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Publication Date

2020-09-01

DOI

10.1016/j.jad.2020.05.131

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Author manuscript

J Affect Disord. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

J Affect Disord. 2020 September 01; 274: 126–135. doi:10.1016/j.jad.2020.05.131.

The Effect of Traumatic Events on the Longitudinal Course and Outcomes of Youth with Bipolar Disorder.

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1. Introduction

Bipolar Spectrum Disorder (BD) in youth is an episodic illness with an average prevalence rate of 3.9%, which is associated with significant psychosocial difficulties, financial burden

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and behavioral health costs, as well as high risk for suicidality and substance abuse (Birmaher, 2018; Peele, 2004; Van Meter et al., 2019). Due to the episodic and potentially lifelong course of early-onset BD, longitudinal studies are needed to understand the factors associated with its trajectory and outcomes, to inform treatment, and to improve outcomes (Birmaher, 2018).

Given the complex causal architecture of BD, the role played by individual risk factors and their likely interactions in determining how an illness trajectory unfolds is not easily determined. Nonetheless, exposure to Traumatic Events (TEs)[1] has emerged as one of the factors having substantial impact on the course of BD (Agnew-Blais and Danese, 2016). TEs are 2.6 times more prevalent in adults with BD compared to healthy controls (Palmier-Claus et al., 2016). Compared to BD adults who have not experienced TEs, BD adults with TEs have earlier BD onset, greater depressive and psychotic symptoms, psychiatric comorbidity and suicidality, greater number of recurrences, and more psychosocial stressors (Anand et al., 2015; Cohen et al., 2004a; Etain et al., 2013; Garno et al., 2005; Gershon et al., 2013; Hammersley et al., 2003; Leverich et al., 2002). TEs could impact health outcomes (Leclerc et al., 2018), and they have been associated with biological changes such as inflammation (Danese et al., 2007) and changes in gray and white matter integrity in various brain areas potentially implicated in emotion regulation and threat sensitivity (Poletti et al., 2016; Stevelink et al., 2018), possibly explaining the functional deficits observed in BD.

Among TEs, sexual and/or physical abuses are the most widely studied, and they are the strongest predictors of an adverse BD course in adults (Aas et al., 2016; Daruy-Filho et al., 2011). Abuse affects neurocognitive performance, worsens functioning and mood symptomatology, increases suicidality, and is associated with higher rates of psychiatric comorbidity in both cross-sectional and longitudinal studies in BD (Farias et al., 2019; Larsson et al., 2013; Leverich et al., 2002; Maniglio, 2013; Savitz et al., 2007).

While much of the research on the impact of TEs on BD has been conducted among adults, fewer studies have examined its impact among BD youth. Like adults, cross-sectional/ concurrent studies and chart reviews show that BD youth are more likely to report TEs than healthy youth and youth with non-BD-psychopathology (Romero et al., 2009b; Rucklidge, 2006; Tillman et al., 2003). These studies also suggest that history of TEs among BD youth is associated with more hospitalizations, decreased treatment response, delayed diagnosis, greater suicidality, higher rates of psychiatric comorbidity, worse psychosocial functioning, and earlier age of BD onset compared to BD youth without TE and non-BD youth (Cazala et al., 2019; Du rocher Schudlich, 2015; Marchand et al., 2005; Rucklidge, 2006).

Longitudinal studies examining clinical and functional outcomes among BD youth with TEs have been few, especially those that have used frequent assessments of trauma over time. Daglas and colleagues showed that BD youth with past TEs had more symptoms of mania and depression, general psychopathology, and poorer social and functional outcomes at a 12-month evaluation, as compared to those without TEs (Daglas et al., 2014). Neria and colleagues followed a large sample of youth and adults hospitalized for bipolar psychosis

[1]TEs: Traumatic Events

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(Neria et al., 2005), finding that childhood-TEs were associated with more severe symptomatology and lower remission rates 24-months after discharge. Kim and colleagues, showed that high stress (repeatedly measured over a 12-month-span) was associated with less mood symptoms improvement after one-year among 38 adolescents with BD compared to those with low stress (Kim et al., 2007). Conus and colleagues studied 118 youth experiencing their first-psychotic-mania using a retrospective file-audit, finding that those with abuse experienced poorer adherence to an 18-month early-intervention treatment than those without abuse exposure (Conus et al., 2010). However, other longitudinal studies showed only partial/no effects of TEs over BD course and onset (Strawn et al., 2010; Tijssen et al., 2010).

Nevertheless, the above-noted studies have been limited by multiple methodological factors including: 1) cross-sectional designs; 2) existing longitudinal designs limited to a maximum of 2 years for BD samples; 3) few assessed symptoms and/or TEs longitudinally; 5) infrequent follow-ups; 5) small sample sizes (N<150); 6) focus only on BD-I participants; 7) unadjusted confounding factors (e.g., socioeconomic status (SES), family history); 8) reliance on chart reviews, self-reports, and lack of direct interviews with the youth participant, and 9) retrospective measures that were covering long periods of time, increasing the likelihood of recall bias (Hardt and Rutter, 2004; Widom et al., 2004). Studies that use frequent prospective assessments of trauma and abuse and allow for the longitudinal examination of TEs impact on the course of early-onset BD could be valuable. Such studies may potentially reveal clinical and psychosocial outcomes not yet studied, providing an opportunity to identify risks and to create effective detection and intervention strategies.

The Course and Outcome of BD Youth (COBY) study is a multisite longitudinal research study of youth with childhood-onset BD followed into adulthood. This study provides a unique opportunity to examine the longitudinal effects of trauma in this age group and includes assessments of traumatic events and clinical course at various time-points. Previous cross-sectional findings from COBY have suggested that youth with BD had higher rates of negative life events and lower rates of positive life events compared to healthy controls, and 20% had a history of abuse (Romero et al., 2009a; Romero et al., 2009b).

