Trauma and abuse; the risk factors and effects on the Longitudinal course and Outcomes of Youth with Bipolar Disorder

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"Trauma and abuse; the risk factors and effects on the Longitudinal course and Outcomes of Youth with Bipolar Disorder"

"Trauma y abuso; factores de riesgo y efectos en el curso longitudinal del trastorno bipolar en jóvenes"

Memoria de tesis doctoral presentada por **María Andreu Pascual** para optar al grado de doctor por la Universidad de Barcelona
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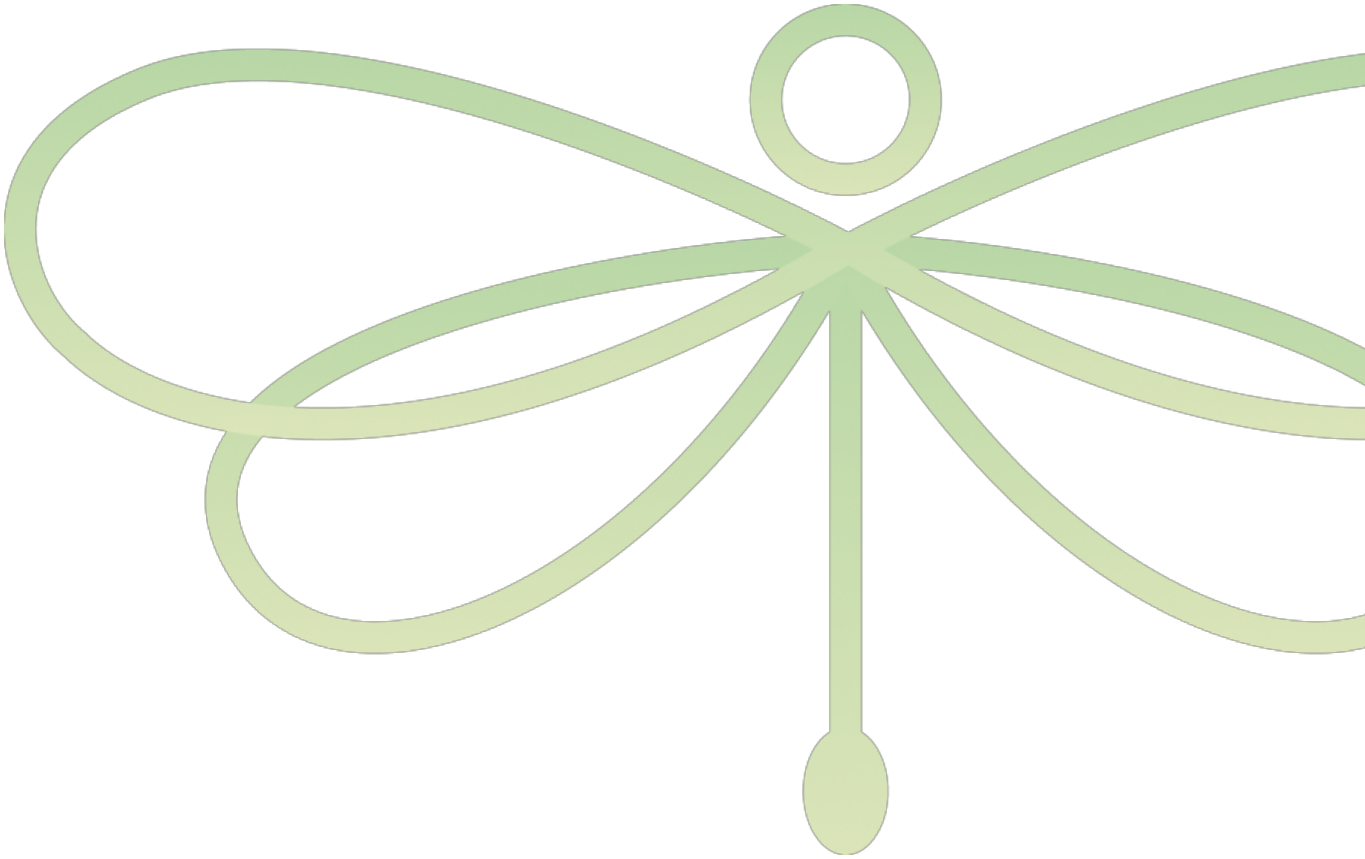
TESIS EN FORMATO COMPENDIO DE ARTÍCULOS

Yo **Boris Birmaher**, confirmo que he dirigido, revisado y leído esta tesis doctoral escrita por María Andreu Pascual. Confirmo asimismo que el trabajo realizado es fruto de investigación original, y no soy conocedor de que se hayan producido plagios a lo largo de la misma.

FRAMEWORK



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"Escribir es atenerse a una doble lógica, la de los recuerdos, y la de la ficción. Reconducir el pasado, organizarlo, mirarlo desde lejos, darle forma e intentar comprender. También para eso escribimos". (*C.Obligado).*

Se tarda mucho en comprender el calado de algunas historias, de algunos viajes, de algunas personas, o algunos pacientes. Con distancia, y un buen ángulo, el caleidoscopio arroja figuras definidas, que una vez descubiertas uno cree que siempre han estado ahí. Nos hemos fusionado con ellas. Forman parte de nosotros.

Esta tesis se inicia con uno de esos viajes aún no definidos, que fue posible en primer lugar gracias a la Fundación Alicia Koplowitz, sin la cual el resto de esta tesis no existiría. Gracias por todo el apoyo y generosidad durante estos años.

A Boris, sin ti esta tesis no sería posible, muchísimas gracias por enseñarme tanto, en lo profesional y en lo personal. Por acompañarme en cada paso, for being a mentor and a father while I was in Pittsburgh. Te debo toda mi curiosidad investigadora, todo mi crecimiento a lo largo de este tiempo. Por enseñarme a hablar con los pacientes, por ayudarme a hacer las preguntas adecuadas, y a ser paciente. Por ser un ejemplo de generosidad, humildad y respeto a nuestra profesión.

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I would like to thank the astonishing research team at Western Psychiatric Hospital, at Bellefield towers, Pittsburgh, where the thoughts and questions that allowed the development of this thesis arise between the three rivers. I can only be grateful to all of you for allowing me to be part of this team during this period. Special thanks to Jessica Levenson, for meeting with me sometimes even at 7 o'clock in the morning at a Starbucks, for all the guidance provided during these years. Thank you specially to MaryKay, Fangzi, John, Danella and Tina for being ALWAYS at the other side of the hallway or the email, for answering patiently all my questions, for having a smile always after one of my questions. Thank you Sansea and all the other fellows that shared with me this life project that lasted 3 years, you have been a special part of my Pittsburgh. I will always feel grateful to share these years with each one of you.

Thank you Xavi and Amit, my pals and colleagues, my friends on the other side of the hallway and, across the globe. Thank you both of you for being by my side during all this process, for sharing with me all your knowledge along the way. Washington will always have a special place in our hearts.

Gracias a los puntales en Pittsburgh, por escuchar, ayudar y compartir conmigo una gran parte de esta larga andadura. Gabriel, Lorena, Carolina, Brennan, Tamara, Patrick, Adriana. You all have been an incredible support for me during this process. Spill is still waiting for us.

To you, Katie, that you cried and celebrated the most when I told you that the first paper was published. My dearest friend across the globe. You told me to believe in me through all this process. Our friendship is more powerful than miles of distance. A Dani,

que siempre estuvo ahí, acompañando y con la seguridad de que algún día yo estaría escribiendo estas palabras.

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por enseñarme el poder de la perseverancia y enseñarme a dedicarme a mi profesión con pasión y devoción. A Andrea, por ser fundamental en mi vida, por haberme enseñado a frustrarme desde la primera piña de colores pintada, por creer en mi, por acompañarme en cada pasito desde que tengo memoria, por enseñarme el poder de la honestidad con una misma. A Teo, esa risa mueve montañas.

A toda mi familia, biológica y política, los que están y los que nos dejaron antes y durante la escritura de esta tesis. Charo, Pacorro y Laura, y a mis abuelos de Rojales, esta tesis también es gracias y para vosotros.

Gracias a Carmen Martín Gaite, por calar tan dentro durante este proceso, por acompañarse durante las noches de esta aventura. Al Friendship Perk Brew, a la cafetería del ACE hotel y a ese porche en South Evaline Street donde esta tesis se gestó, rodeada de luciérnagas, calabazas grabadas y tomando café de calcetín.

Finalmente, esta tesis está dedicada a TI, Tomás. Por tener las agallas de entrar en mi mundo, por colarte en cada palabra, y en cada esquina desdoblada de mis páginas. Por enseñarme a ser paciente, el poder de esa curiosidad nos ha llevado tan lejos, nos queda tanto que aprender… Por acompañarme siempre, apoyándome, fuiste piedra angular para que yo iniciara este viaje. Esta tesis está impregnada de ti desde el inicio al fin. Nunca sabremos leer el pasado, pero ahora, con perspectiva, estás en cada imagen del caleidoscopio.

Financial support

This doctoral thesis for PhD candidate arises from the scientific questions and the immense work of all the COBY team, who recruited patients since 2000 until the present moment to serve the scientific field in order to answer many questions related with bipolar disorders among youth.

This thesis and its work wouldn't have been possible without the financial support of the Alicia Koplowitz Foundation, who brought me the opportunity to do my Child and Adolescent Psychiatry fellowship in Western Psychiatry Hospital, in Pittsburgh, Pennsylavania, USA and provided me also with a short-term research grant to finish my research.

Preface

"It is easier to build strong children than to repair broken men"

(Frederick Douglas)

"Un niño, como una nube nunca es imperfecto. Que un adulto pueda serlo es, como mínimo, discutible"

(Anonymus)

This doctoral thesis arises from the interest in investigating the role of traumatic events (i.e. physical and/or sexual abuse) in the course of bipolar disorder among youth, and to further elucidate what are the risk factors that pose this youth in a vulnerable position to experience their first lifetime physical and/or sexual abuse.

After completing the six-year Medical School in University of Valencia, I did my 4-year training residency program in Psychiatry in Valencia, and I was awarded with two grants by the Alicia Koplowitz Foundation. First, a 2-year clinical fellowship program in Child and Adolescent Psychiatry (2017-2019), followed by an 8-month short term Research visiting scholar grant (2019-2020). The work reflected in this thesis was done during my 3-year fellowship/research scholarship at Western Psychiatric Hospital, in Pittsburgh (Pennsylvania), thanks to the Alicia Koplowitz Foundation who provided me with the funding and resources to move to Pittsburgh and obtain an excellent clinical and research training in Child and Adolescent Psychiatry specifically focused in Pediatric Bipolar Disorders.

During my stay in Pittsburgh, I had the opportunity to be part of the research team at the CABS clinic (Children and Adolescent Bipolar Services). The team has long developed an interest in both assessing and treating youth with Bipolar disorders. Research done in this area comes from the thoughtful clinicians and staff to provide better services to this youth. As a part of the Dr. Birmaher research team at Western Psychiatric Hospital, I was able to develop and conduct the research work presented along this thesis. Being part of this team gave me the opportunity to access to the Course and Outcome of Bipolar Youth (COBY) study, one of the largest and longest of its kind among bipolar youth. Further, I did gain new research skills during my stay that allowed me to conduct the work on my area of interest.

As a result, during this period, I have been able to publish two research manuscripts as a first author. The IF of the first paper is 4.084, which belongs to a Q1 journal in the area. The IF of the second paper is also 4.084. These two papers which are thematically related and constitute my doctoral thesis. The sum of the impact factor (IF) of these papers, according to the Web of Science Journal of Citation Reports is 8.168. I have also published other manuscripts both as first author and as a co-author that are not presented in this thesis.

In my thesis, we first conducted a longitudinal prospective study to evaluate the effects of traumatic events on the longitudinal course and outcomes over the course of bipolar disorder among youth. Afterwards, we designed another longitudinal research study to evaluate the risk factors for first lifetime physical and sexual abuse among this youth.

I do evaluate my almost 3-year stay in Pittsburgh overall as a growing experience, both in my personal and professional life. I feel I have learned how to ask scientific questions, how to conduct a research study, and how to write scientific papers of its kind. It has been a life changing experience, both in a cultural and a personal sense, I can only be grateful to all the people that I encountered along the way during this adventure that helped me grow as a person and professional. I feel this period of my life has been one of the most nourishing experiences life has gifted me, and I feel more prepared and skilled than ever to overcome new challenges in my profession.

LIST OF ABBREVIATIONS

AACAP: American Academy of Child and Adolescent Psychiatry

ADHD: Attention Deficit and Hyperactivity Disorder

A-LIFE: Adolescent Longitudinal Interval Follow-Up Evaluation

BD: Bipolar Disorder

BD-NOS: Bipolar Disorder Not Otherwise Specified

BMI: Body Mass Index

CBQ: Child Behavior Questionnaire

CBT: Cognitive Behavioral Therapy

CD: Conduct Disorder

CFF-CBT: Child and Family Focused Cognitive Behavioral Therapy

CGAS: Children's Global Assessment Scale

CI: Confidence Interval

CNS: Central Nervous System

COBY: Course and Outcome of Bipolar Youth

CNS: Central Nervous System

CYF: Child Youth Families Services

DBD: Disruptive Behavior Disorder

DBT: Dialectical Behavior Therapy

DSM: Diagnostic Statistical Manual

EAS: Early Adverse Sensitization

ETs: Eventos traumáticos

FACES-II: Family Adaptability and Cohesion Evaluation Scale-II

FDA: Federal Drug Administration

FFT-A: Family Focused Therapy for Adolescents

FUP: Follow-up

GAD: Generalized Anxiety Disorder

GAF: Global Assessment Functioning

HR: Hazard Ratio

IC: Intervalo de confianza

ICC: Intraclass Correlation

IQ: Intellectual Quotient

IRB: Institutional Review Board

IFP: Individual Family Psychoeducation

IPSRT: Interpersonal and Social Rhythm Therapy

IQ: Intellectual Quotient

K-SADS-PL: Kiddie Schedule of Affective Disorders Present and Lifetime version

K-DRS: KSADS Depression Rating Scale

K-MRS: KSADS Mania Rating Scale

LASSO: Least Absolute Shrinkage and Selection Operator

LEC: Life Events Checklist

MDD: Major Depressive Disorder

MDE: Major Depressive Episode

MFPG: Multi-family Psychoeducation Groups

NE: No especificado

OCD: Obsessive Compulsive Disorder

ODD: Oppositional Defiant Disorder

OR: Odds Ratio

PSF: Psychosocial Functioning Scale

PSR: Psychiatric Status Rating Scale

PTSD: Post Traumatic Stress Disorder

RCT: Randomized Control Trial

RR: Rate Ratio

SD: Standard Deviation

SES: Socioeconomic Status

SGA: Second Generation Antipsychotics

SI: Suicidal Ideation

SSRI: Selective Serotonine Reuptake Inhibitors

SUD: Substance Use Disorder

TB: Trastorno Bipolar

TDAH: Trastorno por déficit de atención e hiperactividad

TEPT: Trastorno por estrés postraumático

TEs: Traumatic Events

TES: Traumatic Events Screen

TUS: Trastorno por uso de sustancias

LIST OF SCIENTIFIC PAPERS INCLUDED IN THIS THESIS

Thesis presented by two published articles (formato compendio de artículos):

- **I. The Effect of Traumatic Events on the Longitudinal Course of Youth with Bipolar Disorder. SCImago Journal Rank: 1.873. Impact Factor: 4.084. Andreu Pascual, M.,** Levenson, J.C., Merranko, J., Gill, M.K., Hower, H., Yen, S., Strober, M., Goldstein, T.R., Ryan, N., Goldstein, B.I., Weinstock, L.M., Keller, M.B., Axelson, D.A., Birmaher, B**.** ***Journal of Affective Disorders,*** **(2020),** (274), (126-135). doi: https://doi.org/10.1016/j.jad.2020.05.131

- **II. Risk factors preceding new onset abuse among youth with bipolar disorder: A longitudinal prospective analysis. SCImago Journal Rank: 1.873. Impact Factor: 4.084. Andreu-Pascual, M.,** Merranko, J., Gill, M.K., Levenson, J.C., Hafeman, D., Hower, H., Yen, S., Strober, M., Goldstein, B.I., Diler, R., Ryan, N., Weinstock, L.M., Keller, M.B., Axelson, D.A., Birmaher, B**.,** Goldstein, T.R. ***.Journal of Affective Disorders,*** **(2022),** (300), (296-304). ISSN 0165 0327,https://doi.org/10.1016/j.jad.2022.01.003.(https://www.sciencedirect.com/science/article/pii/S0165032722000052)

LIST OF OTHER SCIENTIFIC CONTRIBUTIONS CO-AUTHORED BY THE PH.D. CANDIDATE, NOT INCLUDED IN THIS THESIS

- **I. Insight, sintomatología y funcionamiento neurocognitivo en pacientes con psicosis. Andreu Pascual M,** Vilaplana Pérez A, Pedrós Roselló A, Martínez Mollá P**. Revista de la Asociacion Española de Neuropsiquiatría.** Rev. Asoc. Esp. Neuropsiq. 2018; 38(134): 491-508. doi:10.4321/S0211-57352018000200008

- **II. Trastorno psicótico: Clave para el diagnóstico de esclerosis múltiple. SCImago Journal Rank (SJR):0,1. Andreu Pascual M,** Pedros Roselló A, Vilaplana Perez A, Diago Monferrer T. **Revista de psiquiatría biológica.** Psiq biol. 2015; 22(1): 27-29. El sevier.

- III. **Clinical and cognitive insight in patients with psychosis. Is there a relationship? SCImago Journal Rank (SJR): 2.188. Impact factor: 3.986.** Pedrós A, **Andreu Pascual M**, Vilaplana A, Pomares T, Sorribes G, Barberan M, Tomás A, Tordera V, Martinez P. Schizophrenia Research. Schizophr Res 192 **(2018);** 467-468.

- **IV. Reflectiveness in Cognitive Improvement. Insight in patients with psychosis. Nova Science Publishers. Inc. New York. 2018. ISBN: 978-1-53612-542-9.** Chapter 8: Reflectiveness in Cognitive Improvement. Insight in patients with psychosis. Pedrós Roselló, A; **Andreu Pascual, María**; Vilaplana Perez, A; Pomares Martínez, T; Sorribes Molina, G; Barberan Navalon, M; Tomás Pérez, A; Tordera Tordera, V; Martinez Molla, P. Page 219-233. In: Advances in Psychology Research. ISBN: **978-1-53612-542.** Editor: Alexandra M. Colombus. © 2017 Nova Science Publishers, Inc

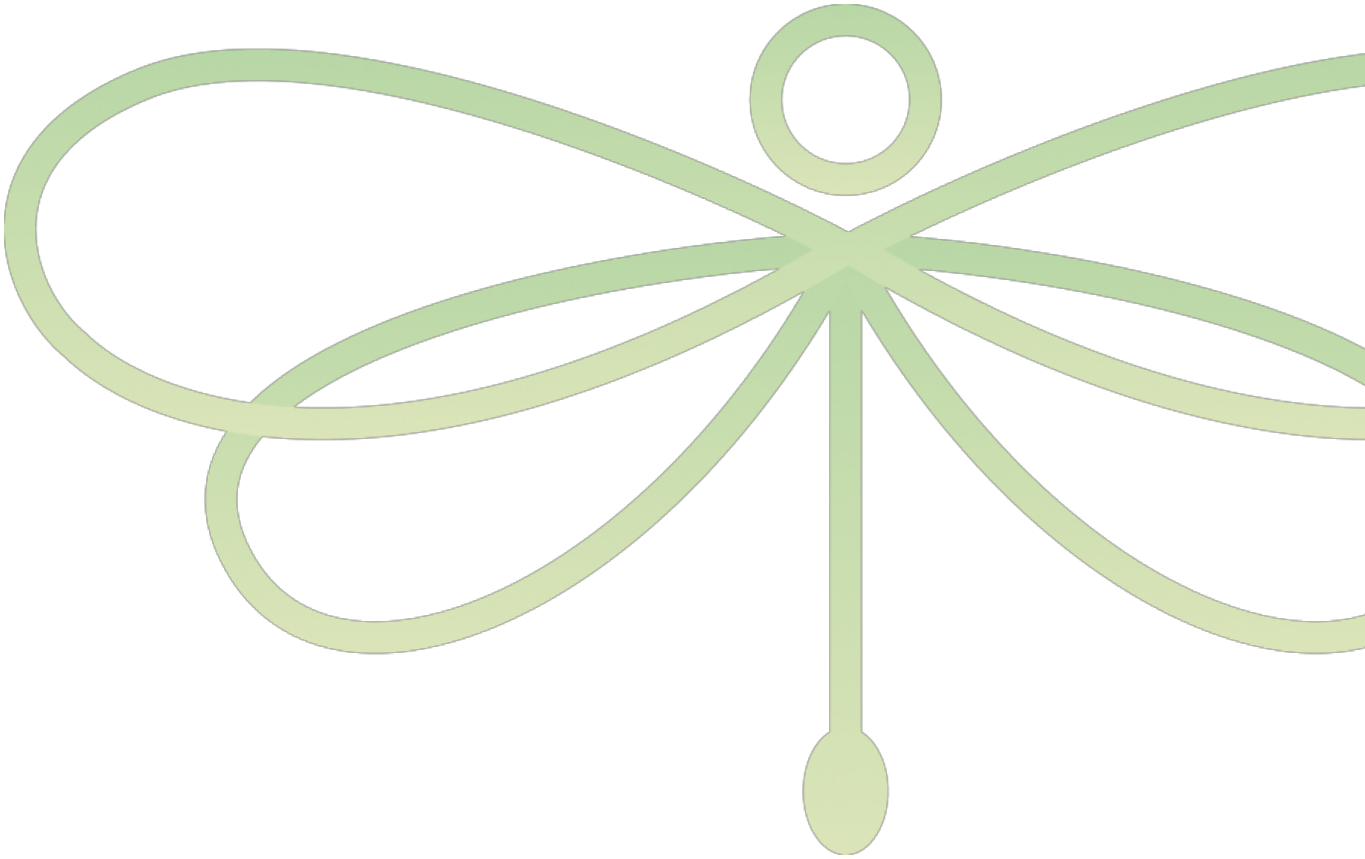
- **V. Multiple sclerosis: perspectives, clinical aspects and cognitive challenges. 160 pages. Nova Science Publishers, Inc. New York. 2017. ISBN: 978-1-63485-835-9.** Chapter 2: Multiple Sclerosis and Mental Ilness: an integrated aproach to de disease process. Pedrós Roselló, A; **Andreu Pascual, María**; Pomares Martínez, T; Vilaplana Pérez, A Chapter ID: 40555. Page 17 – 47. In: Multiple Sclerosis ISBN: 978-1-63485-835-9 Editor: Theodore Sutton © 2017 Nova Science Publishers, Inc .

