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Research report

Adolescent substance use disorder during the early stages of bipolar disorder: A prospective high-risk study

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ABSTRACT

Background: There is a paucity of longitudinal data characterizing the relationship between substance use disorder (SUD) and the early clinical course of bipolar disorder (BD). We studied this relationship in a prospectively assessed cohort of high-risk offspring.

Methods: Eligible families had one parent with confirmed BD based on SADS-L interviews and best estimate diagnostic procedure. Offspring completed KSADS-PL interviews at baseline and were reassessed prospectively. DSM-IV diagnoses were made on blind consensus review using all available information. This analysis included 211 offspring ≥ 12 years, and used GEE and linear mixed models to determine clinical characteristics differentiating those with compared to those without SUD, and CPH models to assess the relationship between SUD and the early stages of BD.

Results: Lifetime SUD was diagnosed in 24% of offspring; cannabis use being most common. The peak hazard of SUD was between 14 and 20 years of age. Male sex (HR 3.285; $p=.0007$), a prior mood disorder (HR 2.437; $p=.0091$) and parental history of SUD (HR 2.999; $p=.0027$) contributed to the risk of SUD in the offspring, while SUD predicted an increased risk of psychosis (HR 3.225; $p=.0074$). The estimated hazard of a major mood disorder in those offspring with compared to those without a prior SUD was almost 3-fold (HR 2.990 ($p \leq 0.01$).

Limitations: The novel clinical staging model requires independent replication.

Conclusions: SUD is a common comorbidity arising during the early course of BD, even before the first activated episode. Further research is needed to understand causative factors and to develop effective early intervention and prevention strategies.

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1. Introduction

There is a well-established association between mood and substance use disorder (SUD), which is particularly strong for bipolar disorder (BD) (Angst et al., 2006). Both clinical (Cassidy et al., 2001; Winokur et al., 1995) and community-based studies (Burke et al., 1990; Kessler et al., 2005; Regier et al., 1990) have documented the elevated prevalence of comorbid BD and SUD; that is, BD and SUD occur in the same individuals more often then would be expected by chance. However, this association is complex and apparently not attributable to a shared genetic diathesis (i.e., not alternative manifestations of the same predisposition) between the two disorders (Duffy et al., 1998b). Recently, Swendsen et al. (2010) discussed the longitudinal findings from the U.S. National Comorbidity Survey, highlighting that mood disorders are risk factors for the subsequent onset of SUD, and suggesting that early effective treatment of the primary illness is an important step in preventing the transition from use to abuse or dependence.

Historically, alcohol has been the most frequently reported substance of abuse or dependence in patients with BD, followed by cannabis and then cocaine, with males at increased rates of all categories of SUD (Kessler et al., 1997; Regier et al., 1990). In an analysis of the prospectively collected data from the Zurich community cohort study, Merikangas et al. (2008) confirmed findings from retrospective clinical and community studies by showing a strong association between BD and the subsequent development of SUD. Specifically, in this longitudinal study, manic symptoms were highly predictive of all categories of SUD

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examined, especially for dependence as compared to abuse (alcohol dependence odds ratio (OR) 4.4; cannabis dependence OR 4.8 and benzodiazepine dependence OR 11.5). Furthermore, having a diagnosis of BDII was highly predictive of the development of alcohol abuse and dependence (OR 9.1 and OR 21.1, respectively). These findings suggested that, even before threshold activated episodes, manic symptoms are a risk factor for the development of SUD in individuals with BD. In other studies, Baethge et al. (2008) reported on the temporal association between alcohol use and depressive symptoms and cannabis use and manic symptoms in a first episode (BDI) clinical sample, suggesting that different substances may be used at different stages or phases of BD and perhaps for different reasons.

Conversely, cannabis use in prospective epidemiological studies has also been linked to an increased risk for the later onset of mania (Henquet et al., 2006). Further, there are observations in different clinical populations of a bidirectional association between psychopathology, especially mood and anxiety disorders, and SUD (Maremmani et al., 2011). Recent observations in younger subjects suggest that cannabis is an increasingly popular substance of misuse in clinical (Goldstein and Bukstein, 2010) and community-based (Lewinsohn et al., 1995) populations. This is especially worrisome given the accruing evidence that cannabis use is associated with an earlier age of onset of psychosis (Large et al., 2011).

SUD has a devastatingly negative effect on the clinical course and prognosis for patients with BD. Comorbid SUD has been associated with an earlier age of onset, shortening of cycle length, delayed time to recovery, higher number of recurrences, more mixed and rapid cycling presentations, chronicity, disability, cognitive impairment and elevated mortality associated with medical decline, as well as suicide (for review see (Salloum and Thase, 2000)). Furthermore, SUD is strongly associated with treatment non-adherence, contributing to the poor prognosis (Cerullo and Strakowski, 2007).