The goals of this study are to extend the prior findings by prospectively examining: 1) the rate and effects of TEs among BD youth; and, specifically, 2) the effects of abuse on participants' course and outcomes over an average period of 8.7 years. Based on the existing literature, we hypothesized that: BD participants with lifetime TEs, particularly those with lifetime history of abuse, will spend less time euthymic, more time with threshold mania and depression, have more recurrences and comorbid disorders (e.g., substance use disorders [SUD] and Post-Traumatic Stress Disorders [PTSD]), and worse functioning, compared to those without past history of TEs.

2. Method

2.1 Participants

Youth participating in the COBY study provided data for this analysis. Details of the COBY sample are described elsewhere (Axelson et al., 2006; Birmaher et al., 2014). Briefly, from

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October 2000 through July 2006, COBY enrolled 446 participants, ages 7 to 17 years 11 months at intake (mean=12.7 ± 3.2 years old, 53% males, and majority White), meeting Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) ((Association, 2004) criteria for BD-I (n = 260), BD-II (n = 32), or BD-Not Otherwise Specified (NOS), based on the COBY operationalized definition (n = 154) (For criteria see (Axelson et al., 2006)). BD onset age was defined by the age of onset of any DSM-IV mood episode or an episode fulfilling the COBY's BD-NOS criteria. Participants were enrolled regardless of current mood state, and recruited from outpatient clinics (84.4%), inpatient units (4.4%), advertisements (6.7%), and referrals from other physicians (4.4%) at the three study sites (University of Pittsburgh, Brown University, and University of California at Los Angeles [UCLA]). Youth with schizophrenia, an intellectual disability, autism, and mood disorders secondary to medical conditions or substance use were excluded from the study.

Since the instrument for screening severe lifetime TEs (Traumatic Events Screen: TES) (Kaufman et al., 1997) (Supplemental Screen 1) was added in 2007; this paper includes 375 participants (mean age 17, age range: 8.7–25.8) who had at least one prospective follow-up visit during which the TES was completed. Participants were prospectively interviewed every 7 months for an average of 8.7years with a retention rate of 94%. Except for the included participants having significantly higher rates of family history of psychosis ($p<0.01$), there were no other significant demographic or clinical differences between the included and excluded samples.

2.2 Procedure

Each university's Institutional Review Board approved the study before enrollment, and informed consent/assent was obtained from the participants and parents at intake. COBY research staff administered semi-structured interview assessments to participants and parents. Participants age 18/older chose whether to include parents'/secondary informants' in study interviews. Participant's symptomatic and psychosocial course was reviewed by a research staff along with a study investigator who was ultimately responsible for the clinical ratings. After caregiver/participants interviews, these rating scores were used for the current analyses.

2.2.1 Measures—At intake, participants and their primary caregivers were directly interviewed for presence of current and lifetime psychopathology using the K-SADS-PL (Kaufman et al., 1997). Mood symptoms severity was assessed using the K-SADS Mania Rating Scales (K-MRS) (Axelson et al., 2003) and the depression section of the K-SADS-P (K-DRS), both derived from the mood disorder sections of the K-SADS-Present Episode (K-SADS-P; 4th revision) (Chambers et al., 1985). Diagnostic Interrater agreement was high for the K-SADS-PL (range 93%−100%). The K-SADS-PL has excellent overall diagnostic reliability with kappa coefficients for psychiatric disorders of ≥0.80 (Kaufman et al., 1997). The intraclass correlation coefficients for the K-SADS-MRS and K-SADS-DEP-P were≥0.83. Kendall's concordance coefficient was 0.85 for major depressive disorder and 0.78 for mania/hypomania. Week-by-week longitudinal changes in psychiatric symptoms were assessed using the Adolescent Longitudinal Interval Follow-Up Evaluation (A-LIFE) (Keller et al., 1987) using this instrument's Psychiatric Status Rating Scales (PSR) with

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good psychometric properties (Warshaw et al., 2001). The PSR used numeric values linked to DSM-IV criteria, ranging from 1 to 6 for mood disorders (scores indicate respectively: ≤2, euthymia, 3–4 subsyndromal symptoms, and ≥5 syndromal symptoms). Full recovery was defined as 8 consecutive weeks with a score of≤2 (minimal/no mood symptoms). Recurrence was defined by the presence of a score of ≥5, with duration of 1-week for mania/hypomania and 2-weeks for depression. PSR reliability in COBY was good/very good (Axelson et al., 2011). Intraclass correlation was 0.85 when assessing percent of time meeting full DSM-IV criteria for a mood episode and 0.82 for subthreshold mood symptoms. Reliability for PSR mood disorder ratings over COBY's course had an average Kendall's W of 0.8.

The presence of lifetime (past/present) TEs was obtained using the Traumatic Events Screen (TES) (Supplemental Screen 1), a brief interview including the 11 items derived from the PTSD section of the K-SADS-PL (Kaufman et al., 1997), plus an additional item (victim of intimate partner violence). The screen included events such as being in serious accident, witnessing a disaster or violence, being the victim of a crime, or experiencing physical/sexual abuse at any point in their lives (i.e., physical abuse in adulthood such as being hurt or threatened by peers/significant others). If a participant endorsed an event, the total number of occurrences and dates of the first, second and most recent event were recorded. Events were ascertained at each follow-up separately for parents and participants, and a summary score for each item was created. The events in the TES are answered as yes/no. In general, if either parent/participant endorsed an event, then the summary score was counted as positive. If there was discrepancy between informants, further clarification was obtained from informants. If a parent reported an event as traumatic, but participant indicated that he/she did not perceive this as traumatic, the event would not be given a positive score. Spearman correlation was strong between summary scores and participant reports at 0.95 and was slightly weaker between summary scores and parent reports at 0.72, indicating that summary scores depended more heavily on participant reports than parent reports. Spearman correlation between parents' and participants' reports was 0.59.