- **VI. Discinesia tardía. Una revision clínica y terapéutica. SCImago Journal Rank (SJR):0,1.** Barberan Navalon M**, Andreu Pascual M**, Sorribes Molina G, Pedros Rosello A.**Revista de psiquiatría biológica.** Psiq biol 2014; 21(1): 9-13. Elsevier.

- **VII. Psicosis y diagnóstico de demencia frontotemporal**. **A propósito de un caso**. **SCImago Journal Rank (SJR):0,1.** Pedrós Roselló A, Sánchez Gil A, **Andreu Pascual M**, Diago Monferrer T. **Revista de psiquiatría biológica.** Psiquiatria Biologica 23 (2016), pp. 125-127. El sevier.

- **VIII. La función diagnóstica en salud mental infantil. ¿Estamos patologizando el sufrimiento propio de la experiencia humana?.** Romero González M, Casanovas Espinar M, Carulla Roig M, Villalta Macía L**, Andreu Pascual M,** Chanes Puiggros L. Revista de psiquiatría infanto-juvenil. Rev psiq infanto-juvenil. 2020; 4 (37): 1-5. ISSN 1130-9512.E_ISSN 2660-7271.

1. SUMMARY/RESUMEN GLOBAL EN ESPAÑOL



TÍTULO: **El efecto de los eventos traumáticos en el curso longitudinal del trastorno bipolar en jóvenes, y Factores de riesgo que preceden el inicio del abuso físico y/o sexual en jóvenes con trastorno bipolar.**

INTRODUCCIÓN

1.1 Trastorno Bipolar en la Infancia

Aunque los casos de Trastorno Bipolar (TB) en la infancia y adolescencia han sido descritos en la literatura durante años, ha sido durante las últimas dos décadas cuando se ha dedicado más investigación a este trastorno durante la infancia (1). Actualmente, se ha aceptado que el TB ocurre en niños y adolescentes. En estudios retrospectivos de adultos con TB se ha objetivado que entre el 60-70 % de los individuos con TB reportan sus primeros síntomas afectivos antes de la edad de 18 años (2). Recientemente, el foco del debate ha ido cambiando desde un escepticismo inicial sobre si el TB podía ser diagnosticado en la infancia a, actualmente, buscar herramientas adecuadas para mejorar el diagnóstico en esta etapa (3).

El TB es una enfermedad grave que afecta al desarrollo normal del niño resultando en un deterioro de funcionamiento psicosocial y está asociada a un aumento del riesgo de suicidio, síntomas psicóticos, conductas sexuales de riesgo, y abuso de sustancias (4). Asimismo, está asociado a múltiples problemas legales, conductuales, sociales y académicos. Por tanto, la investigación centrada en las fases precoces de esta enfermedad es necesaria a fin de conocer mejor el trastorno y poder desarrollar técnicas de prevención, diagnóstico y tratamiento adecuadas para estas fases de la enfermedad.

Nota: a lo largo de esta tesis la palabra jóvenes se usará para designar tanto a niños como a adolescentes.

Para los criterios diagnósticos DSM-V para TB ver Tablas 1-5 de la tesis (Introduction, diagnostic features, section 2.1.1).

1.2 Epidemiología, clínica, curso y pronóstico

El TB en la infancia puede resultar difícil de diagnosticar debido a que los síntomas pueden variar en duración con respecto al adulto y pueden ser difíciles de diferenciar del desarrollo normal del niño. Asimismo, las dificultades de los niños para verbalizar sus emociones, así como la elevada comorbilidad puede interferir en un correcto diagnóstico (5), por lo que los jóvenes deben ser evaluados de manera transversal en diferentes dominios (escuela, amigos, familia…), y obteniendo información colateral de los cuidadores.

Al tomar en consideración cómo los síntomas pueden variar a lo largo del desarrollo se facilita un correcto diagnóstico. Las guías clínicas de la AACAP proporcionan criterios para diagnosticar TB (9). Los síntomas más comunes en la infancia son: irritabilidad, labilidad del humor, distraibilidad y aumento de la actividad dirigida. La grandiosidad y la hipersexualidad son los síntomas más específicos si bien no son los más comunes (57% y 32%) (10).

Un metaanálisis reciente realizado sobre jóvenes con TB (7 a 21 años) reportó que la tasa de prevalencia era entorno a 1.8% mundial (IC al 95% 1,1% a 3,0%) (11). El TB es igualmente frecuente entre niños y niñas, aunque el inicio en la adolescencia es más frecuente entre las niñas frente a los niños (3,3% vs 2,6%), y cabe decir que el diagnóstico de TB aumenta en la adolescencia comparado con la infancia más temprana (11).

El inicio temprano de TB está asociado a un curso adverso de la enfermedad y peor pronóstico. Entre el 70-100% de los jóvenes se recuperan del primer episodio. Aunque, de los que se recuperan un 80% experimentará recurrencias en el periodo de 2 a 5 años (12). Parecido a los adultos, el curso de la enfermedad está asociado a fluctuaciones del ánimo entre un 60-80% del tiempo. El estudio COBY (uno de los estudios con mayor

muestra en esta población, n=413), reportó que el curso de TB en jóvenes con TB-I se parece mucho al de los adultos: la mayoría experimentaran recaídas y recuperaciones, la depresión es la polaridad predominante y los síntomas sub-sindrómicos predominan a lo largo del curso (8).

Algunos factores se han asociado a un peor pronóstico: inicio temprano, bajo nivel socioeconómico, más duración de la enfermedad, episodios mixtos, ciclación rápida, síntomas psicóticos, comorbilidad psicopatológica, exposición a trauma e historia familiar de enfermedades mentales.

1.3 Etiología, comorbilidad y tratamiento

Respecto a la etiología, se considera una enfermedad multicausal, muy ligada a unas bases genéticas que interaccionan constantemente a lo largo del desarrollo con variables del ambiente. La historia familiar de TB es uno de los factores de riesgo más potentes. Algunos estudios longitudinales en hijos de pacientes con TB han objetivado que la labilidad emocional, ansiedad y síntomas sub-sindrómicos están asociados en un 50% de las veces a desarrollar TB en los descendientes (13).Aunque el origen es genético, otras variables sociales y emocionales pueden jugar un papel. La investigación reciente apuesta porque el trauma y los eventos negativos pueden afectar incluso precipitar un episodio afectivo, aunque muchos episodios ocurren sin una causa identificable.

EL TB infantil se acompaña frecuentemente de otros diagnósticos (20-80%), especialmente trastornos de conducta, Trastorno por déficit de atención e hiperactividad (TDAH), ansiedad, y en adolescentes trastornos por uso de sustancias (14-16). Un metaanálisis reciente determinó prevalencias para cada trastorno: TDAH en un 53%, trastorno oposicionista desafiante en un 42%, trastornos de conducta en un 27% y trastornos de ansiedad en un 23% (10). La presencia de estos síntomas supone un reto

para el diagnóstico diferencial ya que muchos de ellos pueden solaparse, y presentan síntomas comunes que resultan difíciles de diferenciar. Además, la comorbilidad puede afectar el curso y la respuesta al tratamiento (17).

Siguiendo las guías de tratamiento, existen 3 estadios de tratamiento en el TB en la infancia: 1) Fase aguda, 2) Fase de continuación, 3) Fase de mantenimiento. El tratamiento agudo ayuda a mejorar los síntomas agudos, el de continuación se emplea para consolidar la respuesta a los tratamientos durante fase aguda, y el de mantenimiento para prevenir recurrencias. El tratamiento de elección es farmacológico, psicosocial, y/o el tratamiento combinado dependiendo de la severidad, fase, subtipo, comorbilidad, edad del joven, así como preferencias tanto del paciente como de la familia.

La psicoeducación resulta una pieza fundamental en el tratamiento, y debe realizarse tanto con el joven como con la familia. La higiene del sueño supone una pieza clave, especialmente considerando que la falta de una rutina de sueño podría empeorar la sintomatología afectiva (18).

El tratamiento de la manía aguda y los episodios mixtos: los estudios disponibles sugieren que la monoterapia con litio, ácido valproico o carbamazepina son comparables en el tratamiento de la manía/episodios mixtos no psicóticos (19). El litio fue la primera medicación aprobada por la US Federal Drug Administration (FDA) para el tratamiento de manía entre los 12-17 años. Otros estudios han sugerido que los antipsicóticos de segunda generación podrían ser más eficaces en esta fase que los tradicionales eutimizantes (19). La FDA ha aprobado varios antipsicóticos para el tratamiento de los episodios maníacos/mixtos en jóvenes: risperidona para la edad de 10-17 años, olanzapina para los 13-17 años, el aripiprazol para edades entre los 10-17 años, y la quetiapina para el mismo rango de edad.

Los clínicos deben considerar empezar el tratamiento de la depresión bipolar aguda con intervenciones como la Terapia Cognitivo Conductual o la Psicoterapia centrada en la Familia, especialmente para las depresiones moderadas. La monoterapia con quetiapina o la combinación de la olanzapina con la fluoxetina en el tratamiento agudo, o la lamotrigina para el tratamiento de mantenimiento podrían ser eficaces (20). Así mismo el tratamiento en monoterapia con lamotrigina, valproico, y la combinación de antiepilépticos o antipsicóticos de segunda generación con antidepresivos (inhibidores selectivos de la serotonina o bupropión) podría resultar efectiva.

Las psicoterapias específicas para el tratamiento de los jóvenes con TB resultan esenciales. Algunas de las psicoterapias que se han estudiado en el tratamiento del TB en la infancia son: *Child and Family Focused Cognitive Bahveior Therapy (CFF-CBT)* (21)*, Multi-family Psychoeducation Groups (MFPG)* y *Individual Family Psychoeducation (IFP)* (22)*, Family Focused Therapy (FFT)* especialmente para adolescentes con TB *(FFT-A)* (23), *terapia dialéctica comportamental adaptada a estos adolescentes* (24), *Interpersonal and Social Rhythm Therapy (IPSRT)* para adolescentes con TB (25).

1.4 Eventos traumáticos en TB

Un evento traumático (ET) es definido en la literatura como un evento peligroso, violento y atemorizante que supone una amenaza (o es percibido como tal) para la vida del niño. Los ET pueden iniciar fuertes emociones, y reacciones físicas que podrían persistir incluso mucho tiempo después del evento, y normalmente exceden la capacidad del niño de lidiar con ellas, determinando que un evento se vuelve traumático ante la inhabilidad de controlarlo, la percepción negativa del mismo y lo repentino de éste (26). Se estima que entorno un 50% de todos los jóvenes en el mundo experimentaran al menos un tipo de evento potencialmente traumático antes de la edad de los 18 años (27).

Dada la complejidad de la etiología del TB, el rol de los factores de riesgo individuales así cómo sus interacciones influyen en la trayectoria de la enfermedad todavía está por determinar. En cualquier caso, los factores de riesgo ambientales como es la exposición a ETs, ha emergido en los últimos años como uno de los factores que presenta mayor impacto significativo en el curso y pronóstico de TB (28).

Eventos traumáticos en la literatura del TB

Los ETs son 2.6 veces más prevalentes en adultos con TB que en controles sanos (29). Comparados con adultos con TB sin experiencia de ETs, los adultos con ETs tienen: inicio de TB más temprano, más síntomas depresivos y psicóticos, mayor comorbilidad psiquiátrica, más riesgo de conductas suicidas, mayor número de recurrencias del trastorno afectivo, y mayor número de estresores psicosociales (30-36). Pudiendo impactar también en la salud del individuo (37) y la calidad de vida (38).

La mayoría de literatura en los efectos del trauma en el TB se ha centrado en la población adulta, con muy pocos estudios centrándose en el impacto del trauma entre la población bipolar infantil. Como en los adultos, la mayoría de estudios transversales, han reportado que los ETs son más frecuentes en el TB que entre jóvenes sanos o con otras patologías mentales (42-44). Estos estudios sugieren que la presencia de ETs entre la población infantil bipolar están asociados con más hospitalizaciones, disminución de la respuesta al tratamiento, dificultad para el diagnóstico, mayor número de conductas suicidas, más comorbilidades psiquiátricas, peor funcionamiento psicosocial, y edad más temprana de inicio del TB comparados con aquellos sujetos con TB de inicio en la infancia que no hayan experimentado ETs (43, 45-47).

Existen pocos estudios longitudinales que examinen las variables clínicas y funcionales a lo largo del tiempo entre los jóvenes con trastorno bipolar, con una falta

significativa de evaluaciones más frecuentes del trauma a lo largo del tiempo. Daglas y colaboradores evaluaron a jóvenes (15 a 28 años) que habían experimentado su primer episodio de manía psicótica, reportando que los jóvenes bipolares con historia de trauma presentaban más síntomas de manía y depresión, más psicopatología, y peor funcionamiento psicosocial a los 12 meses del alta de hospitalización (48). Neria y colaboradores, siguieron una muestra de adultos y niños de hasta 65 años, que habían sido hospitalizados por primer episodio de TB con síntomas psicóticos (49), mostrando que aquellos expuestos a ETs permanecían más sintomáticos a lo largo del seguimiento que aquellos que no reportaron historia de trauma. Así mismo, los ETs que ocurrieron durante la infancia se asociaron con síntomas más severos a los 24 meses del alta comparados tanto con aquellos que no experimentaron trauma como con aquellos que experimentaron el trauma en la edad adulta. Kim y colaboradores, objetivaron que, a mayor estrés, existía menos mejoría de los síntomas después de un año de seguimiento a una muestra de 38 adolescentes con TB comparados con aquellos que sufrieron menos estrés (50). Conus et al. estudió una muestra de 118 jóvenes con su primer episodio de manía psicótica, usando un modelo retrospectivo de revisión de historias, mostrando que aquellos que reportaron historia de abuso mostraron peor adherencia al tratamiento a los 18 meses de seguimiento, así mismo aquellos expuestos al abuso en la infancia presentaban peor funcionamiento pre-mórbido que los que nunca sufrieron abuso (51). No obstante, otros estudios longitudinales han mostrado ningún/poco efecto del trauma sobre el curso longitudinal del TB (52, 53). Así, Strawn y colaboradores encontraron que, a pesar de la elevada prevalencia de trauma entre los jóvenes bipolares, existían pocos síntomas de PTSD y no se documentó mayor número de recurrencias mayores a los 12 meses de seguimiento (52). Tijssen a su vez mostró que el trauma infantil no predecía el inicio de la sintomatología

afectiva, y los síntomas no persistían más allá de 8 años desde el inicio del seguimiento (53).

Aunque el mecanismo por el cual los ETs afectan el curso y el pronóstico del TB no se sabe con certeza, existen múltiples mecanismos biológicos y psicosociales implicados que podrían explicar esta asociación. El sistema nervioso central continúa madurando durante la adolescencia, por lo que los ETs podrían afectar su óptimo desarrollo interfiriendo en la regulación emocional, sistemas de apego, y la adaptación del individuo al ambiente (54). Así mismo la hipótesis de la sensibilización temprana, sugiere que los ETs que ocurren en la infancia temprana podrían tener efectos duraderos sobre el sistema catecolamínico de respuesta al estrés (55), sobre la reactividad corticoidea (56), y sobre el funcionamiento óptimo de la corteza prefrontal y el hipocampo (57). Esto podría potencialmente bajar el umbral para futuros episodios afectivos a través de un peor funcionamiento tanto de la corteza prefrontal como del hipocampo, llevando a un peor curso de la enfermedad bipolar (58).

Por otra parte, los individuos con trastornos afectivos podrían contribuir su propio ambiente de estrés (eventos dependientes del comportamiento del individuo), que podrían jugar un papel en la precipitación de futuros episodios (modelo de generación de estrés) o poner en riesgo a estos sujetos para futuras revictimizaciones (59). Es posible también, que los ETs tempranos se asocien a síntomas prodrómicos (irritabilidad, hipersexualidad…), que podrían perpetuar el círculo. Finalmente el estrés afecta al sueño durante la infancia, pudiendo inducir cambios biológicos en los ritmos circadianos precipitando síntomas del TB (60).

2.1 Abuso físico y sexual en la infancia

Entre los diferentes tipos de trauma, el abuso físico y/o sexual han destacado como de los eventos más estudiados y han resultado ser grandes predictores de la salud tanto física como mental a largo plazo. Definiciones de abuso físico y sexual ver página 84.

El abuso sexual y físico

Se estima a nivel mundial que entorno a un 8% de los niños y un 18 % de las niñas experimentan abusos sexuales, y un 22% de los niños experimentan alguna forma de abuso físico (66). Además, la prevalencia de cualquier tipo de abuso entre las poblaciones clínicas se ha estimado entorno al 45%, con un 19% de ellos reportando más de una forma de abuso (67). Mientras que las tasas de prevalencia de abuso reales son difíciles de conocer con exactitud, un compendio de estudios que emplean medidas auto reportadas sugiere que las tasas de abuso se encuentran gravemente infraestimadas (68). La mayoría de los estudios epidemiológicos se ha llevado a cabo en países desarrollados, Gilbert y colaboradores reportaron que los países europeos industrializados presentaban al menos un 4% de menores que sufrían abusos cada año, con un 80% de ellos identificando a los padres como los principales perpetradores (69).

El abuso implica un grave problema tanto a nivel individual como a nivel público en las sociedades desarrolladas, ya que puede producir tanto daños a corto como a largo plazo en la víctima, y presentar consecuencias serias tanto para la familia como a nivel social a largo plazo, implicando entre otros un enorme consumo de recursos asistenciales y un gran impacto económico (70).

El abuso físico y sexual en la infancia se han asociado a consecuencias inmediatas así como a largo plazo relacionadas con condiciones físicas adversas (diabetes, estados pre-inflamatorios, o trastornos somáticos y del dolor), consecuencias psicológicas (abuso de sustancias, comportamientos agresivos y/o disruptivos, o trastornos de la conducta alimentaria) y problemas psicosociales (déficits cognitivos en el funcionamiento,

absentismo escolar, problemas de relación) que se extienden a lo largo de todo el periodo de la vida (71).

Asimismo, debido a que tanto la infancia como la adolescencia son periodos de aumento de la sensibilidad al estrés en el cerebro en desarrollo, la exposición al abuso en el desarrollo temprano ha sido asociada con aumento del riesgo tanto concurrente como subsecuente en la psicopatología del individuo, y ha estado relacionado con un tercio de todos los trastornos mentales en estudios longitudinales (72, 73). Esto ha estado respaldado por teorías acerca de la plasticidad del sistema nervioso central en los primeros años de vida, que por tanto podría llevar a una mayor influencia de los eventos adversos durante este periodo. Los jóvenes que han sufrido abusos tienen significativamente más alteraciones en las relaciones de apego, retrasos en el desarrollo del sistema nervioso autónomo, déficits en la tolerancia a la frustración, y reportan baja autoestima. Además, presentan problemas en la adquisición del lenguaje así como en el rendimiento escolar (74). Algunos tipos de abusos se han relacionado linealmente con un déficit del funcionamiento psicosocial.

Entre algunas poblaciones clínicas, los estudios reportan de manera consistente que aquellos que reportan historia de abusos en la infancia muestra síntomas más severos de depresión que participantes que no reportan historia de abusos (79). Los cambios neurobiológicos que ocurren en participantes que experimentan abusos, podrían destacar un aumento del riesgo de trastornos afectivos y un peor curso de estas enfermedades, potenciándose por la relación directa entre el trauma en la infancia y las disrupciones en la regulación afectiva.

2.2 Efectos del abuso físico y/o sexual en el TB infantil

Entorno al 65% de adultos experimentan el debut de TB antes de la adultez, y la historia de abuso en la infancia se ha asociado al inicio temprano del TB. En jóvenes con

TB, los estudios han estimado una prevalencia de entre un 3 a 20% para el abuso físico y de un 7 a un 29% (43, 46, 48, 51, 52, 80-82).

Similar a la literatura en adultos con TB, los estudios transversales y retrospectivos que tienen como variable resultado los efectos del abuso, han mostrado que tanto el abuso físico como el sexual se han relacionado con mayor edad, sexo femenino, raza no caucásica, bajo estatus socio-económico, convivir con familia no intacta y familias monoparentales o de acogida, presentar un bajo funcionamiento psicosocial, coeficiente intelectual, autoestima, y mayor número de eventos negativos, comorbilidades psiquiátricas (42, 45, 47, 81, 82). Además de los hallazgos en los estudios transversales, los escasos estudios longitudinales en el trastorno bipolar infantil han reportado que comparados con los jóvenes bipolares sin historia de abuso, los jóvenes con TB e historia de abuso presentaban peor ambiente familiar, más ansiedad comórbida, episodios depresivos más severos, más recurrencias afectivas, mayor estrés global, así como más sentimientos de desesperanza, respuesta disminuida al tratamiento y empeoramiento de los síntomas afectivos después de la ocurrencia del abuso (46, 48, 49, 51, 52).

2.3 Factores de riesgo para experimentar abuso sexual y/o físico en la población general

El enfoque de los factores de riesgo se ha convertido en una parte crucial en la mayoría de los programas de prevención a nivel mundial, incluyendo programas de implementación de los sistemas de salud para evitar los abusos. Los factores de riesgo son definidos por el Instituto de Medicina para la prevención en la ciencia como: "Características, variables y/o riesgos que, si se presentan en un individuo concreto, provocan que este individuo sufra un evento o trastorno más probablemente que otros miembros sin la característica dada. Para ser calificado de factor de riesgo existen una

serie de características que debe cumplir: 1) La variable ha de anteceder al evento; 2) Debe estar asociada con un aumento de la probabilidad de la variable resultado; 3) Debe mostrar cierto grado de estabilidad a lo largo del tiempo." (83, 84).