Most epidemiological and clinical studies have had to rely on cross-sectional and retrospective information to investigate the temporal association between SUD and BD. Given the strong genetic heritability of BD (McGuffin et al., 2010), the prospective study of offspring of parents with confirmed BD over adolescence and early adulthood is a powerful way to clarify the nature of the relationship between these two illnesses. Furthermore, convergent evidence suggests that BD evolves in a predictable sequence of clinical stages in those at familial risk (Duffy et al., 2010). This clinical staging framework provides an approach to refine the study of SUD over the early development of BD, even before the first manic episode. In this manuscript we describe new findings from an ongoing longitudinal study of the offspring of well-characterized bipolar parents focusing on the distribution of clinical characteristics that differentiate those high-risk (HR) offspring with, compared to those without SUD, and assess the risk of SUD in relation to our previously published clinical staging model of evolving BD (Duffy et al., 2010; Duffy, 2010).

2. Methods

2.1. HR families

As described in previous publications (Duffy et al., 1998a, 2007a), in this ongoing study, HR families are identified through specialty outpatient clinics in Ottawa and Halifax which operate according to an identical research protocol. Briefly, eligible families are those in which one parent has a confirmed DSM-IV diagnosis of BD I based on SADS-L interviews conducted by research psychiatrists followed by blind consensus diagnostic reviews including at least 2 additional psychiatrists using all available clinical information (best estimate diagnostic procedure). The other non-bipolar parent is confirmed to be unaffected for lifetime major psychiatric disorders (psychotic, mood and SUD) at the time of recruitment based on direct SADS-L interviews or FH-RDC from the affected parent. The majority of the affected parents are assessed and treated in a tertiary care clinical research environment, and therefore many years of clinical observation and systematic treatment data are available for review. In 17 cases, we included a first-degree family member (sibling or adult offspring) of the original BD I proband who, based on the same methods, met DSM-IV lifetime criteria for a bipolar spectrum disorder (recurrent major depression, BD I or II). The clinical status of all first-degree relatives of the affected parents are confirmed by FH-RDC interviews of the proband and at least one other family member.

Owing to the heterogeneity of BD, we use response to long-term lithium treatment to identify a more homogeneous subgroup of affected parents, known to have a low risk of comorbid psychiatric disorders (Grof et al., 1994, 2002). The research criteria for lithium response (LiR) has been described in detail elsewhere (Turecki et al., 1998), and includes: a documented highly recurrent illness course prior to lithium, and no major recurrences while on adequate lithium monotherapy (as evidenced by therapeutic lithium levels ≥ 0.6 mmol/l) for a minimum of 3 years. Lithium non-response (LiNR) identifies a more heterogeneous subgroup of BD, characterized by elevated rates of comorbid anxiety disorder and SUD (Grof, 2003; Passmore et al., 2003).

2.2. HR offspring

In this analysis, we included all assenting/consenting offspring aged ≥ 12 years from eligible families described above, given that no offspring developed a SUD during childhood. As part of an ongoing longitudinal HR study (Duffy et al., 2007a), all offspring are interviewed annually in direct face-to-face interviews following KSADS-PL format by a research child and adolescent psychiatrist. We also collect collateral information from at least one of the parents, as well as any clinical information provided by the families. DSM-IV diagnoses are made on a blind consensus review by two independent research psychiatrists using all available research and clinical information (best estimate diagnostic procedure). Age of onset of psychiatric disorders is estimated to be the date by which the subject has met full DSM diagnostic criteria for the disorder. All procedures conducted in this study have local research ethics board approval.

2.3. Statistical analysis

To determine the distribution of clinical characteristics between those HR offspring with compared to those without SUD, we used SAS GENMOD and MIXED procedures for Generalized Estimating Equations (GEE) and linear mixed model estimation, respectively. This analysis adjusted for the correlation within a nuclear family, but did not account for the changing numbers at risk over the lifespan or the time order of onset of SUD and other psychopathology. Thus, we used Cox Proportional Hazard (CPH) models with time-varying covariates, adjusting for sex, social economic status (SES) and familial correlation, to investigate the relationship between the risk of SUD and lifetime psychopathology, and to assess the risk SUD over the early clinical stages of BD as defined by Duffy et al., (2010). Finally, we used CPH models with time-varying covariates to determine the contribution of putative risk factors (sex, SES, temperament, DSM-IV mood diagnosis, lithium response status of parent, familial history of SUD) to the risk of SUD in the HR population.

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