Information about lifetime sexual and physical abuse was obtained at the time of study recruitment with the KSADS-PL, and over follow-up with the TES.

SES was ascertained using the 4-factor Hollingshead Scale (Hollingshead, 1975). Participants' psychosocial functioning was assessed using the Psychosocial Functioning Scale (PSF), the Children's Global Assessment Scale (CGAS) (< age 22) and the Global Assessment of Functioning (GAF) (> age 22) (Jones et al., 1995; Keller et al., 1987; Shaffer et al., 1983). The parent/caretaker was interviewed at study intake about his/her own personal psychiatric history using the Structured Clinical Interview for DSM-IV (First, 1996), and first/second degree relatives psychiatric status was ascertained using an enhanced version of the Family History Screen (Weissman et al., 2000).

2.3 Statistical Analyses

Univariate group contrasts were performed via chi-squared, Fisher's exact, and t-tests as appropriate. Contrasts of suicide attempts and self-injury were made via negative binomial regression.

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For the analyses, TEs were divided into six different clusters depending on the nature of the event. TEs were clustered as follows: 1) Witnessing a Traumatic Event, 2) Experiencing an accident, 3) Being victim of violence or abuse, 4) Being confronted with traumatic news, 5) Experiencing other traumatic events, which included an open question about any past TEs such as abortion, separation from family, or bankruptcy, and finally, 6) Any of the above (See Supplemental Screen 1). All analyses involving TEs rates were first run using participants' overall rates of any TEs, and then re-run separately by TE cluster. To test the association between participants' rates of TEs and rates of mood symptoms, Poisson regressions were fit covarying for age at end of follow-up as well as demographics, comorbid diagnoses, and family history retained by Least Absolute Shrinkage and Selection Operator (LASSO). Briefly, a LASSO is a modified form of linear or generalized linear regression that penalizes overfit models via a regularization parameter that proportionally shrinks the magnitude of predictor coefficients toward zero, and in the case of less important predictors, coefficients shrink all the way to zero. In doing so, covariate selection is implicitly performed, as less important variables are removed from the model without the potential biases of other variable selection techniques such as multiple comparisons and collinearity between predictor variables. Cross-validation selected the optimal LASSO regularization parameter via the one-standard-error-rule, which conservatively implements the most regularized model whose model error is within one standard error of the minimum (Hastie T, 2009). Poisson regression effect sizes were estimated via standardized incidence rate ratios (RR). To test the association between participants' rates of TEs during recovery periods and recurrence risk, Andersen and Gill recurrent events Cox proportional hazards regressions (Andersen PK, 1982) were fit covarying for age, BD onset age, and number of previous recurrences, as well as demographics, comorbid diagnoses, and family history retained by backward selection (retention criterion for each model: $p<0.1$); effect sizes were estimated via standardized hazard ratios (HR).

Since PTSD is a common diagnosis among participants with TEs, logistic regression was used to test whether increased TE rates aggregated over follow-up were associated with increased likelihood to develop PTSD onset over follow-up (both considering rates of any TE as well as separately by cluster). Effect sizes were estimated via odds ratios (OR).

Of all TEs, sexual/physical abuse had more specific and reliable occurrence dates, which enabled more sophisticated longitudinal and survival analyses. Mixed logistic regressions modeled the probability of mood symptoms during each follow-up period as a function of age and time-varying lifetime abuse history, which was expressed as a dichotomous variable indicating whether abuse had ever been reported as of each follow-up period (random intercept accounted for within-participant correlation). These models controlled for demographics, comorbid diagnoses, and family history retained by LASSO. Lastly, Kaplan-Meier and Cox proportional hazards regression analyses (controlling for demographics, comorbid diagnoses, and family history retained by LASSO) tested for associations between lifetime abuse history and the subsequent risk to develop new onset non-affective comorbidities.

LASSO models used R 3.5.1(Team, 2019); all other statistical analyses used SAS 9.4 (SAS, 2019).

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3. Results

Of the 375 participants, 46.7% were female (n=175), and 72.0% (n=270), 14.1% (n=53) and 13.9% (n=52) had a diagnosis of BD-I, BD-II and BD-NOS respectively as of their last follow-up assessment. See Table 1 for demographics.

3.1 Prevalence of Traumatic Events

Eighty-four percent (316/375) reported at least one TE during follow-up. Participants with at least one TE subsequently reported TEs in 39% of their follow-up visits. As compared to participants without TEs, univariate analyses showed that those with at least one TE were significantly more likely to have younger intake age, younger BD-onset, lower SES, longer follow-up duration, lower psychosocial functioning, and higher rates of suicidal ideation (SI), Attention Deficit and Hyperactivity Disorder (ADHD), Disruptive Behavior Disorders (DBD), anxiety, and SUD. Also, they had higher rates of family history of depression, mania, ADHD, psychosis, anxiety, SUD, and suicidality (Table 1). Differences in the rates of comorbid disorders remained significant after covarying for between-group significant demographic and family history factors.

As shown in Table 2, among those with at least one lifetime TE, the most prevalent TE clusters were: 1) being confronted with traumatic news (80%), among which the most common event was being confronted with death (73%) (i.e., death or serious illness of a loved one); 2) experiencing an accident (58%), among which the most common event was being in a car accident (35%); and 3) experiencing any kind of violence or abuse (51%), among which the most common events were physical abuse (34%) and being a victim of a violent crime (27%) (See Supplemental Screen 1). TEs occurred approximately once every two years and at higher rate during adulthood than before 18 years old (0.9/year vs. 0.6/year, with rate ratio:1.5; $p<0.0001$).

