Cox proportional hazards models with time-varying covariates. The hazard (risk) of major depression (MD) was multiplied by a factor of 1.962 once subjects had experienced SUD (p=.0392, 95% CI=1.034, 3.725). The hazard of SUD was multiplied by a factor of 2.039 once subjects had experienced MD (p=0.0521, 95% CI=0.994, 4.183). The hazard of BD was multiplied by a factor of 2.663 once subjects had experienced SUD (p=.0100, 95% CI=1.264, 5.614). Finally, there was not a significant hazard of SUD once subjects had experienced BD

Using hazard functions, which give an estimate of the risk of SUD at a specific age for an individual, assuming that that individual is free of SUD (still at risk) up until that age. The peak age of onset for a SUD in both males and females appears to be between ages 15 to 19, with the average age of onset 16.98 (sd = 2.66) years (see figures 2a, 2b).

Table 1. Characteristics of Offspring with compared to those without a lifetime SUD

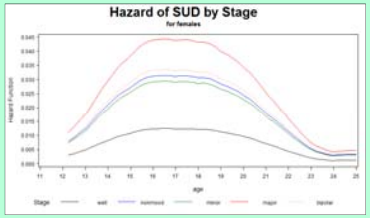
	With SUD		Without SUD		
	n	%	*n*	%	
N = 210	43	20.48	167	79.52	**p-value**
	n	%	*n*	%	
Comorbid Disorders					
ADHD/LD/Cluster A	7	16.28	13	7.78	[b].1396
Sleep Disorder	3	6.98	24	14.37	[a].1964
Anxiety Disorder	12	27.91	32	19.16	[a].2089
Minor Mood[d]Disorder	18	41.86	46	27.54	[a].0690
Major Mood[d] Disorder	28	65.12	54	32.34	[a]<.000 1
Episodic Course[e]	16	37.21	50	29.94	[a].3598
Bipolar Disorder (BDI, BDII, BDnos)	16	37.21	27	16.17	[a].0023
	Mean	**SD**	**Mean**	**SD**	
Minor Mood Age of Onset *(Years)*	15.53	6.02	14.45	5.79	[c].5069
Major Mood Age of Onset *(Years)*	17.61	3.79	17.74	4.21	[c].8890
Hospitalized Ever	4	9.30	9	5.39	[b].3092
Psychotic Features Ever	9	20.93	15	8.98	[b].0553
Last Global Assessment of Functioning (GAF) Score	39	74.28	70	81.46	[d].016
Proband Lithium Response					[a].4013
LiR (responder)	16	37.21	74	44.31	
LiNR (nonresponder)	27	62.79	93	55.69	

Table 2. Cox proportional hazard model showing the risk of SUD in various clinical stages, adjusting for sex and SES

Outcome (dependent variable)	Independent Variables	Hazard Ratio	95% Confidence Interval	p-value
SUD	Male	2.86	(1.51, 5.42)	0.0013
	stage1	2.49	(1.07, 5.77)	0.0336
	stage2	2.21	(0.88, 5.56)	0.0908
	stage3	3.39	(1.32, 8.68)	0.0110
	stage4	2.74	(1.03, 7.29)	0.0441

Figure 2a. Hazard of SUD by stage for females averaged over SES

Figure 2b. Hazard of SUD by stage for males averaged over SES



CONCLUSIONS

This analysis confirms previous findings that SUD is a significant complicating comorbidity for individuals with BD, and adds new information that SUD arises during the early course of evolving illness, not uncommonly before the first activated episode.

As far as we know, this is the first analysis of the risk of SUD based on prospective longitudinal observation in a well characterized high-risk cohort. To refine our understanding of the relationship of the onset of SUD with the early course of BD, we have used a novel staging model based on our prior published findings.

The observations suggest that clinicians should be mindful that SUD may occur very early in the clinical course, particularly in males. In this high-risk cohort, the peak hazard of SUD occurred between 15-19 years of age and was associated with lower GAF and a higher lifetime history of psychotic features, suggesting an increased burden of illness. These observations underscore the importance of clinical vigilance and early intervention. The fact that cannabis now appears to be the drug of choice may have implications for altering the clinical course, and requires further study.

As a limitation, this data does not lend itself to addressing the underlying causative factors related to the risk of SUD in this population. This is a preliminary report of the risk of SUD in the early stages of evolving BD. With longer follow-up, more high-risk offspring may develop SUD which may affect the age of onset and relationship with the clinical course.

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