La literatura reciente que investiga los factores de riesgo para el abuso entre las poblaciones no clínicas intenta integrar la visión del abuso como una manifestación de un contexto más extenso, por tanto la literatura reciente emplea el modelo ecológico del desarrollo humano de Bronfenbrenner (86). Este modelo determina que los factores de riesgo ocurren a través de múltiples dominios de la ecología de la persona: demográficos, sociales y clínicos. En los estudios de la población general, el abuso se ha asociado con factores demográficos (sexo, edad, raza, estatus socioeconómico, educación de los padres, empleo, edad de la madre en el parto o convivencia), factores clínicos (psicopatología del niño y las familias, enfermedades médicas, o discapacidad intelectual) y factores ambientales (apoyo social, conflicto familiar, o historia pasada del abuso en cuidadores y jóvenes) (87-92). Desafortunadamente, muy pocos estudios han investigado estas cuestiones en estudios longitudinales, ya que por definición un factor de riesgo debe preceder un determinado resultado que se evaluará con mayor precisión en un estudio longitudinal.

Algunos dominios son de particular importancia para considerar los factores de riesgo para el abuso. En cuanto al ambiente familiar, el abuso se ha relacionado con la calidad de las relaciones familiares, escasa afectividad entre los padres y niños, experiencias adversas, técnicas de disciplina poco elaboradas, familias monoparentales o amplios núcleos familiares pueden llevar a abuso. La escasa educación paterna, la pobreza, las madres adolescentes, el aislamiento social y el desempleo de los padres se han considerado factores de riesgo para el abuso (92, 93). Los jóvenes con temperamentos complicados o alteraciones de conducta pueden exponerse a un mayor riesgo para sufrir

abusos. Otros factores de riesgo del individuo como el bajo rendimiento académico, el abuso de sustancias, y la delincuencia también se han relacionado con los resultados de los factores de riesgo (94). Además, en este estudio longitudinal el riesgo cumulativo se estudio a través de los diferentes dominios, concluyendo que los factores de riesgo se podrían acumular, de modo que la probabilidad de abuso aumentaría proporcionalmente si aumentaban el número de variables de riesgo (94, 95).

La mayoría de la literatura hasta el momento de los factores de riesgo para el abuso ha empleado medidas retrospectivas para establecer el abuso. A fin de poder establecer adecuadamente los factores de riesgo, necesitamos estudios prospectivos que sigan a los niños durante un adecuado periodo de seguimiento, que nos permitan establecer si el factor de riesgo ha precedido al abuso (ver definición de factores de riesgo). Por otro lado, existen escasos estudios que analicen los factores de riesgo en la población bipolar. El estudio de estos factores de riesgo entre la población infantil es de tremenda importancia debido a que estos jóvenes están en una situación de vulnerabilidad. Y la naturaleza y circunstancias de este trastorno puede exponer a estos jóvenes a riesgos que difieren de otro tipo de poblaciones.

El estudio COBY. ¿Qué hemos aprendido de la muestra COBY hasta el momento? Resultados de estudios previos de trauma y abuso en jóvenes con TB.

El estudio COBY (The Course and Outcome of BD Youth) es un estudio multicéntrico, longitudinal, que investiga jóvenes con trastorno bipolar de inicio en la infancia que han sido seguidos hasta la edad adulta. Este estudio ofrece una oportunidad única para examinar tanto los efectos del trauma y abuso a largo plazo como los factores de riesgo para experimentar abusos en esta población, incluyendo análisis frecuentes del trauma así como de las variables clínicas en diferentes puntos a lo largo del tiempo.

Estudios transversales previos de COBY que comparan TB con jóvenes con trastorno depresivo mayor y/o ansiedad así como con controles sanos, sugieren que los jóvenes con TB y los que padecen ansiedad/depresión tienen tasas más altas de eventos negativos a lo largo de la vida comparados con los controles sanos. Asimismo, los jóvenes con TB presentan menor número de eventos positivos dependientes del comportamiento del sujeto comparados tanto con los controles sanos como con los que padecen trastornos de ansiedad/depresión. Mayor edad, menor estatus socioeconómico, vivir con familia no intacta, raza no caucásica, trastornos comórbidos de ansiedad y de conducta están asociados con un mayor número de eventos negativos (42).

En un estudio transversal previo usando la muestra COBY, se evaluó la prevalencia y los correlatos clínicos abusos sexuales y físicos en esta muestra durante el momento de reclutamiento de la muestra y se examinó su prevalencia de manera retrospectiva. Se documentó que un 20% de la muestra había padecido abusos sexuales y/o físicos tanto en el momento del reclutamiento del estudio como de manera retrospectiva (de los cuales 9% físicos, un 7% sexuales, y un 5% ambos) (82). El análisis indicó que la historia de cualquier abuso estaba correlacionada con vivir con familias no intactas, historia de psicosis, historia de TEPT y trastorno de conducta, e historia familiar de trastornos del humor. El abuso sexual se relacionó con una mayor prevalencia de diagnóstico de TEPT. El abuso físico se asoció con una mayor duración del TB, familia no intacta, mayor prevalencia de TEPT y psicosis, y mayor prevalencia de familiares de primer grado con trastornos del estado de ánimo.

Problemas metodológicos

A pesar de que la literatura previa sobre los efectos del trauma en el curso del TB como los estudios sobre los factores de riesgo para el abuso sexual y/o físico en esta

población han sido informativos, cabe señalar que han estado marcados por una serie de limitaciones metodológicas, incluyendo: 1) La mayoría han empleado diseños transversales, 2) De los escasos estudios longitudinales existentes, pocos han evaluado de manera repetida a lo largo del tiempo tanto sintomatología como eventos traumáticos, 3) El seguimiento ha sido infrecuente o escaso, 4) Las muestras han sido de escaso tamaño, 5) La mayoría de estudios se han limitado a participantes con TB-I reclutados durante la hospitalización, 6) Muchos estudios han fallado en ajustar por variables de confusión como el estatus socioeconómico, la historia familiar, el sexo o la edad, 7) La literatura centrada en los factores de riesgo para el abuso se ha limitado especialmente a muestras de la comunidad, sobretodo limitada a niños involucrados en servicios sociales o de protección al menor, con una falta de estudios en muestras clínicas especialmente en TB, 8) Se han empleado mayoritariamente revisiones de historias clínicas, autoreportajes de los individuos, con una falta de entrevistas clínicas directas con el paciente, usando evaluaciones retrospectivas que cubren largos periodos de tiempo. Esta última limitación acerca del uso de revisión de historias clínicas así como el empleo de medidas retrospectivas que cubren largos periodos de la vida del sujeto suponen la principal limitación de la literatura hasta el momento en el estudio de eventos traumáticos en la población bipolar, debido a que esto supone un significativo sesgo de recuerdo, especialmente cuando hablamos de eventos como el trauma o el abuso que presentan mayor tendencia a ser infra/sobrereportados (97, 98). Además, otros estudios han reportado los potenciales sesgos cuando se emplean técnicas retrospectivas en muestras de adultos con TB debido a que podría estar afectado por el estado actual del ánimo del sujeto (99). Hasta donde sabemos no existen estudios prospectivos que evalúen los factores de riesgo para el abuso sexual y/o físico tanto en jóvenes como en adultos con

TB, además ningún estudio hasta la fecha ha evaluado las variables de riesgo más próximas al primer episodio de abuso en esta población.

Además estudios que empleen análisis prospectivos con repetidas medidas del abuso y el trauma a lo largo del tiempo, son necesarios para poder evaluar de manera fidedigna el impacto del trauma a largo plazo en los jóvenes con TB de inicio en la infancia, de modo que minimicemos los sesgos retrospectivos especialmente de recuerdo, permitiendo asimismo aportar algo más de conocimiento sobre los factores de riesgo principales para experimentar abusos sexuales y/o físicos en esta población clínica. Estos estudios son necesarios para revelar tanto resultados clínicos como psicosociales que aún no se han evaluado, proporcionando una oportunidad para identificar riesgos y así como establecer técnicas eficaces de detección precoz así como de intervención temprana.

HIPÓTESIS

Basándonos en la literatura previa, nuestra primera hipótesis es que: los participantes con TB que hayan padecido eventos traumáticos en algún momento de su vida, particularmente aquellos con historia de abuso, pasarán menos tiempo en eutimia, más tiempo con manía y depresión, tendrán más recurrencias afectivas así como más trastornos comórbidos (por ejemplo: uso de sustancias, TEPT) y un peor funcionamiento psicosocial comparados con aquellos que no padecieron ningún evento traumático en el pasado.

Asimismo, basándonos en la literatura previa, realizamos una segunda hipótesis de que: 1) Los factores de riesgo pasados y durante el reclutamiento para el primer abuso durante el seguimiento incluirán factores que estén previamente identificados en la literatura, incluyendo bajo estatus socioeconómico, escaso soporte social, psicopatología en el niño o en la familia, sexo femenino, y 2) los predictores cercanos

al primer abuso incluirán variables asociadas con abuso en estudios previos, incluyendo mayor edad, trastornos comórbidos, bajo estatus socioeconómico, psicopatología familiar, y cambios en el estatus socioeconómico.

OBJETIVOS

Extender los hallazgos de COBY previos analizando de manera prospectiva las tasas y efectos de los eventos traumáticos sobre la población bipolar infantil, especialmente los efectos del abuso sobre una submuestra de estos participantes seguidos longitudinalmente.

En segundo lugar, extender los hallazgos previos de COBY a través de: 1) examinar de manera prospectiva los factores (pasados y durante el reclutamiento) asociados con el incremento de riesgo del primer abuso físico y/o sexual antes de los 18 años en una submuestra de jóvenes en COBY con TB infantil seguidos a lo largo del tiempo; 2) Llevar a cabo el primer estudio prospectivo que analiza los factores de riesgo que preceden cercanos en el tiempo el primer abuso físico/sexual entre jóvenes con TB.

MÉTODOS

Desde 2000 a 2006, COBY reclutó 446 participantes, edades de 7 a 17 años (media=12,7 años, 53% hombres), que cumplían criterios DSM-IV para TB-I (n=260, TB-II (n=32) o TB-NE (n=154). Los participantes fueron reclutados sin tener en cuenta el estado de ánimo en ese momento. Los criterios de exclusión fueron autismo, esquizofrenia, discapacidad intelectual, y trastornos afectivos secundarios a condiciones médicas, sustancias.

Los procedimientos generales y evaluaciones empleados en el estudio COBY están descritos más detalladamente en la sección de Methods posteriormente.

Los métodos específicos para cada uno de los estudios están descritos a continuación brevemente:

ESTUDIO I: "El efecto de los eventos traumáticos en el curso longitudinal del Trastorno Bipolar en jóvenes"

Participantes: Dado que el instrumento para evaluar los eventos traumáticos (Traumatic Events Screen: TES) (100) fue incluido en 2007, el estudio incluyó 375 participantes que habían tenido al menos una visita de seguimiento durante la cual la TES fue completada.

Evaluación de los eventos traumáticos: La presencia de eventos traumáticos (pasado/presente) fue obtenida mediante la TES, una breve entrevista que incluía 11 ítems derivados de la sección de TEPT de la K-SADS-PL (100). Los eventos se evaluaron durante cada visita de seguimiento, así como el número de ocurrencias y fechas.

Análisis estadístico: Contrastes univariados entre grupos fueron evaluados a través de chi-cuadrado, fisher exact, y t-test. Para evaluar la relación entre la tasa de ETs y los síntomas afectivos, se emplearon regresiones de Poisson, covariando por edad al final del seguimiento, así como variables demográficas, diagnósticos comórbidos, e historia familiar retenidos a través de Least Absolute Shrinkage and Selection Operator (LASSO). Para la asociación entre la tasa de ETs y los periodos de recurrencia y recuperación se emplearon las variables de riesgo proporcional de Cox (101).

De todos los ETs, el abuso físico/sexual tenían fechas más específicas y fiables de ocurrencia, que permitieron un análisis más sofisticado. Estos modelos controlaron por edad, diagnóstico de comorbilidad, e historia familiar retenidos por LASSO. Los modelos de LASSO emplearon R 3.5.1(102); todos los otros análisis estadísticos emplearon SAS 9.4 (103).

ESTUDIO II: "Factores de riesgo que preceden el inicio del abuso físico/sexual en jóvenes con trastorno bipolar: un estudio longitudinal prospectivo"

Participantes: Para asegurar que los predictores pasados precedían al abuso, excluimos los participantes que ya habían reportado historia previa de abuso en el reclutamiento (n=75). Este análisis incluyó 279 participantes (44% mujeres, 83% caucásicos), y contaban con al menos una visita de seguimiento antes de los 18 años. Los participantes contaban con seguimientos cada 7 meses, durante una media de 12 años.

Abuso físico/sexual: La historia de abuso en la infancia (definida como antes de los 18 años) fue evaluada durante el reclutamiento y durante cada seguimiento usando múltiples medidas. Esta información fue obtenida mediante abuso físico/sexual mediante el reclutamiento a través de la sección de PTSD de la KSADS-PL y durante el seguimiento con la TES (definida previamente).

Análisis estadístico: Debido a las diferencias entre el abuso en la infancia y en la adultez, así como las potenciales diferencias en los factores de riesgo entre ambos, los participantes que no tuvieron una visita de seguimiento antes de los 18 años fueron excluidos, a menos que reportaran el abuso antes de los 18 años. Para identificar los predictores más potentes de riesgo de abuso, se emplearon regresiones proporcionales de riesgo de Cox modelando la edad del primer abuso a través de LASSO. La imputación múltiple se usó para imputar las variables desconocidas. Así, la estabilidad de LASSO fue evaluada mediante bootstrapping (104, 105) y computando el porcentaje de las iteraciones en las que el predictor se retenía. Los predictores fueron escogidos basándonos en la literatura. Todos los modelos controlaron por la edad de reclutamiento.

Los predictores durante el seguimiento identificaron de modo similar el primer abuso físico/sexual. Estos modelos fueron usados cautelosamente para identificar cambios que ocurrieron en proximidad temporal (en la última visita de seguimiento) al

primer abuso, incluyendo todos los cambios en la sintomatología clínica y demográfica que ocurrieron en el periodo de evaluación previo.

RESULTADOS

ESTUDIO I: "El efecto de los eventos traumáticos en el curso longitudinal del Trastorno Bipolar en jóvenes"

De los 375 participantes, 46,7% fueron mujeres (n=175), 72,0% (n=270), 14,1% (n=53) y 13,9% (n=52) tenían un diagnóstico de TB-I, TB-II, y TB-NOS respectivamente en su último seguimiento.

Prevalencia de los eventos traumáticos

El 80% (316/375) reportaron al menos un evento traumático durante el seguimiento, reportando eventos traumáticos durante el 39% de las visitas de seguimiento. Comparado con los participantes que no presentaron ETs, los análisis univariados mostraron que a aquellos que presentaron al menos un ET, eran más jóvenes, tuvieron un inicio más temprano del TB, pertenecían a un menor estatus socioeconómico, estuvieron durante mayor tiempo en seguimiento, tuvieron un peor funcionamiento psicosocial, mayores tasas de suicidio y más comorbilidad psiquiátrica.

Entre aquellos que presentaron al menos un evento traumático, los grupos de eventos más destacados fueron: 1) ser confrontados con noticias traumáticas (80%), (ser confrontado con la muerte de un allegado) (73%), 2) Experimentar un accidente (58%), (estar en un accidente de coche) y finalmente, 3) experimentar algún tipo de abuso o violencia (51%), (el más frecuente: el abuso físico) (34%) y ser víctima de un accidente violento (27%).

Asociación entre los ETs y la sintomatología afectiva

Tras ajustar por posibles variables de confusión retenidas a través de LASSO, los participantes que presentaron tasas más elevadas de cualquier tipo de ET reportaron significativamente tasas más bajas de eutimia a lo largo del seguimiento (p=0,001), y significativamente más altas de episodios sub/sindrómicos de depresión mayor durante el seguimiento (p<0,001). La tasa de incidencia estandarizada indicó que comparados con los participantes con una tasa media de ETs, aquellos que presentaban una desviación estándar por encima de la media de ETs, presentaban de un 5-9% de tasas más bajas de eutimia, de un 13-24% más altas de síntomas sindrómicos depresivos, y de un 7-12% más altos de síntomas subsindrómicos depresivos. Además, específicamente para aquellos que tuvieron tasas de violencia y abuso una desviación estándar por encima de la media de ETs, presentaron un 17% más de prevalencia de síntomas de hipo/manía (p=0,008).

Asociacion entre ETs y el diagnóstico de TEPT

Después de ajustar por variables de confusión, aquellos que reportaron tasas medias de cualquier evento traumático tuvieron más del doble de probabilidades de desarrollar TEPT (OR=2,19; p<0,0001). Cuando se analizó específicamente por las distintas categorías, excepto la de presenciar un ET, el resto estaban asociados a un incremento significativo del riesgo de desarrollar TEPT (todos OR>1,40; ps<0,009).

Asociación entre los ETs y riesgo de padecer recurrencias afectivas

Después de ajustar por el número previo de recurrencias afectivas del TB así como de potenciales factores de confusión retenidos por LASSO, las regresiones de Cox mostraron que comparados con los participantes que presentaron una prevalencia media de ETs, aquellos que tuvieron una prevalencia de una desviación estándar por encima de la media de ETs durante los periodos de remisión, tenían un riesgo muy significativo de padecer cualquier tipo de episodio subsecuentemente (HR=1,42; p=0,001). Cuando se analizaron las distintas categorías de ETs, excepto la que englobaba "otros", el resto se asociaron con un aumento del riesgo de recurrencias (HR=1,12-1,61; p<0,03). Los participantes que experimentaron violencia o abuso durante el periodo de remisión presentaron una estimación de 1,6 veces más probabilidad de recurrencia posteriormente.

Relación entre el curso del estado de ánimo y la historia de abusos sexuales y/o físicos.

De los 375 participantes, 167 (44,5%) experimentaron abusos sexuales y/o físicos a lo largo de la vida. Los participantes que habían padecido abusos destacaron que fueron sobretodo niñas/mujeres, que no vivían con ambos progenitores, que tenían más comorbilidades psiquiátricas, mayores conductas suicidas, más psicopatología familiar y peor funcionamiento psicosocial (todas p<0,03) comparados con aquellos que no habían sufrido abuso. No hubo diferencias significativas de edad entre los abusados y los no abusados. Aquellos participantes expuestos al abuso, un 34% reportaron abuso físico y un 17% reportaron abuso sexual. Asimismo, la estimación de curva de Kaplan Meier indicó que el 20% de la muestra había reportado abuso a la edad de 21 años, y un 30% lo había padecido al llegar a la edad de 24 años.

En contraste con otros ETs, las fechas del abuso se recogieron de una manera más precisa en la muestra, además de ser obtenidas y contrastadas a través de dos fuentes

diferentes, lo que permitió un análisis más sofisticado en concreto del abuso. Considerando todas las observaciones longitudinales de los participantes, después de ajustar por las covariables retenidas por LASSO, la regresión logística mixta encontró una asociación significativa entre la historia de abuso a lo largo de la vida (por ejemplo, prevalencia de abuso Vs ausencia de abuso en cada periodo de seguimiento) y la prevalencia de los síntomas afectivos, con un aumento de la probabilidad de padecer síntomas sub/sindrómicos de depresión mayor (OR=1,82 y OR=1,38, p<0,03) y peores síntomas de sub/sindrómicos de hipomanía (OR=1,40; p=0,03), y una tendencia marginal a pasar menos tiempo en eutimia en global (OR=0,75; p=0,056).

En cuanto al riesgo de aparición de novo de nuevas patologías no afectivas. La muestra electa para cada desarrollo de nueva patología no afectiva excluyó a aquellos sujetos para los cuales no se podía establecer si el abuso había precedido la aparición del trastorno. Además, los trastornos que presentaron una prevalencia extremadamente baja no se incluyeron. Las curvas de Kaplan-Meier y las regresiones de Cox (controlando por factores demográficos e historia familiar) únicamente estableció una asociación significativa entre la historia de abuso y el riesgo de desarrollar abuso de sustancias. La curva de Kaplan Meier estimó que el inicio de consumo de sustancias se situaba entorno a los 23,5 años para aquellos con historia de abuso, y en 25,6 años para aquellos que no reportaron historia de abuso (Log-Rank χ2stat=23,88; p<0,0001). Tras ajustar por covariables, la regresión de Cox estimó que aquellos participantes expuestos al abuso tenían el doble de probabilidades de desarrollar trastorno por consumo de sustancias comparados con aquellos que no sufrieron abuso (HR=2,14; p<0,0001).

ESTUDIO II: "Factores de riesgo que preceden el inicio del abuso físico y/o sexual en jóvenes con trastorno bipolar: un estudio longitudinal prospectivo"

Prevalencia del primer abuso durante el seguimiento

Primer abuso durante el seguimiento

Con el fin de garantizar que los predictores pasados y durante el reclutamiento precedieran el abuso, excluimos los participantes con historia de abuso antes del reclutamiento (n=75). Este análisis incluye 279 participantes (44% mujeres, 83% blancos) con TB-I (57%), TB-II (7%) y TB-NOS (35%). De ellos, 42/279 (15%) reportaron un primer abuso durante el seguimiento (62% físico, 26% sexual, 12% ambos), de los cuales 20 (48%) tuvieron una instancia de abuso y 22 (52%) dos o más instancias.

Con la excepción de peor funcionamiento psicosocial y más historia de psicosis (todos los p valores <0,04) entre los participantes que reportaron abuso en el reclutamiento y durante el seguimiento, no hubo otras diferencias significativas entre estos participantes y participantes que reportaron abuso únicamente durante el seguimiento.

Predictores pasados, y durante el reclutamiento para experimentar el primer abuso durante el seguimiento.