3.2 Association between TEs and Mood Symptomatology

After adjusting for potential confounders retained by LASSO (age at end of follow-up, demographics, comorbid diagnoses, and family history), participants who experienced higher rates of any type of TE reported significantly lower rates of euthymia ($p=0.001$;Table 3) and significantly higher rates of sub/threshold Major Depressive Episodes (MDE) over follow-up ($p<0.001$). When analyzing this effect differentially by TE cluster, participants experiencing any TEs reported significantly lower rates of euthymia and significantly higher rates of sub/threshold MDE (all $p\leq0.03$). There were no significant associations between witnessing a TE or experiencing accidents and increased rates of mood symptoms. Estimated standardized incident rate ratios indicated that as compared to average participants (those at the mean rate of TEs), those whose rates of those TEs were one standard deviation above the mean had 5–9% lower rates of euthymia, 13–24% higher rates of threshold MDE, and 7–12% higher rates of subthreshold/worse MDE (depending on type of TE). Further, participants whose rates of violence/abuse were one standard deviation above the mean also had an estimated 17% higher rate of threshold hypo/mania ($p=0.008$).

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3.3 Associations between TEs and PTSD diagnosis

PTSD diagnosis was evaluated throughout each follow-up interval and diagnostic rates were compared between TE clusters. After adjusting for confounders, participants who reported above average rates of any TE had more than double the estimated odds of developing PTSD (OR=2.19, p<0.0001). Specifically, every TE cluster, except witnessing a traumatic event, was significantly associated with increased odds of developing PTSD (all OR>1.40, ps<0.009)

3.4 Association between TEs and risk for Mood Recurrences

After adjusting for number of prior recurrences and potential confounders retained by LASSO, Cox regressions showed that as compared to participants with average number of TEs, those whose rates of any TE during recovery periods were one standard deviation above the mean had significantly increased recurrence risk of any type of episode (HR=1.42, p=0.001; Table 4). When analyzing differentially by TE cluster, all clusters except accidents and “other TEs” (i.e., abortion, separation from parents) were associated with significantly increased recurrence risk (HR=1.12–1.61, p<0.03). Participants who experienced violence/abuse during recovery periods had 1.6 times the estimated hazard of subsequent recurrence risk.

3.5 Mood Course and history of sexual/physical Abuse

Of the 375 participants, 167 (44.5%) reported lifetime sexual and/or physical abuse. Abuse-exposed participants were mostly females, less likely to live with both parents, and had more comorbidities, suicidal behaviors, family psychopathology, and worse functioning (all p<0.03) than those without abuse. There were no significant age differences between participants with/without abuse history. Among abuse-exposed participants, 34% reported physical abuse and 17% reported sexual abuse. Further, Kaplan-Meier estimation indicated that 20% of the sample reported abuse by age 21, and 30% by age 24 (Supplemental Figure 1).

In contrast with other TEs, abuse dates were more specifically and reliably reported in the sample and were obtained by two different sources, which enabled more sophisticated longitudinal analyses involving abuse. Considering all participants’ longitudinal observations, after adjusting for time-varying confounding factors retained by LASSO, mixed logistic regression found a significant association between lifetime history of abuse (i.e., lifetime presence/absence of abuse history for each distinct follow-up period) and prevalence of mood symptoms, with increased likelihood of threshold and subthreshold/worse MDE (OR=1.82 and 1.38, p<0.03) and subthreshold/worse hypomania (OR=1.40, p=0.03), and a marginally non-significant trend for reduced likelihood of euthymia (OR=0.75, p=0.056; Table 5).

The more specific and reliable abuse dates enabled analyses of the association between lifetime abuse history and the risk to develop new onset non-affective disorders. Eligible sample sizes for each new onset non-affective disorder excluded participants for whom we could not establish whether abuse preceded new onset of the disorder. Also, disorders with small prevalence were not included. Kaplan-Meier and Cox regression analyses (controlling

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for demographics and family history retained by LASSO) found no significant association between abuse history and risk of new onset Generalized Anxiety Disorder (GAD) or DBD (Supplemental Table 1). However, a significant effect was established between abuse history and risk of new onset SUD. Kaplan-Meier estimation indicated that mean age of SUD onset was 23.5 years old among participants with abuse and 25.6 years old among those without abuse (Log-Rank χ2stat=23.88, p<0.0001, Figure 1). After adjusting for confounders retained by LASSO, Cox regression estimated that abuse-exposed participants had over twice the hazard of SUD-onset as compared to those without abuse (HR=2.14, p<0.0001).

4. Discussion

To our knowledge, this is the largest sample of youth with BD followed into young adulthood longitudinally, thereby allowing prospective examination of the long-term clinical and social effects of exposure to severe TEs, including sexual/physical abuse.

There were two major findings. First, consistent with our hypotheses, we observed that after adjusting for confounders, participants with a lifetime history of at least one TE (84%), particularly those with exposure to abuse (44.5%) and violence, showed worse mood course, more non-mood psychopathology, lower SES, and poorer psychosocial functioning as compared to those without TEs. Participants with lifetime TEs had earlier BD onset (Cohen's d=0.63) and greater sub/threshold mood symptomatology. Specifically, participants who had above average rates of TEs had up to 24% more threshold MDE and up to 11% more sub/threshold MDE compared to those with average TE rates, and those who experienced above average rates of violence and abuse had up to 17% more hypo/mania than those with average rates of violence/abuse. These participants had more mood recurrences (almost 1.5 times the subsequent risk of recurrence if TEs occurred during recovery periods), more SI, and comorbid disorders (anxiety, ADHD, DBD, SUD, PTSD) and family psychopathology (MDE, mania, ADHD, psychosis, anxiety, SUD, suicidality). Second, after the first abuse incident, participants had more severe MDE and hypo/mania symptoms compared to before the first abuse incident and also compared to participants who never experienced abuse. Participants who had been exposed to abuse had 82% greater odds of threshold MDE, 38% greater odds of subthreshold MDE and 40% greater odds of subthreshold hypomania compared to participants who had not experienced abuse. Abuse-exposed participants were mostly females, less likely to live with both parents, had worse mood course, and had higher rates of SI, suicide attempts, and self-injury. Furthermore, participants with lifetime abuse developed SUD more than twice as frequently and with earlier onset than participants without abuse history.

In a recent meta-analysis, the lifetime prevalence of TEs among adults with BD ranged from 8–77% (Palmier-Claus et al., 2016), while the prevalence of TEs among BD youth in some longitudinal studies has been reported around 40% (Daglas et al., 2014; Neria et al., 2005). The wide range of trauma prevalence in BD in the literature may be accounted for by methodological variability (e.g., definition of trauma, different instruments). The lifetime prevalence of abuse in BD has been reported at 24% in a systematic review (Maniglio, 2013), while concurrent/retrospective studies have reported the prevalence of abuse among BD youth around 11–24% (Conus et al., 2010; Du rocher Schudlich, 2015). The higher

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prevalence in our sample (84% with at least one TE and 45% with physical and/or sexual abuse) may be accounted by the fact that the COBY study included a referral sample and participants were followed for an average of 8.7years, increasing the likelihood to experience TEs. Furthermore, in contrast with other studies, COBY participants had frequent assessments (including self-reports, interviews, and collateral information), increasing the likelihood of identifying TEs.

Similar to prior literature, TEs presence among BD youth in our study was associated with poorer clinical and psychosocial outcomes (Daglas et al., 2014; Daruy-Filho et al., 2011; Marchand et al., 2005), and TEs increased as youth aged (Kim et al., 2007). Consistent with BD youth studies, we replicated the finding that participants with TEs have significantly greater psychiatric comorbidities, such as SUD and PTSD (Du rocher Schudlich, 2015). In addition, our findings uniquely showed that participants who had TEs above the average rate had more symptomatology than those with average TEs rates. Although this association between clinical severity and TEs rate has been reported in youth with other psychopathologies (Boe et al., 2018; Taylor and Gotham, 2016), this has not yet been studied among bipolar youth. Further, the risk of mood recurrence associated with TEs has been mostly described among BD adults (Cohen et al., 2004a; Leverich et al., 2002), with very few studies including BD youth (Neria et al., 2005; Strawn et al., 2010). Our findings showed that rates of even one standard deviation above the average of any TEs experienced during recovery periods predicted a 42% increased risk of subsequent mood recurrence compared to periods without TEs. However, a previously published longitudinal study did not show similar findings, reporting instead that trauma symptoms did not predict mood recurrences (Strawn et al., 2010). This difference may be attributable to the use of trauma symptomatology scores, not the presence of TEs.

While experiencing more TEs than average was generally associated with poorer course and more recurrences in our study, this was not the case for experiencing an accident, and witnessing a TE was not related to more severe mood symptoms. These results are similar to reports showing that experiencing an accident or witnessing trauma were not related to increased suicide risk among community adults and depressed adolescents (Jeon et al., 2014; Nrugham et al., 2010). This could be explained by the relatively independent nature of these events, as their occurrence may be more outside the individual's control. Still, we did not measure whether the TEs were dependent on the participants behaviors, so we cannot assure this explains the difference in findings.

Consistent with the adult BD literature (Carbone et al., 2019), our findings suggest that among various types of trauma, abuse has greater impact on the course of BD youth than other TEs, particularly during recovery periods. Studies among BD youth with abuse exposure are mixed. While some showed that individuals with abuse experience poorer functioning, more severe mood symptoms, more frequent episodes, and more SUD comorbidity compared to those without abuse (Du rocher Schudlich, 2015), others have reported that abuse exposure among BD youth was not associated with poorer symptomatic and functional outcomes (Conus et al., 2010). Unlike our study, prior analyses did not consider temporal associations. In our study, there was a worsening in mood symptoms after abuse occurred. Abuse dates were more reliably reported in COBY, enabling this

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comparison of mood before/after abuse, representing a unique contribution among BD youth literature highlighting the detrimental effects of abuse on mood after it occurs.

Another important finding in our study was that overall, TEs were associated mainly with depression, as shown in other BD studies (Bart et al., 2019; Farias et al., 2019; Shapero et al., 2017). However, when abuse was analyzed separately in our study, it was also associated with increased risk for hypo/mania. Other studies have also reported that abuse seems to pose a high risk for mania onset/recurrences and is associated with more severe manic symptoms compared to those without abuse (Du rocher Schudlich, 2015; Gilman et al., 2015), but other TEs were not evaluated. Although there are no clear explanations for this finding, abuse-exposed participants might have had more prior manic episodes than participants with other TEs, and abuse could contribute to increase subsequent mania risk (i.e., episode sensitization). Yet, analyses of prior episode polarities were not evaluated separately for abuse-exposed participants as compared to other participants with other TEs.

Although it is not known how TEs could affect the course and outcome of BD, there are several biological and psychosocial mechanisms that may explain this association. The central nervous system (CNS) is still maturing in adolescence; thus, TEs could affect its optimal development by interfering in affective regulation, attachment, and adaptation to environment (Cicchetti and Toth, 2005). Moreover, the early adversity sensitization (EAS) hypothesis suggests that early-TEs could have enduring effects on the catecholamine-stress-response (Otte et al., 2005), hyper-reactivity of corticoid systems (Heim and Nemeroff, 2001), and functioning of prefrontal cortex and hippocampus (Bremner, 2002). This could potentially lower the threshold for future mood episodes, leading to worsened BD course (Shapero et al., 2017). Further, individuals with mood disorders could actively contribute to their stressful environment (dependent events), which could be putatively associated with their behavior and could play a role in the precipitation of future episodes (stress generation model) or place them at risk for future re-victimization and TEs (Hammen, 2006). It is also possible that early-TEs could be associated with prodromal BD symptoms (i.e., irritability, hypersexuality), that could perpetuate this daunting cycle. Finally, stress affects sleep in childhood, potentially inducing biological changes in circadian rhythms, precipitating BD symptoms (Landgraf et al., 2014).