Abuso físico. Las regresiones de los riesgos proporcionales de Cox seleccionadas a través de LASSO determinaron que los participantes con síntomas depresivos más severos (HR=1,29). Asimismo, existía un efecto interactivo entre las familias con un bajo estatus socioeconómico e historia familiar de TUS incrementándose el riesgo para el abuso físico (HR invertida=1,19).

Abuso sexual. El mayor predictor pasado para el abuso sexual fue el sexo femenino (HR= 2,41).

Predictores durante el seguimiento que precedieron cercanos en el tiempo el primer abuso

Abuso físico. Mayor edad (HR=1,42), síntomas de trastorno disruptivo del comportamiento (HR=1,39), y la interacción entre el bajo estatus socioeconómico y la historia familiar de TUS (HR=0,86) predijeron el primer abuso físico. La buena relación con amigos protegía frente a la experimentación de abuso físico (HR=0,72).

Abuso sexual. Tras descubrir inicialmente que vivir con ambos padres era un factor protector (HR=0,8), sustituimos esta variable por una que aportase más información como fue "cualquier cambio en el ámbito de vivienda". Los cambios en los integrantes del domicilio determinaron un aumento importante del abuso físico en el siguiente periodo de seguimiento (HR=2,76). Casi todas las instancias implicaban que el joven pasara a vivir con la madre biológica y un novio o padrastro que acudía a vivir al domicilio. El sexo femenino incrementó el riesgo de abuso en el periodo de seguimiento inmediatamente anterior a la primera instancia de abuso (HR=4,33). Las buenas relaciones interpersonales con amigos disminuyeron el riesgo de abuso sexual (HR=0,70).

Tras observar que la depresión durante el reclutamiento, pero no durante el seguimiento, era un factor predictor de abuso físico, implementamos un análisis de sensibilidad usando LASSO. La depresión fue retenida por el LASSO en un 26% de las iteraciones. Los modelos fueron repetidos tras introducir las variables de las relaciones interpersonales durante el seguimiento, resultando en la retención de estas variables en lugar de la depresión en el 100% de las iteraciones. Por tanto, el rol de la depresión como

un factor de riesgo sería explicado más bien por la ausencia de factores protectores (por ejemplo, las relaciones interpersonales).

Estimamos el riesgo a 5 años para ilustrar los cambios acumulativos de riesgo de abuso físico/sexual dependiendo de la presencia/ausencia de estos factores de riesgo y protectores.

Los análisis previos fueron repetidos además incluyendo a aquellos sujetos que habían reportado abuso en el momento del reclutamiento (n=75). La historia pasada de abuso físico o sexual determina un riesgo importante para el abuso respectivo de cada uno de los abusos en el siguiente periodo de seguimiento (HR= 1,99; HR=1,66; respectivamente). Además, si existía historia de abuso en el pasado, el diagnóstico de TUS incrementó el riesgo de sufrir abuso físico (HR=1,54) en el siguiente periodo de seguimiento. El resto de los análisis fueron similares.

DISCUSIÓN Y CONCLUSIONES

El presente trabajo es el resultado fruto de la investigación de la mayor muestra llevada a cabo en jóvenes con TB seguidos longitudinalmente hasta la edad adulta, permitiendo por tanto el análisis prospectivo de los efectos a largo plazo tanto clínicos como sociales de la exposición a ETs, incluyendo abuso sexual y físico. Es además el primer estudio en analizar los factores de riesgo cercanos en el tiempo para esta muestra analizados de manera prospectiva y repetida en el tiempo para experimentar el primer abuso físico y/o sexual. Analizando tanto los factores de riesgo pasados/durante el reclutamiento, así como los factores de riesgo durante el seguimiento que precedieron inmediatamente en el tiempo a la primera instancia de abuso reportada durante el seguimiento.

ESTUDIO I: "El efecto de los eventos traumáticos en el curso longitudinal del Trastorno Bipolar en jóvenes"

Hubo dos resultados importantes en el primer estudio. Primero, consistente con nuestra primera hipótesis, observamos que después de ajustar por covariables, los participantes con historia vital de trauma (84%), particularmente aquellos expuestos al abuso (44.5%) y violencia, mostraron peor curso del estado de ánimo, más sintomatología no afectiva, peor estatus socioeconómico, peor funcionamiento psicosocial comparado con aquellos que no padecieron ETs. Los participantes con historia vital de ETs tuvieron un inicio más temprano de debut del TB, y más sintomatología afectiva. Específicamente, los participantes que presentaban prevalencias por encima de la media de ETs tuvieron hasta un 24% más de síntomas de trastorno depresivo y hasta un 11% de sintomatología subsindrómica depresiva. Aquellos que experimentaron historia de abusos por encima de la media, presentaron hasta un 17% más de síntomas de hipo/manía que aquellos con cifras medias de abusos. Estos participantes presentaron mayor número de recurrencias afectivas (casi 1,5 veces más riesgo consecutivo de recaída si los ETs ocurrían durante los periodos de remisión), más ideación suicida, más psicopatología comórbida, más historia familiar de psicopatología. Segundo, después del primer abuso reportado, los participantes tuvieron más síntomas severos de depresión e hipo/manía comparados con antes del primer abuso así como comparado con aquellos que nunca lo experimentaron. Los participantes que habían sido expuestos al abuso presentaron un 82% más de probabilidades de presentar síntomas sindrómicos depresivos, 38% más de síntomas subdepresivos y un 40% más de probabilidades de presentar hipomanía comparados con los participantes que nunca tuvieron abuso. Los participantes que experimentaron abuso fueron sobretodo mujeres/niñas, participantes que no vivían con ambos progenitores, tenían un peor curso de la enfermedad afectiva, más tasas de ideación suicida, de tentativas suicidas y conductas autolesivas. Además, los participantes que presentaron

historia de abuso desarrollaron trastorno por abuso de sustancias más temprano y con el doble de frecuencia que los no abusados.

En un metanálisis reciente, la prevalencia de trauma entre los adultos con TB varió entre 8-77% (29), mientras que la prevalencia entre los jóvenes en estudios longitudinales se reportó entorno al 40% (48, 49). El amplio rango de prevalencias en la literatura del TB podría estar relacionado con variabilidad en los métodos (por ejemplo: definición de trauma, distintos instrumentos...). La prevalencia vital del abuso en TB se ha reportado entorno a un 24% en revisiones sistemáticas (106), mientras que estudios retrospectivos han reportado una prevalencia del abuso entre los jóvenes con TB de entorno a un 11-24% (46, 51). La mayor prevalencia en nuestra muestra (84% al menos un trauma, y un 45% abusos sexuales y/o físicos) podría estar relacionada con el hecho de que COBY incluyó una muestra clínica derivada de otros dispositivos y los participantes fueron seguidos durante una media de 8.7 años, aumentando la probabilidad de que experimentaran eventos traumáticos. Además, comparado con otros estudios, la muestra COBY fue sometida a múltiples evaluaciones (incluyendo entrevistas autoreportadas, entrevistas, así como información colateral), aumentando la probabilidad de identificar los ETs.

Parecido a la literatura previa, la presencia de ETs entre los jóvenes con TB en nuestro estudio se asoció con un curso clínico errático como con peores resultados psicosociales (47, 48, 107). Consistente con la literatura en TB infantil, replicamos los hallazgos que asociaban los ETs con mayor comorbilidad psiquiátrica como el TEPT (46). Además, nuestros hallazgos mostraron de manera novedosa que aquellos que habían padecido tasas de trauma más elevadas que el resto tenían más sintomatología afectiva que aquellos con la prevalencia de ETs dentro de la media. Aunque esta asociación entre la severidad clínica y el trauma ha sido reportada en jóvenes con otras psicopatologías

(108, 109), esto no se había estudiado entre jóvenes con TB. Además, el riesgo de recurrencia del trastorno afectivo en relación con la presencia de trauma se había descrito sobretodo en adultos con TB (32, 35), con muy pocos estudios incluyendo TB infantil. Nuestros resultados mostraron tasas al menos una desviación estándar por encima de la media de ETs, predecía un 42% de riesgo aumentado de recurrencia del trastorno afectivo comparado con periodos libres de síntomas afectivos. No obstante, un estudio longitudinal publicado previamente no mostró resultados similares, afirmando que la sintomatología traumática no predecía la recurrencia del trastorno afectivo (52).

Consistente con la literatura de adultos con TB (112), nuestros hallazgos sugieren que, entre los distintos tipos de trauma, el abuso tiene un impacto mucho mayor que otros eventos, particularmente en los periodos de recuperación. Los hallazgos en la literatura de los jóvenes con TB son variados. Mientras algunos relacionan que aquellos individuos abusados experimentaran peor funcionamiento, mayor severidad de los síntomas afectivos, más frecuencia de los episodios y más comorbilidad con abuso de sustancias comparados con los no abusados (46). Otros han reportado que el abuso no estaba asociado a un peor curso clínico y peores resultados funcionales (51). A diferencia de nuestro estudio, los análisis previos no consideraron las asociaciones temporales. En nuestro estudio, había un empeoramiento de los síntomas después de la ocurrencia del abuso. Dado que las fechas del abuso se obtuvieron de modo más fidedigno que otros ETs en COBY, permitió la comparación del estado afectivo antes y después del abuso, representando una contribución única a la literatura del TB infantil, subrayando los efectos devastadores del abuso sobre el afecto después de su ocurrencia.

Otro hallazgo importante en nuestro estudio fue que principalmente los ETs se asociaron con los síntomas depresivos, como mostraron otros estudios en TB (58, 113, 114). No obstante, cuando el abuso se analizó de manera separada en nuestro estudio, se

asoció también a un mayor riesgo de hipo/manía. Otros estudios han reportado que el abuso parece suponer un mayor riesgo tanto para la aparición como para la recurrencia de la manía, comparados con los no abusados (46, 115), aunque este estudio no incluyó otros ETs. Aunque no existe explicaciones causales para este hallazgo, los participantes abusados podrían haber tenido más episodios previos de manía que otros ETs, y el abuso podría haber contribuido a aumentar el riesgo de manía en relación con la polaridad previa de los episodios. No obstante, el estudio de las polaridades previas de los episodios no fue evaluado para los participantes que experimentaron abusos comparados con otros ETs.

Aunque no es bien sabido cómo el trauma afecta al curso de la enfermedad bipolar, existen numerosos mecanismos biológicos y psicosociales que podrían explicar esto. El sistema nervioso central sigue madurando durante la adolescencia por tanto los ETs podrían afectar su desarrollo óptimo interfiriendo en la regulación afectiva, el apego y la adaptación al ambiente (54). Además, la hipótesis de la sensibilización temprana sugiere que los traumas tempranos podrían tener efectos duraderos en el sistema catecolaminérgico (55), hiperreactividad en el sistema de liberación del cortisol (56), y el funcionamiento prefrontal y el hipocampo (57). Esto podría rebajar el umbral para futuros episodios llevando a un peor curso de la enfermedad (58). Además, los sujetos con trastornos afectivos podrían contribuir a su ambiente estresante (eventos dependientes), que podría estar asociado a su comportamiento y jugar un rol en la precipitación de episodios futuros (hipótesis de generación del estrés) o ponerlos en un mayor riesgo para la revictimización y los ETs (59). También sería posible que los traumas tempranos se hubieran asociado a síntomas prodrómicos del TB (irritabilidad, hipersexualidad) que podrían perpetuar este ciclo. Finalmente, el estrés afecta al sueño durante la infancia, afectando a los ritmos circadianos y precipitando potencialmente síntomas afectivos (60).

Al examinar todas las nuevas comorbilidades no afectivas, encontramos que el trastorno por consumo de sustancias de nueva aparición permanecía como el único trastorno que era precedido por el abuso. Los participantes expuestos al abuso tenían al menos el doble de riesgo de iniciar el consumo de sustancias, así como de iniciar el consumo a edades más tempranas que aquellos sin abuso. Otros estudios han reportado además que el abuso tanto en jóvenes como adultos con TB está asociado a trastorno por consumo de sustancias (46, 80, 116). En contraste con nuestro estudio, estos estudios eran correlacionales y por tanto la dirección de la asociación no estaba determinada. Otros han mostrado que el TB de inicio en la infancia en sí mismo supone un mayor riesgo para el inicio de consumo de sustancias comparados con el inicio del TB en la edad adulta, aunque el papel del abuso en estos artículos no fue examinado (117, 118). La interacción entre la genética (por ejemplo: historia familiar de consumo de sustancias), otros sistemas de estrés (liberación de corticoides) y los efectos del abuso temprano en el cerebro podrían explicar parcialmente esta asociación. Por otro lado, los supervivientes al abuso podrían iniciar el consumo de sustancias como estrategia de afrontamiento para aliviar recuerdos y vivencias dolorosas así como el malestar asociado (119). Los mecanismos que median el inicio del abuso de sustancias entre los jóvenes con TB expuestos al abuso deberían estudiarse con mayor profundidad a fin de encontrar mecanismos que expliquen esta asociación.

ESTUDIO II: "Factores de riesgo que preceden el inicio del abuso físico y/o sexual en jóvenes con trastorno bipolar: un estudio longitudinal prospectivo"

En este segundo estudio, teníamos como objetivo examinar los factores de riesgo (tanto pasados, durante el reclutamiento como durante el seguimiento) para sufrir el primer abuso físico/sexual entre jóvenes con TB, específicamente aquellos que

precedieron en el tiempo al primer abuso. La literatura en factores de riesgo para el primer abuso entre población bipolar es limitada (tanto adultos como población pediátrica).

Nuestros hallazgos evidencian los riesgos sustanciales de experimentar abuso entre los jóvenes con TB, cuando se excluyeron los participantes que reportaron abuso, un 15% de los jóvenes con TB reportaron una primera instancia de abuso a lo largo de los 12 años de seguimiento (62% físico, 26% sexual, 12% ambas).

Los factores de riesgo más potentes pasados y en el reclutamiento para el primer abuso físico fueron síntomas depresivos más severos, y el efecto interactivo de familias con bajo estatus socioeconómico e historia de TUS. Ser mujer era el factor de riesgo pasado más potente pasado para el primer abuso sexual. Para el abuso físico, mayor edad, más síntomas disruptivos, y el efecto interactivo de bajo estatus socioeconómico con familias con historia de TUS, fueron predictores cercanos en el tiempo al primer abuso físico. Para el sexual, ser mujer y no vivir con ambos padres biológicos (específicamente cambios recientes en la vivienda), fueron los factores de riesgo más significativos para padecer el primer abuso sexual en el siguiente periodo. Las buenas relaciones interpersonales con amigos evaluadas de manera prospectiva, se asociaron a un riesgo disminuido de sufrir abuso físico y/o sexual.

Nuestro estudio evaluó la prevalencia del primer debut de abuso de manera prospectiva. A nuestro conocimiento, COBY es el único estudio entre jóvenes con TB que evalúa la prevalencia del abuso de manera prospectiva, siendo ésta un 15%. Dos estudios realizados entre población normativa estimaron una prevalencia de abuso del 7 y el 20% respectivamente (99, 120). Nuestro estudio a diferencia de otros que emplean las muestras de servicios sociales, nuestro estudio empleó el reporte tanto de los jóvenes como de los cuidadores, en otros estudios se ha evidenciado que el reporte de abuso es de 4 a 6 veces mayor si se emplean escalas autoevaluadas (70, 121). Nuestro estudio aporta

a la literatura la perspectiva de identificar los factores de riesgo para experimentar abuso más próximo en el tiempo de manera prospectiva, permitiendo establecer nuevas perspectivas de evaluación y prevención.

Mientras que el bajo estatus socioeconómico y la historia familiar de TUS tanto en el reclutamiento como durante el seguimiento fueron factores de riesgo independientes para el primer abuso físico, la interacción entre estos resultó ser el mayor predictor de abuso. Otros estudios de adultos/jóvenes han reportado que el bajo estatus socioeconómico, y la psicopatología familiar por separado se asocian con ambos tipos de abuso (32, 82). Además, se ha puesto de manifiesto la importancia de la salud mental en los padres sobre la salud mental de sus hijos (122).

Asimismo, la mayor edad durante el seguimiento se asoció a un incremento del riesgo de primer abuso físico, otros estudios no han reportado esto (47). Algunos estudios en la comunidad han reportado que la mayor edad podría ser un factor de riesgo para ciertos tipos de abuso (por ejemplo, sexual), que se incrementa durante la adolescencia, cuando las interacciones con iguales se incrementan. No obstante COBY no posee la información de los perpetradores por lo que no podemos asegurar que esto explique los hallazgos.

La depresión severa en el reclutamiento se asoció con un mayor riesgo de sufrir el primer abuso físico. El trauma infantil se ha asociado con depresión a lo largo de la vida, parcialmente explicado por la dimensión cognitiva de la depresión y resultando en la disregulación emocional (123, 124). Los eventos traumáticos han jugado un papel en la etiología de la depresión, así como en la influencia en el curso de la depresión y la ansiedad (125). Estudios retrospectivos han asociado asimismo la depresión con el abuso físico (28, 107). Nuestros hallazgos sugiriendo que el la depresión bipolar en el reclutamiento suponía un mayor riesgo para sufrir abuso físico fueron analizados en

mayor profundidad, mostrando que este riesgo estaba asociado a algunos de los síntomas nucleares de la depresión como es el aislamiento, la baja autoestima… que podrían impactar en las relaciones interpersonales, y ponen a estos sujetos en una posición de mayor vulnerabilidad por el hecho de presentar menos factores de protección (por ejemplo, relaciones interpersonales). Este es el primer estudio que analiza una secuencia temporal entre jóvenes con TB para sufrir abuso, por tanto, no podemos comparar estos hallazgos.

Los jóvenes que presentan trastornos disruptivos comórbidos también predijeron abuso físico. Otros estudios muestran comorbilidad en jóvenes con TB asociada a abuso físico (45, 47). Jóvenes con otros trastornos asociados (por ejemplo: TDAH) también se encuentran en mayor riesgo de padecer abuso (126). Algunos estudios analizan el enlace entre TB y las dificultades de parentalidad que coexisten con trastornos disruptivos (127), lo cual dificulta aún más la experiencia de estos jóvenes.

Además, para el abuso sexual, encontramos que las chicas presentaban más de cuatro veces el riesgo para presentar abuso tanto en el reclutamiento como durante el seguimiento. Otros estudios en adultos y jóvenes (47, 51, 128), han reportado tasas más altas de abuso entre chicas comparado con los chicos (89, 129). Existen múltiples variables asociadas como son los sesgos culturales, la actitud que la sociedad juega frente a las victimas, etc.

No vivir con ambos padres biológicos durante el seguimiento suponía un elevado riesgo de experimentar el primer abuso sexual durante el seguimiento. De hecho, evaluamos los cambios prospectivos durante el seguimiento de estatus de convivencia, encontrando que el cambio más frecuente que se relacionaba con posterioridad con abuso era vivir con una madre biológica y una pareja de la madre masculina, incrementándose el riesgo hasta tres veces. En la literatura de TB, tener padres divorciados o solteros ha

estado asociado al abuso, pero no había sido previamente demostrado como un factor de riesgo previo al primer abuso (43, 51). Estudios prospectivos en muestras comunitarias han encontrado también que vivir en familias monoparentales y tener un padre no biológico en el domicilio aumentan el riesgo de abuso (88).

En el análisis de sensibilidad incluyendo a aquellos participantes que ya habían presentado abuso, haber experimentado ambos abusos suponía un riesgo incrementado para padecer abuso recurrente en el futuro. La historia pasada de abuso se ha reportado como un factor de riesgo significativo para abuso entre jóvenes investigados por servicios sociales (93).

Las buenas relaciones interpersonales con amigos durante el seguimiento estuvieron asociadas a una disminución del riesgo de sufrir abuso físico/sexual. Esto supone un hallazgo relevante ya que una de las secuelas del abuso en muchas ocasiones es el aislamiento social, el incremento de la ideación suicida, así como la patología comórbida (71). El pobre apoyo social y el aislamiento se han relacionado vastamente con incremento del riesgo de abuso (93, 130). A nuestro saber, no existen actualmente estudios que reporten los factores protectores para el abuso entre muestras de jóvenes con TB, aunque en estudios en la comunidad tener buenos amigos ha sido asociado con riesgo disminuido de abuso (93). Las investigaciones futuras deberán centrarse en expandir como afectan las relaciones interpersonales en estos jóvenes. Independientemente de la naturaleza de esta predicción, estos hallazgos sugieren la importancia de sustentar buenas relaciones interpersonales entre jóvenes con TB y centrar parte del tratamiento en estas relaciones interpersonales podría proteger frente a futuros abusos.

FORTALEZAS Y LIMITACIONES

La mayor fortaleza de esta tesis es que la muestra COBY representa una de las mayores muestras seguidas durante mayor tiempo de jóvenes con TB de inicio en la infancia seguidos hasta la edad adulta. Ambos estudios siguieron a los jóvenes de manera prospectiva, evaluaron los eventos traumáticos, el abuso y los cambios sociodemográficos. COBY tuvo evaluaciones frecuentes durante el seguimiento lo cual es de gran valor para la literatura de trauma y abuso al minimizar sesgos de recuerdo (97, 98, 131). Para el estudio I, la severidad clínica y la tasa de eventos traumáticos no habían sido estudiados antes. Además, consideramos las asociaciones temporales que representaron una novedosa contribución a la literatura. Para el estudio II, representa el primer estudio en evaluar de manera prospectiva los factores de riesgo para el abuso de nuevo, permitiendo por primera vez establecer predictores para el primer abuso. Los estudios de factores de riesgo por definición deben ser prospectivos a fin de que el factor de riesgo esté presente antes que el resultado.

Sin embargo, un número de limitaciones deben ser reportadas. Primero, los datos prospectivos fueron recolectados longitudinalmente y evaluados de manera retrospectiva en cada evaluación. Segundo, como estudio longitudinal fenomenológico, COBY no reclutó un grupo control. Tercero, los participantes de COBY fueron reclutados de diferentes sitios clínicos. Cuarto, los participantes fueron en su mayoría blancos, limitando la generalización del estudio. Quinto, todos los participantes tenían un diagnóstico de TB al inicio del estudio.