Among all new onset non-affective disorders examined, we found that SUD onset remained the only disorder predicted by abuse. Abuse-exposed participants had almost twice the risk of SUD onset and developed it at a younger age than those without abuse. Other studies have also reported that abuse was associated with SUD among bipolar youth/adults (Brown et al., 2005; Du rocher Schudlich, 2015; Maniglio, 2013). In contrast to our study, these studies were correlational and therefore, the direction of this association was not determined. Others have showed that childhood-onset-BD by itself poses a higher risk of SUD than adult-onset, although the role of abuse was not examined (Goldstein and Levitt, 2006; Wilens et al., 2016). The interplay between genetics (e.g. SUD family history), other stress systems (corticoid release expression), and the effects of early-abuse history in the brain could partially explain the association. Moreover, abuse survivors might use substances as a coping strategy in order to alleviate painful internal states (Roesler and Dafler, 1993). Specific

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mechanisms that mediate SUD onset among abuse-exposed BD youth should be further studied.

4.1 Limitations

The results presented should be considered in light of the following limitations. First, prospective data was gathered longitudinally in COBY and assessed retrospectively at every follow-up period encompassing an average of 7-months. While all reports of TEs are retrospective by nature, our design limited the interval between assessments to minimize retrospective recall. Second, TEs were ascertained with the TES, which contains a limited number of severe events, excluding minor, but significant events, or qualifying information on the dependence/independence on the participants' behavior, or if the event was perceived as a threat/traumatic and its severity. Emotional abuse and neglect were not ascertained with the TES. Moreover, comparison of the effects of sexual abuse and physical abuse were not separately analyzed. However, a future paper will address this issue. Third, as a longitudinal phenomenology study, COBY did not recruit a control group. Fourth, COBY participants were recruited from different clinical settings and thus might not be representative of general population. Nonetheless, similar course/morbidity of BD youth has been observed in non-clinical populations (Lewinsohn et al., 2000). Fifth, participants were predominantly White; thus, findings might not be representative of cultural minority groups. Sixth, all participants had a BD diagnosis at the time of study entry. Thus, it was not possible to reliably ascertain whether the TEs occurred before/after the BD diagnosis. Finally, except for abuse, other TEs dates captured by the TES were approximate; thus, we used a conservative approach in limiting our discussion of causality regarding the TEs effects on mood symptoms course. Nevertheless, our results indicate that TEs, particularly abuse, could contribute to worse overall BD course and outcomes.

4.2 Conclusions

Our findings provide further evidence of the impact of severe lifetime TEs on the course and outcome of early-onset BD, showing that TEs, especially sexual/physical abuse and violence were associated with more severe mood symptomatology, increased risk of mood recurrences, SI, and increased rates of comorbid disorders across all follow-up. Further, the prospective nature of our study showed that after abuse occurrence, participants experienced worsening of their mood symptomatology and were more likely to develop new-onset SUD.

The high volume and frequency of COBY follow-ups allowed for TEs assessment in a way that minimized the retrospective nature of reporting, representing an important contribution given prior literature recall biases. History of TEs, and particularly abuse, appear to be a marker that identifies high risk patients indicating that trauma screening and early intervention is recommended to minimize or potentially prevent the associated consequences.

Given the effects of TEs on the course and outcome of BD youth, it is important to periodically assess for TEs following the recommendations described in prior TEs literature (Read, 2007). Moreover, although not specific for BD youth, more specific treatments for TEs such as Trauma-Focused-Cognitive-Behavioral Therapy, which is designed to improve

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family functioning and decrease interpersonal stress associated with TEs, should be considered (Cohen et al., 2004b). Finally, studies focusing on putative biological and psychosocial mechanisms of the effects of exposure to TEs to develop more specific interventions for BD youth are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Andreu Pascual has received a grant from the Alicia Koplowitz Foundation. **Dr. Levenson** receives salary support and grant funding from NICHD, grant funding American Academy of Sleep Medicine Foundation and the University of Pittsburgh, and royalties from American Psychological Association Book. **Dr. Birmaher** reports grants from NIMH, during the conduct of the study; royalties from Random House, Woltas Kluwer (UpToDate) and Lippincott, Williams & Wilkins, outside of the submitted work. **Ms. Hower** has received research support from NIMH, and honoraria from the Department of Defense (DOD). **Dr. Yen** has received research support from NIMH, NCCIH, and the American Foundation for Suicide Prevention. **Dr. Strober** has received research support from NIMH, and support from the Resnick Endowed Chair in Eating Disorders. **Dr. T. Goldstein** reports grants from NIMH, The American Foundation for Suicide Prevention, University of Pittsburgh Clinical and Translational Science Institute (CTSI) and The Brain and Behavior Foundation and royalties from Guilford Press, outside the submitted work**. Dr. B Goldstein** reports grants from Brain & Behavior Research Foundation, Brain Canada, Canadian Institutes of Health Research, Heart & Stroke Foundation, and the departments of psychiatry of Sunnybrook Health Sciences Centre and the University of Toronto Department of Psychiatry. **Dr. Ryan** reports grants from NIH. **Dr. Weinstock** has received research support from NIMH, NCCIH, the NIH OBSSR, and NIJ. **Dr. Keller** has received research support from NIMH and the John J. McDonnell and Margaret T. O'Brien Foundation. **Dr. Axelson** reports grants from NIMH, during the conduct of the study; personal fees from Janssen Research and Development, LLC, and UpToDate, outside the submitted work. **Mr. Merranko, Ms. Gill** report no financial relationships with commercial interests.

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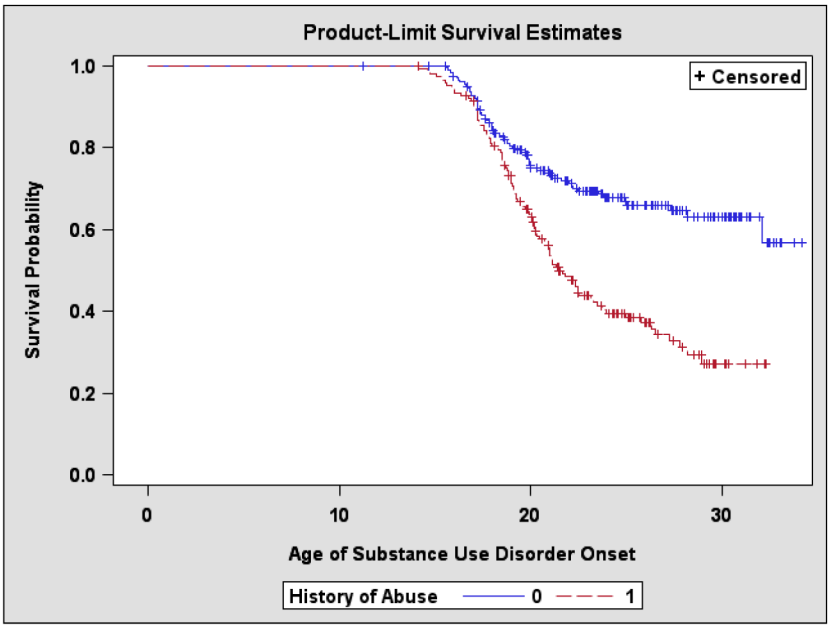

Figure 1.

Kaplan-Meier survival estimation: substance use disorder risk stratified by history of abuse * *Model controls for demographics, comorbid diagnoses, and family history retained by Least Absolute Shrinkage and Selection Operator (LASSO).

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Table 1:

Intake demographic, diagnostic, clinical, family history and psychosocial variables associated with traumatic events

	variable	Mean ± SD or N (%)		Test Stat	p-value
		No Traumatic Events (n=59)	Traumatic Events (n=316)		
Demographics	Baseline Age	18.3 (3.5)	16.7 (3.8)	t=2.98	**0.003**
	Baseline SES	4.5 (0.8)	4.1 (1.1)	t=3.06	**0.003**
	Female	32 (54.2)	143 (45.3)	χ_2=1.61	0.2
	White	47 (79.7)	260 (82.3)	χ_2=0.23	0.6
	Both Parents	20 (33.9)	95 (30.1)	χ_2=0.34	0.6
	Follow-up Length	5.5 (3.6)	8.3 (2.0)	t=5.94	**<0.0001**
Lifetime Clinical Variables	Bipolar Onset Age	11.3 (4.0)	8.9 (3.8)	t=4.42	**<0.0001**
	Bipolar Disorder Subtype				
	BD-I	46 (78.0)	224 (70.9)		
	BD-II	8 (13.6)	45 (14.2)	χ_2=1.83	0.4
	BD-NOS	5 (8.5)	47 (14.9)		
	ADHD	23 (39.0)	223 (70.6)	χ_2=21.98	**<0.0001**
	Disruptive Behavior Disorders	22 (37.3)	194 (61.4)	χ_2=11.83	**0.0006**
	Anxiety Disorder	24 (40.7)	234 (74.1)	χ_2=25.80	**<0.0001**
	PTSD	2 (3.4)	81 (25.6)	χ_2=14.27	**0.0002**
	SUD	9 (15.3)	153 (48.4)	χ_2=22.28	**<0.0001**
	Suicidal Ideation	6 (10.2)	93 (29.4)	χ_2=9.49	**0.002**
Suicidality, Self-Injury	Suicide Attempts (per year)	0.06 (0.2)	0.08 (0.2)	Negative Binomial Wald χ_2=0.03	0.9
	Self-Injury (per year)	0.05 (0.2)	0.11 (0.4)	Negative Binomial Wald χ_2=1.56	0.2
Family History	Depression	43 (72.9)	286 (90.5)	χ_2=14.35	**0.0002**
	Mania	22 (37.3)	198 (62.7)	χ_2=13.20	**0.0003**
	ADHD	18 (30.5)	158 (50.0)	χ_2=7.58	**0.006**
	CD	18 (30.5)	122 (38.6)	χ_2=1.39	0.2
	Schizophrenia	4 (6.8)	26 (8.2)	Fisher's Exact	1
	Psychosis	0 (0)	69 (21.8)	Fisher's Exact	**<0.0001**
	Anxiety	35 (59.3)	244 (77.2)	χ_2=8.36	**0.004**
	SUD	35 (59.3)	229 (72.5)	χ_2=4.12	**0.04**
	Suicidality	23 (39.0)	173 (54.8)	χ_2=4.95	**0.03**

SD=Standard Deviation; SES=Socio Economic Status; CGAS=Children's Global Assessment Scale; GAF=Global Assessment of Functioning; BD=Bipolar Disorder; ADHD=Attention Deficit and Hyperactivity Disorder; CD=Conduct Disorder; SUD=Substance Use Disorder; PTSD= Post-Traumatic Stress Disorder. a=Hollingshead Redlich criteria

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Table 2:

Traumatic events descriptive statistics (clusters, specific types, and mean rate of events) over follow-up period