Específicamente para el estudio I, algunas limitaciones deben contemplarse. Primero, los ETs fueron evaluados con la TES, que contiene un numero limitado de eventos severos, excluyendo los eventos menores, no calificaba tampoco la dependencia/independencia de los eventos en el comportamiento del participante, o si el evento era percibido como una amenaza o no, y su severidad. Segundo, el abuso

emocional no se evaluó. Tercero, excepto para el abuso, las fechas de los ETs eran aproximadas, por lo que debemos usar un enfoque conservador en la discusión de la causalidad de los eventos sobre el curso del afecto.

Particularmente para el estudio II; algunas limitaciones incluyen: severidad, frecuencia del abuso, información del abusador, historia del abuso parental, estrategias de parentalidad, otras formas de abuso, intervenciones/servicios para el abuso no fueron evaluados de manera sistemática. El abuso no fue corroborado con otras fuentes debido a la confidencialidad.

CONCLUSIONES

1. Nuestros hallazgos aportan evidencia del impacto de los eventos traumáticos severos en la vida en el curso y pronóstico de la enfermedad bipolar de aparición temprana, mostrando que, el trauma, especialmente el abuso físico y/o sexual así como la violencia estuvieron asociados a sintomatología afectiva más severa, incremento del riesgo de recurrencias, ideación suicida, así como aumento en las tasas de comorbilidad psiquiátrica a lo largo de todo el seguimiento.
2. La naturaleza prospectiva del estudio mostró que después de la ocurrencia del abuso, los participantes experimentaban un empeoramiento en la sintomatología afectiva y eran más propensos a desarrollar trastorno por consumo de sustancias de nueva aparición.
3. El elevado volumen y frecuencia de los seguimientos en COBY permitió evaluar el trauma de modo que se minimizaran los sesgos retrospectivos al reportarlos, representando una importante contribución a la literatura debido a los sesgos de recuerdo existentes hasta el momento.

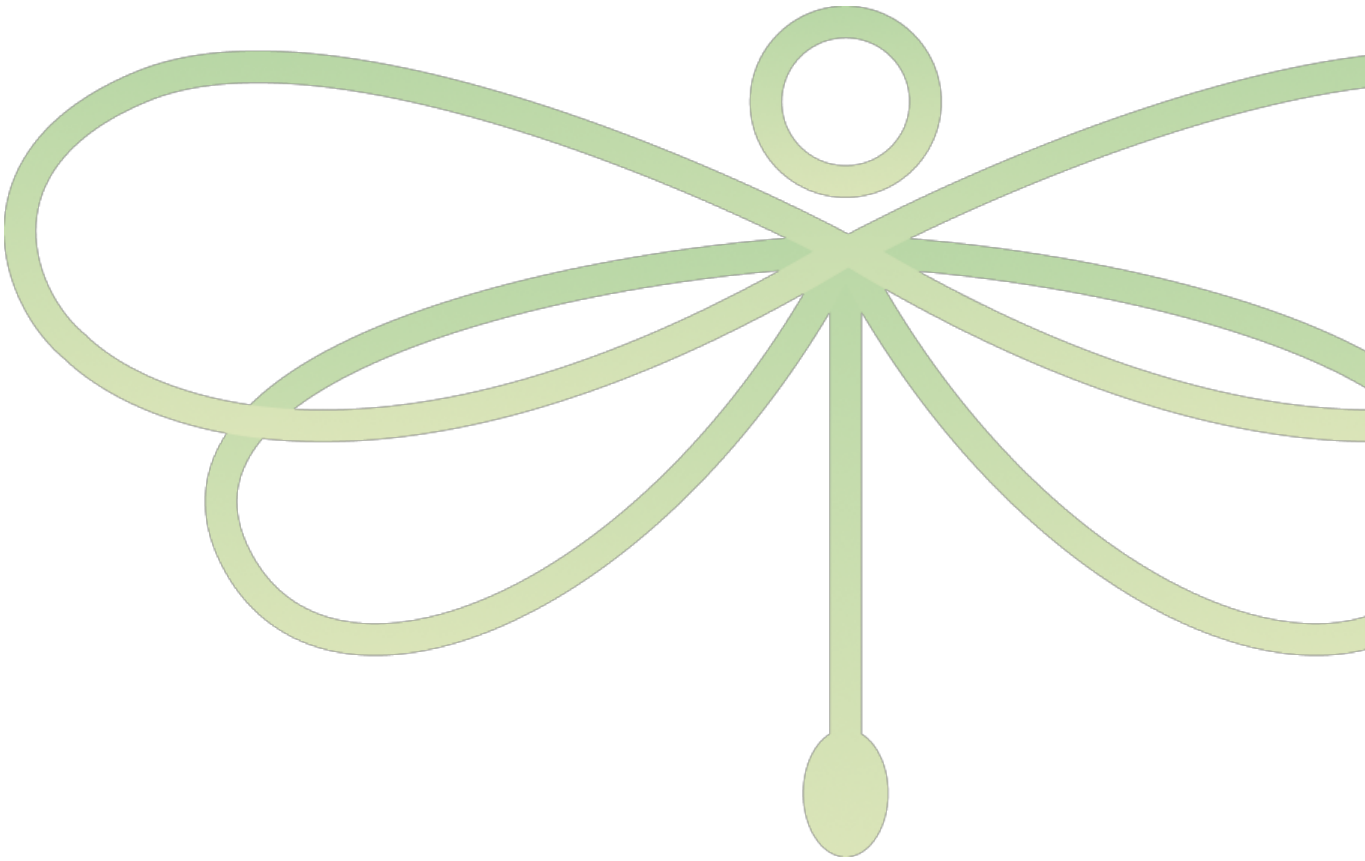
4. La existencia de la historia de trauma, particularmente abuso, parece ser un marcador que identifica pacientes de alto riesgo indicando que la detección, así como la intervención precoz del trauma es altamente recomendada para minimizar o prevenir potencialmente las consecuencias asociadas.
5. Debido a los efectos del trauma en el curso y pronóstico de la enfermedad bipolar, es importante evaluar periódicamente la presencia de trauma siguiendo las recomendaciones descritas en la literatura. La consideración de reportar a las autoridades es algo importante a tener presente cuando se reporta el abuso.
6. Aunque no específicamente para el TB infantil, tratamientos específicos para el trauma como la Terapia Cognitivo Conductual centrada en el Trauma, que está diseñada para mejorar el funcionamiento familiar y disminuir el estrés interpersonal asociado al trauma podrían ser consideradas (133). Para finalizar, estudios que se centren en mecanismos biológicos y psicosociales de los efectos del abuso y el trauma son necesarios a fin de desarrollar intervenciones más específicas para el TB infantil.
7. El segundo estudio representa el primer estudio en evaluar de manera prospectiva los factores de riesgo tanto en el pasado y reclutamiento como durante el seguimiento que precedieron el primer abuso físico y/o sexual entre jóvenes con trastorno bipolar. Nuestro estudio amplía la perspectiva de la literatura al aportar una secuencia temporal acerca de los factores de riesgo que preceden al abuso de manera longitudinal. Estos hallazgos permiten la adecuada evaluación y prevención, incluyendo evaluaciones frecuentes y exhaustivas del abuso.
8. Los clínicos que tratan a jóvenes con TB deben prestar atención no solo a variables estáticas como son: mujeres, familias monoparentales, o la edad. Así como también prestar a atención a ciertas variables que sean modificables como son: severidad de la

depresión, uso de sustancias en la familia o síntomas de trastorno disruptivo de conducta.

9. Los síntomas depresivos en el reclutamiento y más concretamente la falta de factores de protección asociados como son las relaciones interpersonales se relacionaron con un incremento en el riesgo de abuso. Esto nos lleva a tratar enérgicamente la sintomatología afectiva en estos jóvenes.
10. Identificar individuos de mayor riesgo y circunstancias de vulnerabilidad como el bajo estatus socioeconómico en familias con trastorno de consumo de sustancias o cambios en la situación familiar de Convivencia debería ayudar a los clínicos a informar estrategias para reducir el riesgo de abuso.
11. Aquellos participantes con historia pasada de abuso y consume de sustancias tenían mayor riesgo de abuso físico recurrente. Esta asociación debería servir para evaluar detenidamente estas variables entre los jóvenes con TB.
12. Las buenas relaciones interpersonales con amigos muestran claramente ser factores protectores. Las terapias específicas que potencien las relaciones interpersonales podrían proteger a estos jóvenes del abuso.
13. Los hallazgos refuerzan la necesidad de identificar a los pacientes más vulnerables, mitigar su condición e interrumpir la elevada vulnerabilidad relacionada con la futura potencial victimización.
14. El cerebro continúa desarrollándose hasta los 25 años, y el trauma puede tener un impacto sobre el desarrollo sináptico. La anticipación de un entorno seguro debería ser una prioridad. Algunas guías clínicas reportan cómo los pediatras pueden aproximarse a la detección precoz de estos casos (134).
15. Los estudios venideros deberían centrarse en evaluar los factores de riesgo de una manera más proximal al abuso, así como evaluar características como los abusadores,

la frecuencia del abuso y otras variables culturales y familiares, que podrían revelar hallazgos prometedores en cuanto a estrategias de prevención entre la población con TB de inicio precoz.

2. INTRODUCTION



INTRODUCTION

2.1 Bipolar disorder in youth

Although cases of Bipolar Disorder (BD) among youth have been described in the literature for years, it is only in the recent past two decades that specific research has been conducted (1). It is now widely accepted that BD occurs in children and adolescents. Adult retrospective studies have consistently shown that around 60% to 70% of individuals with BD report their first mood symptoms before age 18 (2). The focus of the debate has shifted in recent years from skepticism of whether BD could be diagnosed among youth, to try to find better assessment procedures that could lead to a more accurate diagnosis (3).

BD is a serious illness that affects the normal development of the child, resulting in an impairment of psychosocial functioning and it is associated with increased risk of suicide, psychotic symptoms, sexual risk behaviors, and substance use disorders (4), moreover it is associated with several legal, behavioral, social and academic consequences. Thus, research should focus on the early stages of this disorder to better understand it.

Throughout this thesis, unless otherwise specified, the word youth denotes both children and adolescents.

2.1.1 Diagnostic features

BD is classified under mood disorders, and it is defined in its classic form by the presence of recurrent episodes of mania or hypomania with or without episodes of depression.

Except for cyclothymia, DSM-5 diagnostic criteria are the same for adults and for youth, and they are specified by different BD types below.

Bipolar disorder I: Requires meeting manic episode criterion (See Table 1), with or without meeting criteria for Major depressive disorder (MDD).

Bipolar disorder II: Requires meeting criteria for at least one hypomanic episode (See Table 2) (hypomania should last at least 4 consecutive days), and at least one major depressive episode (See Table 3). It should have never been a manic episode.

Cyclothymic Disorder: Characterized by numerous hypomanic episodes that alternate with numerous periods of depressed mood or loss of interest or pleasure that do not meet all the criteria for BD or for an MDD, that last at least one year (versus two years in adults) (135).

BD-Not Otherwise Specified: It is usually used when features of hypomania or mixed episodes do not meet full criteria for any of the specific subtypes. Given the complexity for fulfilling criteria for BD in children and that usually youth might meet clinical criteria but not the duration, researchers have developed clearer definitions to identify BD-NOS. The Course and Outcome of Bipolar Youth study (COBY) has developed a more standardized and structured definition of BD-NOS using a large sample of youth with BD followed for 15 years (See Table 4 for criteria). They should meet criteria for hypomanic episodes (one less symptom to meet the criteria) for long history (at least two days most time of the day) or at least 4 days shorter (more than 4 hours each day) (5).

Table 1: DSM-5 criteria for Manic Episode

Manic Episode
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and persistently increased goal-directed activity, or elevated energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior: ꕥ Increased self-esteem or grandiosity ꕥ Decreased need for sleep ꕥ More talkative than usual or pressured speech ꕥ Flight of ideas or subjective experience of racing thoughts ꕥ Distractibility, as reported or observed ꕥ Increase in goal-directed activity or psychomotor agitation (i.e., purposeless, non-goal-directed activity) ꕥ Excessive involvement in activities that have a high potential for painful consequences or reckless acts
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D. The episode is not attributable to the physiological effects of a substance or to another medical condition.
Note: A full manic episode that emerges during antidepressant treatment [e.g., medication, electroconvulsive therapy (ECT)], but persists at a fully syndromal level beyond the physiological effect of treatment is sufficient evidence for a manic episode, and therefore, a bipolar I diagnosis.

Table 2: DSM-5 criteria for hypomanic episode

Hypomanic Episode:
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and persistently increased activity, or increased energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
B. During the period of mood disturbance and increased energy and activity, 3 (or more) of the above symptoms (4 if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree. See criterion B for manic episode.
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
F. The episode is not attributable to the physiological effects of a substance or a medical condition.
Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, ECT) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess or agitation following antidepressant use) are not taken as sufficient for a diagnosis of a hypomanic episode nor necessarily indicative of a bipolar diathesis.

Table 3: DSM-5 criteria for Major Depressive Episode.

Major Depressive Episode
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. ꕤ Depressed most of the day, nearly every day as indicated by subjective report or observation made by others ꕤ Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day ꕤ Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day ꕤ Insomnia or hypersomnia nearly every day ꕤ Psychomotor agitation or retardation nearly every day ꕤ Fatigue or loss of energy nearly every day ꕤ Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day ꕤ Diminished ability to think or concentrate, or indecisiveness, nearly every day ꕤ Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode.
Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance- induced or are attributable to the physiological effects of another medical condition.

Table 4: BD-NOS standardized criteria

BD-NOS criteria
A. Child do not meet criteria DSM-V criteria for either BD-I or BD-II
B. A distinct period of persistently and abnormally elevated mood, expansive or irritable, plus the following: - ≥ 2 of the DSM-V criteria B of mania (3 if the mood is predominantly irritable), that are clearly associated with the onset of abnormal mood. - A clear change in functioning associated with change in the mood - Presence of irritable or elated mood and manic symptoms during a significant part of the day, minimum 4 hours within a 24-hour period for a day (≥ 4 hours, not need to be consecutive). - A minimum of 4 days (not necessarily consecutive) meeting the mood, symptoms, duration and functional change criteria over the subject´s lifetime, which could be two 2-day episodes, four 1-day episodes or another variation.
C. Mood symptoms should be inappropriate for the developmental age or the environment
D. Change in mood is not related with substance use or pharmacological treatment
E. Exclusion criteria: schizophrenia, intellectual disability, severe autism spectrum disorders, mood symptoms related to a medical condition, substance use or secondary to pharmacological treatment
F. Children determined to have the onset of BD before comorbid substance use disorder are included.
G. Mild autism spectrum disorders should be included if the mood symptoms are clearly episodic and are best accounted by the bipolar diagnosis.

2.1.2 Clinical features

BD in children and adolescents might be difficult to diagnose given that symptoms could be vague, shorter in duration and difficult to differentiate from normal child development. Further, children have difficulties verbalizing their emotions and they experience other comorbid disorders, that may play a role in the difficulty of a correct BD diagnosis (5). Although some youth might meet full DSM-5 criteria when examined,

normative youth can exhibit some behaviors that might resemble manic-like symptoms to some extent, especially in certain environments (i.e., birthday parties…), nonetheless they are reactive to specific stimuli and they are limited in time.

Functioning should be examined across the psychosocial domains that are relevant to the assessed youth (school, family, peers). Given the lack of insight associated with mania, it is imperative to obtain information from caregivers or other adults involved in the child´s life.

BD in youth can be diagnosed using DSM-5 criteria, however it is noteworthy to mention different considerations for diagnosing BD among youth:

- Criteria must exceed expectations of normal developmental stage
- They must cluster in episodes
- Cannot be accounted by other frequent disorders in early development such as Attention Deficit and Hyperactivity Disorder (ADHD) or Oppositional Defiant Disorder (ODD)
- Cannot be explained by child´s environment
- Must affect different areas of the child´s functioning

The most common symptoms across all subtypes in childhood are: increased energy, irritability, mood lability, distractibility, and increased goal directed activity. Grandiosity and hypersexuality are the most specific symptoms but not as common (57% and 32% respectively) (10). Grandiosity can be a difficult symptom to diagnose in children because it is normal for children in early developmental stages to overestimate their abilities, therefore it should be a change from the child´s usual behavior and self-image. Further, hypersexuality must be inappropriate for the age, and not accounted by history of sexual abuse or early exposure to sexualized videos or TV content.

Consideration of how symptoms might manifest differently across development can facilitate accurate diagnosis. For instance, children during pre-school age are less likely to exhibit behaviors such as spending lots of money or having sexual relationships with multiple partners. Presentation might change depending on the age of presentation. Whereas adolescents with BD show more adult like symptomatology, early childhood onset might present with mood lability, irritability and anger issues (8). Manic symptoms also change depending on the developmental state. Mania among adolescents has higher prevalence of euphoria, psychotic symptoms, labile mood and mixed and depressed symptoms (6, 7). Among younger children, mania could be manifested as labile mood, and erratic changes in energy level rather than persistent. Irritability, belligerence and mixed symptoms are more common than euphoria among school-age children. Mixed episodes in this age, frequently have predominance of irritability and explosiveness, causing chronic impairment and changes in their baseline functioning. Children with BD depression present frequently with anger, and dysphoria, and are more likely to have comorbid conduct, anxiety and substance use disorders than unipolar depression (136). American Academy of Child and Adolescent Psychiatry (AACAP) guidelines have raised awareness about difficulties in diagnosing BD before age 6, with very few studies reporting cases in the preschool years and with uncertain validity (9). That said, some groups have presented samples of preschoolers who present symptoms of hypo/mania (137-139) reporting that preschool mania is commonly associated with strong family history of mood disorders and ADHD diagnosis (138).

2.1.3 Epidemiology

A recent meta-analysis about epidemiology of BD in youth (ages 7 to 21) reported that the rate was around 1.8% worldwide (95% Confidence Interval, 1.1%-3.0%) (11).

This finding is consistent with epidemiology in adult populations. Further, this study showed that prevalence of BD-I and BD-II in United States was not different to prevalence in other countries. BD is equally common among females and males, although adolescent onset is more common among females versus males (3.3% vs 2.6% respectively). Diagnosis increase when reaching adolescence compared to childhood (11).

2.1.4 Clinical course and prognosis

Early onset (meaning onset before age 18) of BD is associated with more severe course of the illness and poorer outcomes compared to later onset. Around 70-100% of children and adolescents with bipolar disorder will eventually recover. However, of those who recover up to 80% will experience one or more recurrences in a period of 2-5 years (12). Moreover, similar to adult studies, the prospective course of these youth is characterized by mood fluctuations varying from 60-80% of the follow-up time. A recent study, using the COBY sample, evaluated more individualized course trajectories for a period of 9 years, and identified four longitudinal mood trajectories: "predominantly euthymic" (24%), "moderately euthymic" (35%), "ill with improving course" (19%) and "predominantly ill course" (22%). To account for this heterogeneity, besides different developmental BD subtypes, other factors such as early age of onset, family history of BD and substance use, more baseline history of depression, suicidality and history of sexual abuse have been related with worse illness course. In this study, between 24-43% will recover and became euthymic 8 years after their initial episode (140).

Some factors have been described to be associated with worse prognosis such as: early onset, low socioeconomic status (SES), more duration of the illness, mixed episodes or rapid cycling, presence of psychotic symptoms, sub-syndromal symptoms, comorbidities, exposure to trauma and family history of psychopathology (46, 141).

Geller and colleagues published an 8-year follow-up study using a cohort of children with BD-I, and participants spent 60% of their time symptomatic, and continue experiencing mood episodes in young-adulthood (142). The COBY study (one of the largest of its kind, n=413), pose that course of youth with BD-I mirrors that of adults: most experience episodic recovery and recurrences, depression is the prevailing polarity and sub-syndromal symptoms predominate (8).

2.1.5 Etiology

BD has been considered to have a multi-causal etiology, with its roots strongly linked to genetic and environmental factors continuously interacting across the neurodevelopment. Family history has been shown to be the strongest predictor to develop BD, twin and family studies have reported highly inheritance of the illness, being as high as 70% for identical twins. Other factors such as presence of prior manic or hypomanic episodes might be a risk factor for the development of manic, mixed or hypomanic episodes (143). Other longitudinal prospective studies have suggested that the offspring of adults with BD, that present symptoms such as mood lability, anxiety, sub-syndromal manic symptoms and early onset BD, were at 50% risk to develop BD over their lifetime (13).

Despite BD has a genetic component, there are other social, and emotional variables that play a role in the illness onset. Recent research has suggested that trauma and life events could trigger an episode of BD, however many episodes occur without an identifiable cause.

2.1.6 Comorbidities

Bipolar disorder in youth is often accompanied by other psychiatric disorders (20-80%), particularly disruptive behavior disorders (DBD), ADHD, anxiety disorders, and in adolescents, substance use disorders (SUD) (14-16). A recent meta-analysis reported weighted rates of comorbid disorders such as: ADHD 53-90%, ODD 42-88%, conduct disorders 27%, and anxiety disorders 23% (10). Given that the sample had a young mean age, substance use disorder was limited to 9%, although it increased as subjects aged (144, 145), and juvenile BD onset is known to be a risk factor for SUD.

ADHD is the most common psychopathology among youth with BD with childhood onset (<12 years old), and some studies have reported that up to 90% of some samples could report this prevalence (146). The understanding of ODD among youth with BD ranges from ODD being a secondary illness or being a prodrome or early manifestation of youth with BD. CD and mania are part of the well documented relationship between CD and major depression, as a part of the "affective storms", that can be very frequent. Some studies have brought into attention that BD onset among children may be particularly disorganized and explosive.

Studies report that more than half the youth with BD reported at least two or more lifetime prevalence of anxiety disorders. Panic disorder has been reported a prevalence from 21-33%, and OCD (15-35%). The agitation, racing thoughts and feelings of distress of severe OCD can mimic BD subjects.

Around 40-76% of youth had been exposed to a traumatic event by age 17, which increases the probability of this youth to be diagnosed with PTSD. Emerging evidence suggests that trauma also compromises the course of BD (146).

The presence of all the above-mentioned disorders conveys a special challenge for the differential diagnosis, given that some of the symptoms might overlap. Up to 55% of youth with BD do not receive treatment and rates of diagnostic specific treatment lag well

behind those youth with ADHD or MDD (147). Furthermore, comorbid disorders influence the response to treatment and might adversely affect the clinical course of BD, worsening the prognosis among this population (17).

2.1.7 Treatment

Following treatment guidelines, BD has 3 stages of treatment: 1) Acute, 2) Continuation, 3) Maintenance. Acute stage treatment aims to ameliorate acute symptoms, continuation treatment is required to consolidate the response during the acute phase and maintenance to avoid recurrences. The choice of pharmacological, psychosocial, or combined treatment depends on the severity, phase, subtype, comorbidity, child´s age, family and patient preferences.

Psychoeducation is always needed when starting a treatment. Family members and the patient should be educated about the causes, symptoms, course, different treatments of BD, and the risks associated with each treatment option, as opposed to no treatment at all. Sleep hygiene and routine are important, especially in view of sleep deprivation leading to worsening of mood symptoms (18).

Acute mania/mixed episodes: available studies (16 open label and 9 double-blinded) suggest that monotherapy with lithium, valproate or carbamazepine are comparable in treating non-psychotic mania/mixed episodes (19). Lithium was the first medication to be approved by the US Federal Drug Administration (FDA) for the treatment of mania in youth ages 12-17. Other studies have suggested that second generation antipsychotics (SGA) may be more efficacious than the traditional mood stabilizers (19). The US FDA has approved several SGAs for the acute treatment of manic/mixed episodes in youth: risperidone for 10-17 years old, olanzapine for 13-17 years old, aripiprazole for 10-17 years old, and quetiapine for 10-17 years old.

Acute bipolar depression: Clinicians may consider starting treatment with psychosocial interventions such as Cognitive Behavior Therapy (CBT) or Family Focused psychotherapy, especially for mild to moderate depressions. Quetiapine monotherapy or the combination of olanzapine with fluoxetine in acute treatment or lamotrigine in maintenance are efficacious (20). Other options suggested for the acute treatment of adults with BD depression include monotherapy with lamotrigine, valproate, and the combination of anticonvulsants or SGA with an antidepressant (a serotonin reuptake inhibitor [SSRI] or bupropion), these medications may be helpful in youth as well, but further randomized controlled trials (RCTs) are needed.

Psychotherapy treatments are necessary for all youth with BD, since they have been developed to provide psychoeducation, manage crisis, improve coping skills and adherence to treatment and manage comorbid conditions. In addition, this may help to prevent recurrences (18). Therapies such as *Child and Family Focused Cognitive Bahveior Therapy (CFF-CBT)* (21)*, Multi-family Psychoeducation Groups (MFPG)* and *Individual Family Psychoeducation (IFP)* (22)*, Family Focused Therapy (FFT)* specifically for adolescents with BD *(FFT-A)* (23), *adapted Dialectical Behavior Therapy (DBT)* for the treatment of adolescents with BD (24), *Interpersonal and Social Rhythm Therapy (IPSRT)* for adolescents with BD (25), are some of the therapies used to treat youth with BD.

2.2 Traumatic Events in BD

A traumatic event (TE) is defined in the literature as a frightening, dangerous or violent event that poses a threat or it is perceived as a threat to the child´s life or bodily integrity. This may be through direct experiencing; witnessing a TE; learning that TEs happened to a close family member or friend; or repeated or extreme exposure. TEs can

initiate strong emotions and physical reactions that can persist long after the event, and they usually exceed the ability to cope of the child. Carlson and colleagues proposed that three aspects of undesirable life events make an event traumatic: the inability to control it, the perception that is a negative experience and its suddenness (26). It is estimated that around 50% of all youth worldwide will experience at least one type of potentially TE before age 18 (27).

Given the complexity in the 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, environmental factors such as exposure to TEs, has emerged in recent years as one of the factors having substantial impact on the course and prognosis of BD (28).

2.2.1 Traumatic Events among adults with BD

TEs are 2.6 times more prevalent in adults with BD compared to healthy controls (29). Compared to BD adults without TE experience, 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 (30-36). Bear in mind that differences in trauma definitions sometimes make it difficult to compare one or more forms of childhood trauma.

TEs could impact health outcomes among BD subjects (38), with some studies reporting that childhood TEs have been associated with cardiometabolic risk among adults who experience mood disorders (37), and that some forms of abuse have been related with changes in Body Mass Index (BMI) (38).

Bender and colleagues compared 77 BD adult participants with 88 controls, reported that BD had more dependent events over follow-up than controls. This study supported stress generation theory of unipolar depression also in BD and events are

polarity specific. BD had more dependent life events, hypomania predicted more positive events, depression predicted less positive events (148).

In a critical review, the better controlled studies showed a direct correlation between childhood abuse and brain measures, being the most prominent deficits in the function and structure of lateral and ventromedial frontal-limbic brain areas and networks that mediate behavioral and affect control (149). Verbal and visual impairments, deficits in working memory, attention, and motor inhibition, have been consistently observed in maltreated children and adults. The brain regions most consistently affected are ventromedial and orbitofrontal-limbic regions, amygdala, hippocampus, corpus callosum, cerebellum in maltreated children (149).

2.2.2 Traumatic Events among youth with BD

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 studies and chart reviews show that BD youth are more likely to report TEs than healthy youth and youth with non-BD-psychopathology (42-44). These studies also suggest that the TEs presence 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 (43, 45-47).

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 evaluated youth (15 to 28 years old) that experienced their first episode of psychotic mania, and they reported that youth with BD with history of TEs had more symptoms of mania and depression, general

psychopathology, and poorer social and functional outcomes at a 12-month evaluation since inpatient discharge, as compared to those without history of TEs (48). Neria and colleagues followed a large sample of youth and adults up to 65 years old hospitalized for first bipolar psychosis (49), finding that those exposed to TEs were more symptomatic across follow-up compared to those who did not report past trauma history. Moreover, TEs that happened during childhood were associated with more severe symptomatology after 24-months of discharge compared to both those with no TEs experience and those who experienced TEs during adulthood. Kim and colleagues, showed that high stress (repeatedly measured over 12-month-span), was associated with less mood symptoms improvement after one-year among 38 adolescents with BD compared to those with low stress (50). Conus and colleagues studied 118 youth experiencing their first-psychotic-mania, using a retrospective file-audit, finding that those who reported abuse experienced poorer adherence to an 18-month early-intervention treatment than those without abuse exposure, further those exposed to childhood abuse had lower premorbid functioning than those that had no history of abuse exposure (51). However, other longitudinal studies have showed partial or no effects of TEs over the BD course and onset (52, 53). Strawn and colleagues however, found that despite prevalence of trauma exposure was high in patients with first manic or mixed episode, rates of trauma symptomatology were low and presence of trauma symptoms did not predict risk of recurrence after 12 months (52). Also, in a prospective study of a random population-based sample, Tijssen and colleagues reported that childhood TEs did not predict onset of mood symptomatology and, for individuals with past TEs, mood symptoms did not persist after 8 years of follow-up (53).

TEs in early life have also been associated with biological changes such as insufficient glucocorticoid signaling in adulthood possibly affecting inflammation processes, and posing these subjects at risk to develop risk of inflammatory origins related

diseases later in life (39). Childhood trauma appears to be a complex etiological agent that varies its impact depending on the timing, type and severity of exposure (150). Further, childhood TEs are associated with brain abnormalities, such as altered amygdala activity and volume, and lower integrity of white matter microstructure across the brain in individuals with BD (40). Other studies have also reported changes in gray matter associated with TEs in individuals with BD. These changes in gray and white matter integrity in various brain areas that are potentially implicated in emotion regulation and threat sensitivity (40, 41), might offer a plausible explanation of the functional deficits observed in this disorder.

2.3 Childhood physical and sexual abuse

Among all different forms of TEs, physical and/or sexual abuse are the most widely studied and are strongest predictors of the different physical and mental health outcomes.

Childhood physical abuse: Physical abuse of a child is defined as: those acts of commission by a caregiver that cause actual physical harm or have the potential to harm. This includes hit with a hand or object, being kicked, shaken, thrown, burned, stabbed or chocked by a parent or caregiver (65). Caregivers can be parents, foster parents, extended family, family friends or other members of the community. In regard to physical abuse it is important to consider the cultural context, since physical punishment is largely extended in many industrialized societies. Child physical abuse exists on a continuum from minor to severe.

Childhood sexual abuse: Child sexual abuse is defined as: the involvement of a child in sexual activity that he/she does not fully comprehend, is unable to give inform consent to, or for which is not developmentally prepared, or else that violates the laws

and social taboos of the society (61). This includes any type of inappropriate touching, forced oral, anal, or genital penetration, forced exposure of private parts, sexual harassment by adults or older children or other peers that are in a position of power over the abused child (151, 152). It has been reported that the most common form of sexual abuse reported is inappropriate touching (9-14%), whereas penetration it is much less likely (1-8%). Half of the instances of abuse usually happen once or twice (153). Usually perpetrators are within family members or family environment (62), and most of them are males. Average age to experience sexual abuse is usually 9-11 years old (154). Around 51% of lifetime abuse occur prior to age 18 (155), and 29% prior to age 12. Sexual abuse happens more frequently among females than males.

Physical and sexual abuse

It is estimated that around 8% of boys and 18% of girls worldwide experience sexual abuse, and 22% of children experience physical abuse (66). Moreover, the prevalence of any type of maltreatment among clinical populations has been estimated around 45%, with 19% of them reporting more than one form of abuse (67). While true rates of abuse will never be known, a synthesis of self-reported studies suggests official documented rates of abuse are grossly underestimate (68). Most of the epidemiological studies have been conducted in developed countries, Gilbert and colleagues reported that in European industrialized countries almost 4% of minors suffer abuse every year, with 80% of the cases reporting parents as perpetrators (70).

Abuse represents a substantial individual and public health concern in the developed societies. It causes immediate harm, has many long-term consequences for the victim, and has serious deleterious effects for the family and society at large, including significant economic burden (70).

Physical and/or sexual abuse during childhood have been associated concurrently and in the long term with severe adverse physical conditions (i.e., diabetes, proinflammatory states or pain conditions), mental health problems (i.e., substance use, aggressive/disruptive behaviors, or eating disorders) and psychosocial outcomes (i.e., deficits in cognitive functioning, school attainment, and relationship problems) across the lifespan (71). Moreover, since childhood and adolescence are periods of increased sensitivity to stress in the developing brain, the exposure to abuse in early development has been associated with increased risk of concurrent and subsequent psychopathology, and related with one third of all mental health disorders in longitudinal studies (72, 73). This is supported by theories of the CNS being more "plastic" in the early years of childhood, which consequently may lead to a more profound influence of adverse events during this period (54). Youth who have suffered abuse have significantly more disturbances in attachment relationships, delays in autonomous functioning, deficits in frustration tolerance, and low self-esteem. Further, problems in language acquisition as well as in school performance have also been reported (72, 75). Some types of abuse have been linearly associated with reduced psychosocial functioning (74). Studies that have examined resiliency contemplating multiple domains of functioning, and have reported that a quarter or fewer of all abused children could be considered resilient (156).

Child abuse and neglect are related with structural and functional deficits in different brain circuits and areas that can mediate a wide variety of social, emotional and cognitive processes (hippocampal volume deficits, atrophy of the corpus callosum, and enhanced amygdala response to stress) (75). Further, cortisol regulation, externalizing behavior and social difficulties are all related with the negative impacts of childhood abuse experiences. The longitudinal study of such families with maltreated children could

be especially difficult since these families experience a high mobility, and many times they lack the financial support or time (157).

Depending on the age of exposure, youth exposed to abuse can present different outcomes. For preschool age children, unspecific somatic symptoms are commonly reported among youth who have experienced abuse, such as: enuresis, encopresis, stomachaches or headaches. Although other clinical symptoms have also been reported, such as psychomotor delays, anxiety, Post Traumatic Stress Disorder (PTSD), and sexualized behaviors (76). Among school age children, other symptoms such as externalizing behaviors, dissociative symptoms, and low performance in school have been commonly reported (78). Finally, teenagers that have suffered from abuse are more likely to develop substance use disorders and eating disorders, to engage in delinquency, suicidal behaviors, early and risky sexual behaviors (77).

Among some clinical populations, some studies have reported consistently that participants who report history of childhood abuse show more severe symptoms of depression than participants who do not report such experiences (79). The neurobiological changes that happen in abused participants, may point an increased risk of mood disorders and a more severe course of the illness, since childhood trauma may lead to disturbances in affective regulations.

2.3.1 Sexual and physical abuse effects among adults with BD

As reported before, among all types of TEs, sexual and/or physical abuses are the most widely studied, and they have been reported as strong predictors of an adverse BD course in adults (107, 158). They affect neurocognitive performance, worsen functioning and mood symptomatology, increase suicidality, and are associated with higher rates of

psychiatric comorbidity in both cross-sectional and longitudinal studies in BD (32, 74, 80, 114, 159).

Among all forms of psychopathology, extensive research has focused on the association of childhood abuse and Bipolar Disorder (BD), with two recent metanalyses reporting estimates as high as 57% of adults with BD report childhood abuse history (9-40% for sexual abuse and 9-33% for physical abuse) (28, 107). In a meta-analyses, Garno and colleagues, differentiating between types of abuse reported that physical abuse was more prevalent (24%) than sexual abuse (21%) (31).

Thus far, the literature in BD and abuse has mostly focus on the detrimental effects of abuse in the BD course. Abuse among subjects with BD has been associated with many factors including, among others, female sex, psychiatric comorbidities (i.e., Substance use disorder [SUD] or conduct disorders [CD]), psychotic symptoms, and family history of mood disorders. Patients who experienced sexual and/or physical abuse tend to have more severe and frequent mood episodes, suicidality, rapid cycling, poor functioning, worse cognitive performance, delayed BD diagnosis and appropriate treatment, poor physical health and increased risk for further victimization after age 17 (28, 29, 49, 80, 107, 160-165). Childhood abuse also seems to be associated with the mental health status between mood episodes. Etain and colleagues (166) found that child abuse was correlated with emotional instability in a sample of euthymic BD participants. Further, some studies report that subclinical conditions of bipolar symptoms are associated with recollections of child abuse. While manic and hypomanic symptoms do not differ depending on the past history of abuse, depressive symptoms are clearly higher among participants who report abusive experiences (167). Further, in this study the effects of gender were analyzed, and female sex combined with past history of abuse are a risk pattern for

depression later in life. However, most of the studies done in abuse among BD were cross-sectional, limiting the ability to identify predictors for new onset abuse.

2.3.2 Sexual and physical abuse effects among youth with BD

Up to 65% of adults experience the first onset of BD before adulthood, and history of childhood abuse has been associated with early onset of BD. In youth with BD, studies have estimated a prevalence between 3 to 20% for physical abuse and 7 to 29% for sexual abuse (43, 46, 48, 51, 52, 80-82).

Similar to the adult BD literature, cross-sectional and retrospective studies that have as outcome variable the effects of abuse, have shown that physical and/or sexual abuse have been associated with older age, female sex, non-Caucasian race, low SES, living with non-intact and single parents families, or foster care homes, having low psychosocial functioning, Intellectual Quotient (IQ), self-esteem, and more negative events, psychiatric comorbidities (i.e., SUD, Post Traumatic Stress Disorder (PTSD)), suicidality, psychosis, and family history of SUD or mood disorders (42, 43, 45, 47, 81, 82). In addition to the findings in the cross-sectional studies, the few longitudinal studies in BD youth reported that in comparison to BD youth without history of abuse, youth with BD with past history of abuse had worse family environment, more comorbid anxiety, severe mood episodes, mood recurrences, general distress and hopeless feelings, decrease response to treatment, and worsening mood symptoms (more hypo/mania, more depression and more psychiatric comorbidities) after the abuse occurrence (46, 48, 49, 51, 52).

2.3.3 Risk factors for experiencing sexual and physical abuse in the general population

The risk factor approach has become a crucial part of the part of the prevention strategies in most of the worldwide programs, including study of implementation

strategies to prevent childhood abuse. The influential report of prevention science by the Institute of Medicine defined risk factors as follows: “Characteristics, variables or hazards that, if present for a given individual, make it more likely that this individual will develop a disorder or suffered an event”(83, 84) or “a measurable characterization of a subject that precedes the outcome of interest and which can be used to divide the population into two groups (high and low risk)” (168). To qualify as risk factor there are a number of variables that it must be present: 1) The variable must precede the event; 2) The variable must be associated with an increased probability of disorder; 3) The variable must show some degree of stability if considering long periods of time. Some risk factors play a causal role, while others merely mark or identify the potential for a disorder (83, 84). Identifying risk factors has a number of advantages. Theoretically, it narrows the search of causal risk factors to the set of antecedent characteristics that are most strongly related to the outcome. Practically, such an approach can promote tailoring interventions to the specific risk factors and combinations, and the timing of those risks. Moreover, the risk factor paradigm is easy to understand and communicate, and it is readily accepted by policy makers, practitioners and general public (169). Must be noted that not all the individuals exposed to a risk factor will develop the outcomes. Thus, the resilience may be due, at least in part, to protective factors. Protective factors have been identified as “factors that may ameliorate, modify or alter a person´s response to some hazards that predispose to a negative outcome”. In example, social support may reduce the likelihood of child abuse to happen (85). Abuse is a highly complex phenomenon, and what determines if it will take place is the balance of stressors and supports. Therefore, the risk factor approach should serve both clinicians and policy makers to prevent abuse among population.

Some "Unitary theories" have been applied to the study of risk factors for abuse, such as parental psychopathology, environmental theories of poverty, and social learning theories of intergenerational family violence. However, recent literature investigating risk factors for child abuse among non-clinical samples aims to integrate a framework where child abuse is a manifestation of broader ecosystem dysfunction, therefore recent literature primarily uses Bronfenbrenner´s Ecological Model of Human Development framework (86). This framework determines that risk factors occur across multiple developmental domains or levels of a person´s ecology (86): demographic, psychosocial and clinical. In general population studies, abuse has been associated with demographic factors (sex, age, race, socioeconomic status [SES], parental education and employment, maternal age at child´s birth or living situation), clinical factors (family and children psychopathology, medical illnesses or intellectual disabilities) and environmental factors (social support, family conflict or past history of abuse in both caregivers and youth) (87, 88, 90-92, 170). Unfortunately, very few prior studies have investigated these issues in prospective longitudinal studies, even though by definition, a risk factor must precede a particular outcome.

Several domains are particularly important to consider as risk factors for abuse. Regarding family environment, abuse has been related with the quality of the family relationships experienced during childhood, low affective ties between parent-child and adverse experiences, inappropriate discipline techniques, single parenthoods or large family sizes may lead to abuse outcomes. Low parental education, family poverty, teenage mothers, social isolation and unemployment of the parents are considered risk factors for abuse (92, 93). Youth exhibiting difficult temperaments and behaviors are placed at risk for abuse. Other child individual risk factors such as low school performance, substance use, and delinquency have also been related with abuse outcomes

(94). Further, in this longitudinal study, cumulative risk was studied across different domains, concluding that when risk factors load accumulate, the likelihood of abuse increases. This perspective is quite consistent with the risk factor approach arguing that stressors pile up on the youth and overwhelm the coping strategies (94, 95).

Literature reviews on the risk factors for abuse in community samples have found that the strongest effect sizes for abuse are parent factors that are independent of the child, such as parent anger or hyper-reactivity, and family factors such as high family conflict and low cohesion, and low parent participation in the school. Moreover, the quality of the relationships is strongly related to physical abuse. Child social competence was moderately related, however in this review demographic factors such as age and sex were not found to be related with abuse outcomes (87, 92).

Physical abuse has been the most studied form of family violence, and there has been some research studying not only the general risk factors but also studying the risk factors that occurred in close temporality to the abuse in community samples. When considering risk factors that precede close in time abuse; child behavior problems, high risk parenting strategies, mother´s high reactivity, stressful events happening in the family environment and mother´s dysphoria have been considered near-term risk factors for physical abuse in child´s physical abuse (Black 2001b). In this review, past or distal risk factors (those that occur far before first abuse) for abuse were considered accounting for parent characteristics (younger parents, with lower education levels, unemployed, lower SES, ethnic minority groups, with past history of abuse, and with depression and substance use disorder were more likely to abuse their children), child characteristics (older children, with externalizing and internalizing problems were shown to be at higher risk for physical abuse) and family characteristics (low income families, with low social support and families with low adaptability and cohesion).

Most of the studies done in sexual abuse among children do not differentiate between intra- and/or extra-familiar child sexual abuse, although the risk factors for each of these forms might differ. Black and colleagues (170), also did a review on risk factors for child sexual abuse, and used the same approach, dividing risk factors in child characteristics (females sex, ethnic minority groups, and low IQ had higher risk for sexual abuse) and family characteristics (low family income, parental unemployment, stepfamilies, single parent households, parents with depression, anger issues and with high rates of stressful events had children with increased risk for sexual abuse). Given the low yearly prevalence of sexual abuse, larger samples and with good statistical power would be warranted.

Many of the literature so far done in risk factors for abuse has used retrospective measures or relied in cross-sectional studies to assess for abuse, in order to be able to establish predictors for abuse, there is a great need of prospective studies that follow the youth for a large amount of time. Moreover, studies analyzing risk factors for abuse among clinical populations (such as BD) are scarce. The study of risk factors among BD youth is particularly important given that this youth represent a vulnerable population group and the nature and circumstances of this disorder might pose youth at a particular high risk to experience abuse that differ from those in community samples.

2.4 The COBY study. What have we learned from COBY sample so far?

The Course and Outcome of BD Youth (COBY) study is a multisite longitudinal research study of youth with childhood-onset BD followed into young adulthood. This study provides a unique opportunity to examine both the longitudinal effects of trauma in the course of BD, but also what are the risk factors that precede new onset abuse among

this youth; by including frequent assessments of TEs, clinical and psychosocial variables at various time-points.