Traumatic Events Descriptive Statistics (N=375)	Percent of Sample Who Reported Event	Mean Rate of Events per Year (SD)
Witness Traumatic Event	31%	0.06 (0.14)
Witness to Natural Disaster	7%	0.01 (0.02)
Witness to Violent Crime	20%	0.03 (0.10)
Witness to Domestic Violence	11%	0.02 (0.08)
Accidents	58%	0.12 (0.20)
Car Accident	35%	0.05 (0.09)
Fire	9%	0.01 (0.07)
Other Accident	36%	0.06 (0.12)
Violence and Abuse	51%	0.17 (0.35)
Victim of Violent Crime	27%	0.04 (0.13)
Physical Assault	21%	0.02 (0.05)
Sexual Assault	4%	0.00 (0.02)
Victim of Intimate Partner Violence	14%	0.05 (0.21)
Physical Abuse	34%	0.04 (0.08)
Sexual Abuse	17%	0.01 (0.05)
Confronted with Traumatic News	80%	0.25 (0.23)
Death	73%	0.15 (0.16)
Other Traumatic News	53%	0.10 (0.14)
Other (divorce, separation, bankruptcy…)	62%	0.11 (0.14)
Any of the Above	84%	0.71 (0.64)

SD=Standard deviation

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Table 3:

Poisson regressions of PSR* mood states (% of time) as a function of traumatic events rate

Traumatic Event Cluster	Mood State	Standardized Rate Ratio **	Wald χ^2	p-value
Any	Euthymia	0.92 (0.88, 0.97)	10.31	**0.001**
	Threshold MDE ***	1.24 (1.12, 1.37)	18.12	**<0.0001**
	Threshold Hypo/mania	1.12 (0.96, 1.30)	2.03	0.2
	Subthreshold MDE	1.11 (1.05, 1.18)	11.35	**0.0008**
	Subthreshold Hypo/mania	1.05 (0.98, 1.14)	2.01	0.2
Witness Traumatic Event	Euthymia	0.96 (0.92, 1.01)	2.59	0.1
	Threshold MDE	1.09 (0.99, 1.20)	3.13	0.08
	Threshold Hypo/mania	1.10 (0.97, 1.24)	1.99	0.2
	Subthreshold MDE	1.04 (0.99, 1.11)	2.19	0.1
	Subthreshold Hypo/mania	1.06 (0.99, 1.13)	3.11	0.08
Accidents	Euthymia	1.00 (0.96, 1.05)	0.03	0.9
	Threshold MDE	1.06 (0.95, 1.17)	1.00	0.3
	Threshold Hypo/mania	0.87 (0.71, 1.06)	1.94	0.2
	Subthreshold MDE	1.01 (0.95, 1.08)	0.12	0.7
	Subthreshold Hypo/mania	0.97 (0.90, 1.05)	0.52	0.5
Violence and Abuse	Euthymia	0.95 (0.90, 0.99)	5.05	**0.02**
	Threshold MDE	1.13 (1.03, 1.23)	7.42	**0.006**
	Threshold Hypo/mania	1.17 (1.04, 1.31)	7.02	**0.008**
	Subthreshold MDE	1.07 (1.01, 1.13)	5.70	**0.02**
	Subthreshold Hypo/mania	1.04 (0.97, 1.12)	1.35	0.2
Confronted with Traumatic News	Euthymia	0.94 (0.90, 0.99)	6.02	**0.01**
	Threshold MDE	1.17 (1.04, 1.31)	7.14	**0.008**
	Threshold Hypo/mania	1.02 (0.87, 1.20)	0.05	0.8
	Subthreshold MDE	1.08 (1.01, 1.15)	4.94	**0.03**
	Subthreshold Hypo/mania	1.06 (0.98, 1.14)	2.29	0.1
Other (divorce, separation, bankruptcy…)	Euthymia	0.94 (0.90, 0.99)	5.93	**0.01**
	Threshold MDE	1.20 (1.09, 1.32)	13.47	**0.0002**
	Threshold Hypo/mania	0.98 (0.83, 1.15)	0.08	0.8
	Subthreshold MDE	1.12 (1.05, 1.19)	12.69	**0.0004**
	Subthreshold Hypo/mania	1.01 (0.94, 1.09)	0.12	0.7

*PSR=Psychiatric Status Rating Scale; numeric values linked to DSM-IV criteria, range 1–6 for mood disorders. Scores ≤2 indicate euthymia, scores of 3–4 indicate subsyndromal symptoms, and scores ≥5 syndromal symptoms.

**Models adjust for age at end of follow-up + demographics, comorbid diagnoses, and family history retained by LASSO.

***MDE=Major Depressive Episode

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Table 4.

Cox regressions of recurrence * risk as a function of traumatic events rate during recovery periods

Traumatic Event Cluster	Standardized Hazard Ratio **	Wald χ^2	p-value
Any	1.42 (1.15, 1.76)	10.48	**0.001**
Witness Traumatic Event	1.12 (1.04, 1.20)	9.45	**0.002**
Accidents	1.04 (0.90, 1.19)	0.25	0.6
Violence and Abuse	1.61 (1.07, 2.40)	5.31	**0.02**
Confronted with Traumatic News	1.11 (1.01, 1.22)	5.02	**0.03**
Other (divorce, separation, bankruptcy…)	1.11 (0.95, 1.30)	1.67	0.2

* Recurrence was defined by the presence of a score of ≥5 in the Psychiatric Status Rating Scale, with duration of 1-week for mania/hypomania and 2-weeks for depression.

** Models adjust for age, BD onset age, and number of previous recurrences (0 vs. 1 vs. 2+) + demographics, comorbid diagnoses, and family history retained by backward selection (p-value<0.1).

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Table 5:

Mixed logistic regressions of mood symptoms as a function of presence vs. absence of lifetime abuse

Mood State	Odds Ratio	F-stat	p-value
Euthymia	0.75 (0.56, 1.01)	3.63	0.06
Threshold MDE	1.82 (1.37, 2.42)	16.96	**<0.0001**
Threshold Hypo/mania	1.16 (0.81, 1.67)	0.65	0.4
Subthreshold MDE	1.38 (1.04, 1.84)	4.90	**0.03**
Subthreshold Hypo/mania	1.40 (1.03, 1.89)	4.66	**0.03**

Models adjust for current age + demographics, comorbid diagnoses, and family history retained by LASSO