Previous cross-sectional findings from COBY comparing youth with BD with youth with major depressive episodes and/or anxiety and also compared to healthy controls, have suggested that youth with BD and depressed/anxious youth had higher rates of negative life events compared to healthy controls. Further, youth with BD had fewer total and dependent positive life events compared to both depressed/anxious and healthy controls. Older age, low SES, living with non-intact family, non-Caucasian race, anxiety and disruptive disorders were associated with greater number of negative life events (42).

In a prior cross-sectional analysis, COBY group aimed to examine the prevalence and correlates of retrospectively assessed sexual and/or physical abuse in youth with BD at the time of the study entry. It was documented that 20% (9% physical, 7% sexual and 5% both) of the sample had experienced sexual and physical abuse at the time of the study entry, both cross-sectionally and retrospectively (82). This analysis indicated that history of any abuse was correlated with living with non-intact families, lifetime history of psychosis, lifetime history of PTSD and Conduct Disorder (CD), and family history of mood disorders (82). Sexual abuse was associated with greater lifetime prevalence of PTSD diagnosis. Physical abuse was associated with longer duration of BD illness, non-intact family, greater lifetime prevalence of PTSD and psychosis, and greater prevalence of first-degree family history of mood disorders.

A recent paper using the COBY sample evaluated the longitudinal course of depressive symptom severity among youth with BD, and moderating influences of cognitive disruptions (sustained attention and affective information processing) and exposure to child maltreatment. Results suggest that specific aspects of lower sustained

attention and history of childhood physical and/or sexual abuse may moderate depressive symptoms over time. These findings suggest that severity of depressive symptoms may be exacerbated by environmental risk and cognitive disruptions earlier in development when maturation of attentional processes is occurring more rapidly (96).

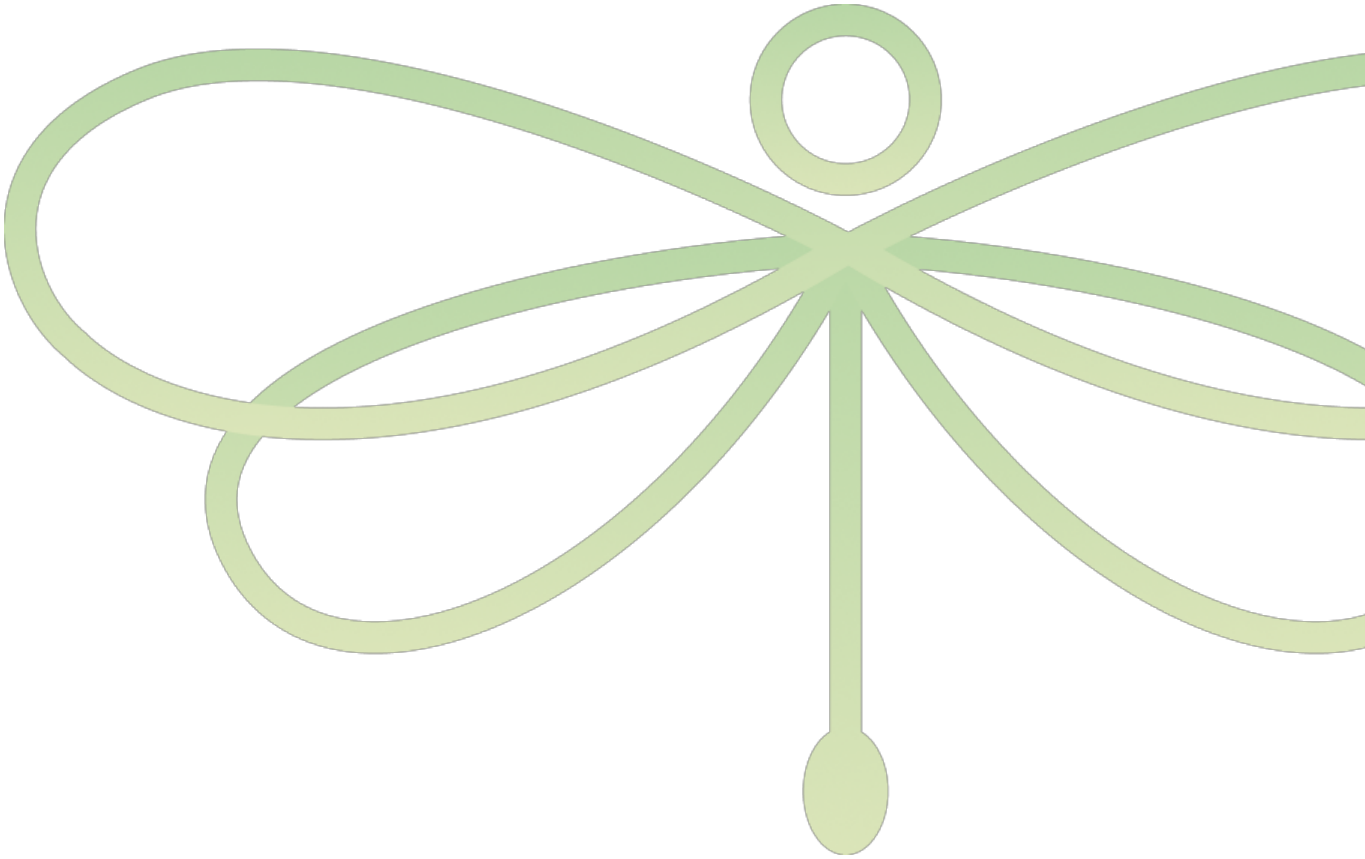
2.5 Methodological problems

Although informative, prior literature focused on both effects of trauma in the course of BD illness and also the studies done on risk factors for sexual and physical abuse in this population, have been limited by multiple methodological factors, including: 1) The majority of the studies were done using cross-sectional designs, 2) Few of the existing longitudinal designs have collected symptoms and/or history of trauma repeatedly overtime; 3) They have infrequent follow-ups; 4) Small sample sizes; 5) Most of the studies have been limited to participants with BD-I recruited through inpatient units; 6) There was a lack of adjustment of confounders such as socioeconomic status (SES), family history, sex or age; 8) Literature in risk factors for abuse have been mainly limited to community samples, mostly limited to children involved in Child Protective Services, with a gap in the literature in clinical populations, especially among BD; 9) reliance on chart reviews, self-reports, and lack of direct interviews with the participant youth and use of retrospective measures that were covering long periods of time. This reliance on chart reviews and retrospective measures accounting for extended periods of time, may be the primary limitation of the TEs prior literature given that these approaches pose a particular high risk for recall bias, especially for TEs and abuse, which are more likely be under/over reported (97, 98). Further, other studies have acknowledged the potential biases when using adult samples that retrospectively report abuse, the report might be affected by the current mood state of the subject (99). Further, to evaluate risk

factors the risk factor must be present prior to the outcome, which implies the need of prospective studies among BD youth to do so. To our knowledge there are no prospective studies evaluating risk factors for new onset physical and/or sexual abuse in either BD youth or adults, further none of the studies have evaluated the time-varying risk factors that precede close in time first lifetime abuse occurrence.

Studies using frequent prospective assessments of trauma and abuse are warranted, allowing longitudinal examination of TEs impact on the course of early-onset BD while minimizing retrospective recall of events and, further allowing to shed some light on what the main risk factors are to experience new onset physical and/or sexual abuse in this clinical population. Such studies, may potentially reveal clinical and psychosocial outcomes not yet studied, providing an opportunity to create effective detection and intervention strategies.

3. HYPOTHESIS

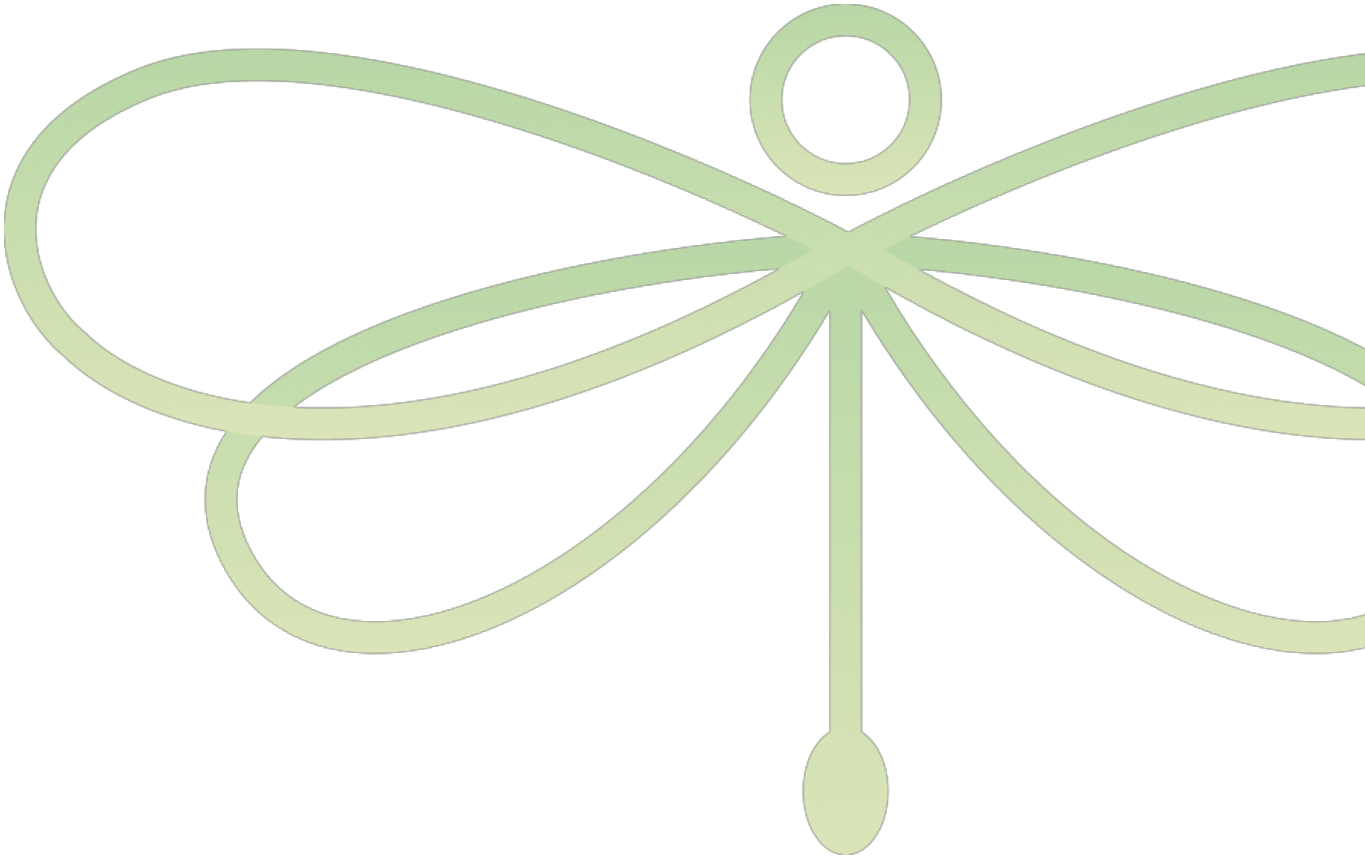


3.1 HYPOTHESIS FOR BOTH STUDIES INCLUDED IN THIS THESIS:

First, 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.

Second, we hypothesized that: 1) past and intake predictors for new onset abuse during follow-up would include sociodemographic and clinical factors previously identified in the literature, including low SES, lack of social support, more severe mood symptoms, increased comorbid disorders and female sex; 2) Although there are no prior studies that evaluate near-term predictors for new onset abuse, based on clinical experience and distal literature, we hypothesized that predictors ascertained during follow-up preceding new onset abuse would similarly involve variables associated with abuse in prior studies, including age, female sex, low SES, living with one parent, presence of comorbid disorders and family psychopathology.

4.AIMS

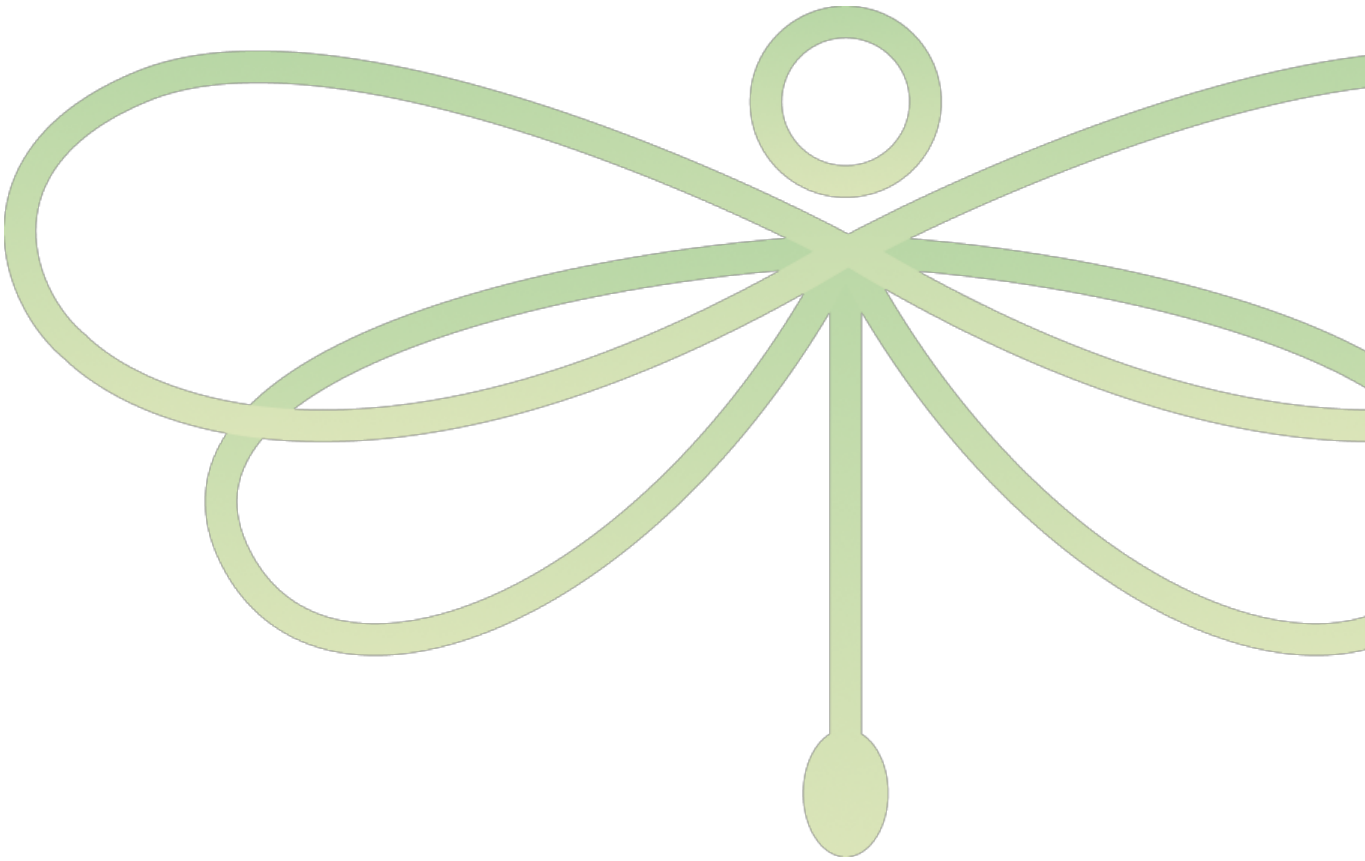


3.1 AIMS FOR BOTH STUDIES INCLUDED IN THIS THESIS:

In the first place, to extend prior COBY findings by prospectively examining the rates and effects of TEs among BD youth; and, specifically, the effects of abuse on a subsample of participants' course and outcomes over an average follow-up period of 8.7 years.

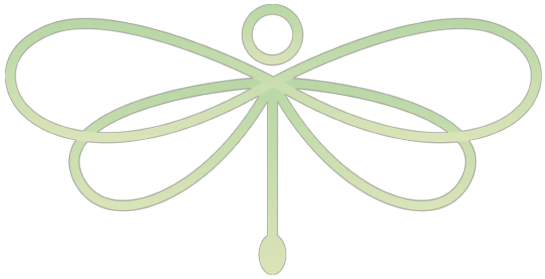
Secondary, the prospective design of COBY allows us to provide new insights in the BD youth literature and to extend prior COBY findings by: 1) identifying past and intake risk factors for new onset physical and/or sexual abuse among a subsample of COBY youth with BD (n=279) followed for an average of 12 years; 2) conducting, to the best of our knowledge, the first examination of predictors that temporally precede new onset physical and/or sexual abuse among youth with BD over follow-up.

5. MATERIALS, METHODS AND RESULTS



5.1 Study I.

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



The Effect of Traumatic Events on the Longitudinal Course of Youth with Bipolar Disorder. Andreu Pascual, M., Levenson, J.C., Merranko, J., Gill, M.K., Hower, H., Yen, S., Strober, M., Goldstein, T.R., Ryan, N., Goldstein, B.I., Weinstock, L.M., Keller, M.B., Axelson, D.A., Birmaher, B**.** ***Journal of Affective Disorders,*** **(2020),** (274), (126-135). doi: https://doi.org/10.1016/j.jad.2020.05.131

STUDY I SUMMARY: "The Effect of Traumatic Events on the Longitudinal Course and Outcomes of Youth with Bipolar Disorder"

5.1.1 Background and Aims.

Exposure to severe Traumatic Events (TEs) has been associated with poor course and outcomes among individuals with Bipolar Disorder (BD). However, there is limited research on TEs among youth with BD, and few studies are longitudinal. This study prospectively followed a large sample of BD youth, examining the associations of lifetime TEs with their mood and functioning.

5.1.2 Summary of the methods.

a) Participants: Since the instrument for screening severe lifetime TEs (Traumatic Events Screen: TES) (100) (Supplement 1) was added in 2007; this study 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 8.7 years 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.

b) Assessment of Traumatic Events: The presence of lifetime (past/present) TEs was obtained using the Traumatic Events Screen (TES) (Supplement 1), a brief interview including the 11 items derived from the PTSD section of the K-SADS-PL (100), 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.

c) 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.

For this study, 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 Supplement 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). 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 (186). 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 (101) 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 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(102); all other statistical analyses used SAS 9.4 (103).

5.1.3 Summary of the results.

For the first study, among the 375 participants that were included, 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.

a) **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. Accounting for covariates, participants with one or more lifetime TEs (84%) showed earlier BD onset, poorer psychosocial functioning, worse mood symptoms, and more suicidal ideation, comorbidities, and family psychopathology than those without TEs.

b) Association between TEs and Mood Symptomatology: Participants who experienced higher rates of any type of TE reported significantly lower rates of euthymia ($p=0.001$) and significantly higher rates of sub/threshold Major Depressive Episodes (MDE) over follow-up ($p<0.001$). 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 ($p=0.008$).

c) **Association 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 ($OR=2.19$, $p<0.0001$).

d) Association between TEs and 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). Participants who experienced violence/abuse during recovery periods had 1.6 times the estimated hazard of subsequent recurrence risk.

e) Mood couse and history of physical/sexual abuse: Abused participants (34% physical; 17% sexual) showed earlier onset of substance use disorders, more suicidality and comorbidities compared to those without abuse. 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). 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). 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).

5.1.4 Main 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 and to provide specific treatments to ameliorate its impact. 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.

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Research paper

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

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ABSTRACT

Background: Exposure to severe Traumatic Events (TEs) has been associated with poor course and outcomes among individuals with Bipolar Disorder (BD). However, there is limited research on TEs among youth with BD, and few studies are longitudinal. This study prospectively followed a large sample of BD youth, examining the associations of lifetime TEs with their mood and functioning.

Methods: BD participants (n = 375; mean age = 17; range 8-25y) were assessed, on average, every 7 months for a median 8.7 years. Psychopathology and lifetime trauma history were prospectively evaluated using the Longitudinal Interval Follow-Up Evaluation, and a traumatic events screening.

Results: Accounting for covariates, participants with one or more lifetime TEs (84%) showed earlier BD onset, poorer psychosocial functioning, worse mood symptoms, and more suicidal ideation, comorbidities, and family psychopathology than those without TEs. TEs during recovery periods increased recurrence risk ($p < 0.02$). More TEs were associated with poorer mood course, particularly among victims of violence/abuse ($p < 0.02$). Abused participants (34% physical; 17% sexual) showed earlier onset of substance use disorders, more suicidality and comorbidities compared to those without abuse. Comparisons of mood course before and after abuse occurred, and with participants without abuse, showed worsening mood symptoms after, specifically hypo/mania ($p < 0.03$).

Limitations: Prospective data was gathered longitudinally but assessed retrospectively at every follow-up; given approximate dates causality cannot be inferred; TEs severity was not assessed.

Conclusions: Severe TEs, particularly abuse, were associated with poorer course and outcomes among BD youth. Prompt screening of trauma and early intervention may be warranted to minimize TEs impact.

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 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

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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 (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 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

[1] TEs: Traumatic Events

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 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 et al., 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.

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 et al., 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, 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.

Table 1
Intake demographic, diagnostic, clinical, family history and psychosocial variables associated with traumatic events

	Variable	Mean ± SD or N (%) No Traumatic Events n = 59)	Traumatic Events n = 316)	Test Stat	p-value
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)	$\chi2 = 1.61$	0.2
	White	47 (79.7)	260 (82.3)	$\chi2 = 0.23$	0.6
	Both Parents	20 (33.9)	95 (30.1)	$\chi2 = 0.34$	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			$\chi2 = 1.83$	0.4
	BD-I	46 (78.0)	224 (70.9)		
	BD-II	8 (13.6)	45 (14.2)		
	BD-NOS	5 (8.5)	47 (14.9)		
	ADHD	23 (39.0)	223 (70.6)	$\chi2 = 21.98$	**< 0.0001**
	Disruptive Behavior Disorders	22 (37.3)	194 (61.4)	$\chi2 = 11.83$	**0.0006**
	Anxiety Disorder	24 (40.7)	234 (74.1)	$\chi2 = 25.80$	**< 0.0001**
	PTSD	2 (3.4)	81 (25.6)	$\chi2 = 14.27$	**0.0002**
	SUD	9 (15.3)	153 (48.4)	$\chi2 = 22.28$	**< 0.0001**
Suicidality,Self-Injury	Suicidal Ideation	6 (10.2)	93 (29.4)	$\chi2 = 9.49$	**0.002**
	Suicide Attempts (per year)	0.06 (0.2)	0.08 (0.2)	Negative Binomial Wald $\chi2 = 0.03$	0.9
	Self-Injury (per year)	0.05 (0.2)	0.11 (0.4)	Negative Binomial Wald $\chi2 = 1.56$	0.2
Family History	Depression	43 (72.9)	286 (90.5)	$\chi2 = 14.35$	**0.0002**
	Mania	22 (37.3)	198 (62.7)	$\chi2 = 13.20$	**0.0003**
	ADHD	18 (30.5)	158 (50.0)	$\chi2 = 7.58$	**0.006**
	CD	18 (30.5)	122 (38.6)	$\chi2 = 1.39$	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)	$\chi2 = 8.36$	**0.004**
	SUD	35 (59.3)	229 (72.5)	$\chi2 = 4.12$	**0.04**
	Suicidality	23 (39.0)	173 (54.8)	$\chi2 = 4.95$	**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

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

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%)

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 eported Event	Mean Rate of Events er 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

(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

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

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 $p \leq 0.03$). 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 ($p = 0.008$).

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 ($HR = 1.12\text{-}1.61$, $p < 0.03$). 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,

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).

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

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 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

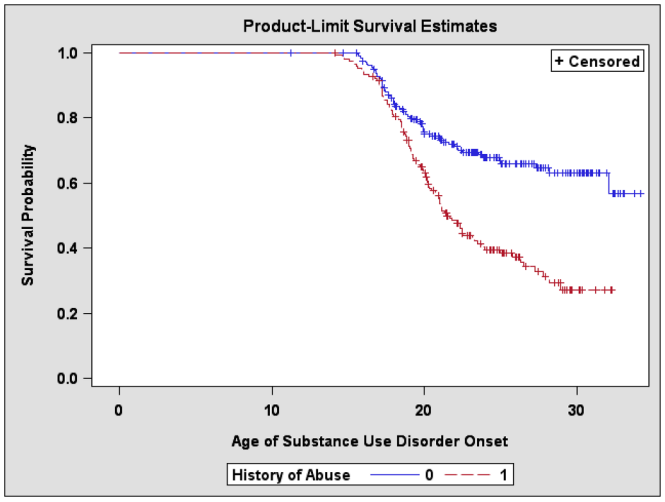

Figure 1. Kaplan-Meier survival estimation: substance use disorder risk stratified by history of abuse *
*Model controls for demographics, comorbid diagnoses, and family history retained by Least Absolute Shrinkage and Selection Operator (LASSO).

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 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 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 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.

5. 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 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.

Authorship contributions

Conception and design of study: M. Andreu Pascual, B. Birmaher, J. Levenson Statistical expert: J. Merranko Analysis and/or interpretation of data: J. Merranko, M. Andreu Pascual, B. Birmaher, J. Levenson Drafting the manuscript: M. Andreu Pascual, J. Merranko, J. Levenson, B. Birmaher

Revising the manuscript critically for important intellectual content: M. Kay Gill, H. Hower, S. Yen, M. Strober, T. Goldstein, B. Goldstein, N.D. Ryan, L.Weinstock, M. Keller, D. Axelson. Approval of the version of the manuscript to be published: M. Andreu Pascual, J. Levenson, J. Merranko, M. Kay Gill, H. Hower, S. Yen, M. Strober, T. Goldstein, B. Goldstein, N.D. Ryan, L.Weinstock, M. Keller, D. Axelson, B. Birmaher.

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Supplementary materials

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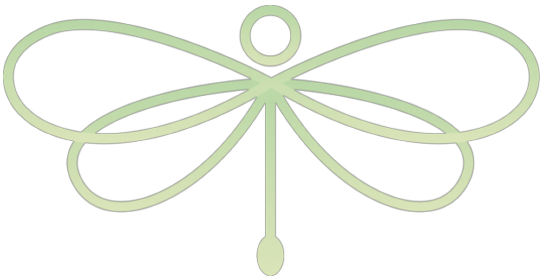
5.2 Study II.

Risk factors preceding new onset abuse among youth with bipolar disorder: A longitudinal prospective analysis.



Risk factors preceding new onset abuse among youth with bipolar disorder: A longitudinal prospective analysis. Andreu-Pascual, M., Merranko, J., Gill, M.K., Levenson, J.C., Hafeman, D., Hower, H., Yen, S., Strober, M., Goldstein, B.I., Diler, R., Ryan, N., Weinstock, L.M., Keller, M.B., Axelson, D.A., Birmaher, B**.,** Goldstein, T.R. ***Journal of Affective Disorders,* (2022),** (300), (296-304). ISSN 0165 0327. Doi:https://doi.org/10.1016/j.jad.2022.01.003.

STUDY II SUMMARY: "Risk factors preceding new onset abuse among youth with bipolar disorder: A longitudinal prospective analysis"

5.2.1 Background and Aims

Childhood abuse negatively impacts the course of Bipolar Disorder (BD). Yet, no study has examined risk factors associated with prospectively evaluated physical/sexual abuse, specifically, those preceding first abuse among BD youth. We investigate past/intake/follow-up factors preceding first physical and/or sexual abuse among youth with BD.

5.2.2 Summary of the methods

a) Participants: For this second study, to ensure that past/intake predictors preceded the abuse, we excluded participants with abuse history prior to intake (n=75). This analysis included 279 participants (44% female, 83% White) with BD-I (57%), BD-II (7%), and BD-NOS (35%). Participants completed at least 4 years of follow-up assessments and had at least one follow-up assessment before age 18 (mean age at intake= 12.4, range 7 to 17 years old; mean age throughout follow-up = 18.3, range 7 to 32 years old). Participants were prospectively interviewed on average every 7 months, for an average of 12 years, with a 90% retention rate. Included participants were significantly younger (Cohen's d=0.47, p<0.0001) and had earlier BD onset (Cohen's d=0.23, p=0.03), compared to excluded participants.

b) Sexual and/or physical abuse evaluation: Participant's history of child abuse (defined in the current thesis as physical or sexual abuse occurring prior to age 18) was assessed at intake and at each follow-up using multiple measures. Information about lifetime physical and/or sexual abuse was obtained at the time of study recruitment with the KSADS-PL PTSD section, and over follow-up with the TES (defined in section above

3.4.1). Lifetime history of child abuse was operationalized as endorsement of physical or sexual abuse on any of these measures at intake or any follow-up assessments.

The specific questions in the K-SADS-PL for evaluating physical abuse included: *"When your parents got mad at you, did they hit you?", "Have you ever been hit so that you had bruises or marks on your body, or were hurt in some way? What happened?"*. For physical abuse, inclusion criteria were bruises sustained on more than one occasion, or more serious injury sustained.

The questions in the K-SADS-PL related to presence of sexual abuse were as follows: "*Did anyone ever touch you in your private parts when they shouldn't have? What happened*?", "*Has someone ever touched you in a way that made you feel bad*?", "*Has anyone who shouldn't have ever made you undress, touch you between the legs, make you get in bed with him/her, or make you play with his private parts*?", or "*Was CYF ever involved with your family*?". Criteria included: isolated or repeated incidents of genital fondling, oral sex, or vaginal or anal intercourse.

c) Statistical analyses: Given the differences in the nature of childhood vs. adulthood abuse as well as the potential differences in risk factors between the two, recruited COBY participants who did not have a follow-up assessment before age 18 were excluded from this second study unless they reported abuse that occurred before age 18. UNICEF (1990) defines childhood as every age under 18, therefore childhood abuse was defined for this analyses when participants reported experiencing abuse before age 18, both for children and adolescents up until that age (187).

To identify the strongest predictors of childhood abuse risk, Cox proportional hazards regression modeled age of first abuse (right-censoring at age 18) implementing LASSO for feature selection (186). Briefly, LASSO was defined in section 3.3.1, under Statistical analyses for the first section of the analyses (186). Multiple imputation was

used to impute missing values (five iterations); LASSO was separately implemented within each imputation iteration (lambdas selected via three-fold cross-validation within each iteration), and results were pooled across the five iterations (188). Lastly, the stability of the LASSO results was assessed by bootstrapping (104, 105) the process described above (1000 iterations with multiple imputation and pooled LASSO uniquely implemented within each iteration) and computing the percent of iterations in which each predictor was retained (higher percentages indicate more important predictors). Predictor variables entered into the analysis were chosen based on the literature, including demographic, clinical, and family history factors, and hypothesized interactive effects between predictors including: social support as a protective factor, family history of substance abuse as a risk factor among low SES families, and more negative life events associated with abuse risk in families with worse family functioning. All baseline models controlled for age at intake.

Follow-up prediction models similarly identified factors preceding new onset physical/sexual abuse (as well as non-event censored cases). These models were useful for identifying changes that occurred in close temporal proximity (as per last follow-up interview) to first instance of abuse, including all clinical symptomatology (diagnosis, and relevant clinical variables) and any demographic changes occurring during the prior follow-up period.

5.2.3 Summary of the results

a) **New onset abuse during FUP:** This analysis includes 279 participants (44% female, 83% White) with BD-I (57%), BD-II (7%), and BD-NOS (35%). Fifteen-percent of youth reported new-onset abuse during follow-up (62% physical, 26% sexual; 12% both).

b) Past and intake predictors for new onset abuse during follow-up: Physical abuse. Participants with more severe depressive symptoms (HR=1.29, 95% of iterations) and those with an interaction between low SES and family history of SUD were at higher risk for physical abuse over follow-up (inverted HR=1.19, 85% of iterations) than participants without presence of those factors. Notably, 79% of participants who suffered physical abuse had family history of SUD, and in 65% of those cases, at least one of the family members with SUD was a parent**.** Sexual abuse. The strongest predictor of sexual abuse selected by LASSO was female sex (HR=2.41, 97% of iterations).

c) Predictors ascertained during follow-up preceding new onset abuse: Physical abuse. Older age (HR=1.42, 100% of iterations), comorbid Disruptive Behavior Disorder (HR=1.39, 100% of iterations), and the interaction between low SES and family history of SUD (HR=0.86, 100% of iterations) predicted new onset physical abuse. Good interpersonal relationships with friends was associated with significantly lower risk for physical abuse (HR=0.72, 100% of iterations). Sexual abuse. Changes in living status were associated with increased risk of sexual abuse during the next follow-up period (HR=2.76, 100% of iterations). Nearly all these instances of sexual abuse involved child living with biological mother along with a non-biologically related father (e.g., boyfriend, husband) who moved into the household. Female sex was associated with increased sexual abuse risk during the next follow-up period (HR=4.33, 100% of iterations). Good interpersonal relationships with friends were associated with decreased sexual abuse risk (HR=0.70, 100% of iterations). Since depression was a significant risk factor for physical abuse at intake but not during follow-up, a sensitivity analysis reimplemented the follow-up LASSO using only factors that were also available at intake. Depression was retained by LASSO (26% of bootstrap iterations). Rerunning this model after reintroducing interpersonal relationships during follow-up as a predictor resulted in the retention of this

variable instead of depression in 100% of bootstrap iterations. Thus, depression's role as a predictor of future abuse risk may be explained by the absence of protective factors (i.e., interpersonal relationships).

d) **Past, intake and follow-up risk factors including participants who experienced past abuse:** The above analyses were also completed with the included participants (n=279) plus the initially excluded participants who had physical/sexual abuse history prior to intake (n=75). Abuse history was a significant abuse predictor during follow-up (HR= 1.99, 100% of iterations; HR=1.66, 100% of iterations, respectively). Moreover, if past abuse was present, participant SUD increased physical abuse risk (HR=1.54, 31% of iterations) in the upcoming follow-up period. All other predictors noted in the above analyses were similar and remained significant.

5.2.4 Main conclusions

This is the first study to prospectively evaluate risk factors both at intake and over follow-up temporally preceding new onset physical and/or sexual abuse among youth with BD. Our study broadens prior research scope on this population by establishing temporal precedence of risk factors for new onset abuse through longitudinal analyses, instead of using cross-sectional associations. These results have several clinical implications, including the importance of providers identifying high risk individuals and circumstances (i.e., those with above noted predictors of female sex, severe depression, DBD, not living with both biological parents, low SES in families with SUD) that may inform strategies to diminish abuse risk.

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Risk factors preceding new onset abuse among youth with bipolar disorder: A longitudinal prospective analysis

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ABSTRACT

Background: Childhood abuse negatively impacts the course of Bipolar Disorder (BD). Yet, no study has examined risk factors associated with prospectively evaluated physical/sexual abuse, specifically, those preceding first abuse among BD youth. We investigate past/intake/follow-up factors preceding first physical/sexual abuse among BD youth.

Methods: Childhood-onset BD participants ($n = 279$ youth, mean age at intake = 12, mean length of follow-up = 12 years) enrolled in the Course and Outcome of Bipolar Youth (COBY) study. Demographic, clinical and family history variables were assessed every 7 months on average using Longitudinal Interval Follow-up Evaluation and Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL). Abuse was evaluated at intake using the K-SADS-PL, over follow-up with a Traumatic Events Screen. Family psychopathology was assessed using Family History Screen/Structured Clinical Interview for Diagnostic Statistical Manual-IV.

Results: Fifteen-percent of youth reported new-onset abuse during follow-up (62% physical, 26% sexual; 12% both). Intake predictors included more severe depressive symptoms (HR = 1.29), low socioeconomic-status (SES) in families with substance abuse (HR = 0.84) (physical abuse), and female sex (HR = 2.41) (sexual abuse). Follow-up predictors preceding physical abuse included: older age (HR = 1.42), disruptive disorders (HR = 1.39), and the interaction between low SES and family substance abuse (HR = 0.86). For sexual abuse, female sex (HR = 4.33) and a non-biologically related father presence in the household (HR = 2.76). Good relationships with friends (prospectively evaluated) protected against physical/sexual abuse (HR = 0.72/0.70, respectively).

Limitations: Prospective data was gathered longitudinally but assessed retrospectively at every follow-up; perpetrator information and abuse severity were not available.

Conclusions: Identifying factors temporally preceding new onset physical/sexual abuse may hold promise for identifying high-risk youth with BD.

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1. Introduction

Worldwide, up to 22% of youth have experienced physical abuse, and up to 18% have experienced sexual abuse (Stoltenborgh et al., 2015). Research on risk factors for childhood abuse (physical/sexual abuse before age 18) has mostly been conducted in community studies, identifying multiple sociodemographic risk factors including: female sex, older age, non-White race, low Socio-Economic Status (SES), parental education and social support, high family conflict, and presence of parental abuse history (Black et al., 2001a, 2001b; Stith et al., 2009; White et al., 2015).

Abuse early in development is associated with severe adverse outcomes across the lifespan in multiple domains, including physical health (e.g., diabetes, pain conditions), psychosocial functioning (e.g., cognitive dysfunction, relationship problems), and mental health (e.g., substance use, disruptive behaviors) (Carr et al., 2018b; Felitti et al., 2019). Regarding mental health outcomes specifically, 45% of adults with psychopathology retrospectively report some type of childhood maltreatment, with 19% reporting multiple forms of abuse (Nelson et al., 2017).

Extensive research has specifically focused on the association of childhood abuse and Bipolar Disorder (BD). Two large meta-analyses indicate up to 57% of adults with BD report history of childhood abuse (9%−33% physical abuse, and 9%−40% sexual abuse) (Agnew--Blais and Danese, 2016; Daruy-Filho et al., 2011); among youth with BD, 3–20% report physical abuse history, and 7–29% report sexual abuse history (Benarous et al., 2017; Conus et al., 2010; Daglas et al., 2014; Du rocher Schudlich, 2015; Maniglio, 2013b; Romero et al., 2009; Rucklidge, 2006). In our prior cross-sectional analysis from the Course and Outcome of Bipolar Youth (COBY) study, a multi-site longitudinal naturalistic study of youth with childhood-onset BD followed into adulthood, we documented rates of abuse using retrospective data gathered at study intake. Twenty-one percent of participants reported physical and/or sexual abuse history (9% physical, 7% sexual and 5% both), demographic and clinical correlates of abuse included living with non-intact families, history of psychosis, comorbid Post Traumatic Stress Disorder (PTSD) and Conduct Disorder (CD), and family history of mood disorders (Romero et al., 2009).

Thus far, the BD literature mainly documents detrimental associations of abuse and BD course (e.g., increased suicidality, mood recurrences, more comorbidity) (Cazala et al., 2019; Daruy-Filho et al., 2011; Marchand et al., 2005; Palmier-Claus et al., 2016; Rucklidge, 2006). Yet, to the best of our knowledge, no study to date has examined the specific risk factors (which by definition must be present prior to the outcome) that temporally precede new onset childhood abuse among youth with BD. The study of such risk factors requires prospective data to enable the identification of youth at risk for abuse, and in turn inform strategies that may mitigate long-term effects.

In the few longitudinal studies with this population, youth with BD with abuse history had worse family environment, more comorbid anxiety, mood recurrences, general distress, hopelessness, and severe mood episodes, as well as a decreased response to treatment (Conus et al., 2010; Daglas et al., 2014; Du rocher Schudlich, 2015; Neria et al., 2005). A recent COBY prospective analysis investigated the effects of severe lifetime traumatic events, including abuse, on the longitudinal course of BD among youth (Andreu Pascual et al., 2020). This study prospectively followed youth with BD and examined the associations of different types of lifetime traumatic events (e.g., accidents, death, abuse) with mood and functioning over time, demonstrating that those with more traumatic experiences had poorer psychosocial functioning, worse mood symptoms, increased mood recurrences and comorbidities. Critically, the prospective data allowed investigation of time-varying mood changes before and after the abuse. Specifically, abused participants showed greater suicidality, Substance Use Disorder (SUD), and worsening mood symptoms, specifically hypo/mania after abuse occurrence. However, this study did not evaluate specific prospective risk factors for abuse among COBY youth. Although informative, the above noted studies have one or more of the following limitations: 1) most are retrospective; 2) many lack repeated assessments that would enable temporal clarity; 3) mainly limited to community (vs clinical) samples, and largely involved children in Child Protective Services (CPS, presumably most severe cases); 4) confounding variables such as age, race or SES are not always accounted for; and 5) the research designs prohibit the analysis of temporal associations between past and prospectively ascertained factors that precede new onset abuse. Thus, prospective studies that identify risk factors that precede new onset physical and/or sexual abuse among youth with BD are warranted. Such data, while critical to inform providers and policy makers of future abuse in this high-risk group does not provide evidence of causality.

The prospective design of COBY allows us to provide new insights in the BD youth literature and to extend prior COBY findings by: 1) identifying past and intake risk factors for new onset physical and/or sexual abuse among COBY youth with BD ($n = 279$) followed for an average of 12 years; 2) conducting, to the best of our knowledge, the first examination of predictors that temporally precede new onset physical and/or sexual abuse among youth with BD over follow-up. Given the above literature, we hypothesized that: 1) past and intake predictors for new onset abuse during follow-up would include sociodemographic and clinical factors previously identified in the literature, including low SES, lack of social support, more severe mood symptoms, increased comorbid disorders and female sex; 2) Although there are no prior studies that evaluate near-term predictors for new onset abuse, based on clinical experience and distal literature, we hypothesized that predictors ascertained during follow-up preceding new onset abuse would similarly involve variables associated with abuse in prior studies, including age, female sex, low SES, living with one parent, presence of comorbid disorders and family psychopathology.

2. Methods

2.1. Participants

Details of the COBY sample are described elsewhere (Axelson et al., 2006; Birmaher et al., 2014). Briefly, from October 2000 through July 2006, COBY enrolled 446 participants through three academic medical centers: Brown University ($n = 144$), University of California at Los Angeles (UCLA) ($n = 90$), and University of Pittsburgh ($n = 204$). Participants were ages 7 to 17 years 11 months at intake (mean = 12.7 ± 3.2 years, 53% males, 82% White), who met 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 ($n = 154$) (see(Axelson et al., 2006)). BD onset age was defined by any DSM-IV mood episode onset or an episode fulfilling COBY 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 other provider referral (4.4%) at the three sites. Youth with schizophrenia, intellectual disability, autism, and mood disorders secondary to medical conditions or substance use were excluded from the study.

The present analysis includes 279 participants who completed at least 4 years of follow-up assessments and had at least one follow-up assessment before age 18 (mean age throughout follow-up = 18.0, range 7–32). Participants were prospectively interviewed on average every 7 months, for an average of 12 years, with a 90% retention rate. Included participants were significantly younger (Cohen's $d = 0.47$, $p < 0.0001$) and had earlier BD onset (Cohen's $d = 0.23$, $p = 0.03$), compared to excluded participants.

2.2. Procedure

Each University's Institutional Review Board approved the study before enrollment, and informed consent/assent was obtained from

participants and parents/primary caregivers at intake. Trained COBY staff administered semi-structured interview assessments to participants and parents. Participants aged ≥ 18 chose whether to include parents/secondary informants in study interviews. Following assessment, research staff reviewed ratings with a study investigator that yielded final consensus ratings.

2.2.1. Measures

At intake, participants/parents were interviewed for presence of current and lifetime psychopathology using the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Mood symptom severity was assessed through the K-SADS Mania Rating Scales (K-MRS) (Axelson et al., 2003) and depression section of the K-SADS-P (K-DRS), both derived from the K-SADS-Present Episode mood disorder section (K-SADS-P; 4th revision) (Chambers et al., 1985). Diagnostic interrater agreement was high for the K-SADS-PL (range 93%−100%). The intraclass correlation coefficients (ICC) for the K-SADS-MRS, K-SADS-DEP-P were ≥ 0.83. Kendall's concordance coefficients W were 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), Psychiatric Status Rating Scale (PSR). PSRs use numeric values linked to DSM-IV criteria, ranging 1–6 for mood disorders (scores indicate, respectively: ≤ 2euthymia, 3–4subsyndromal symptoms, ≥ 5syndromal symptoms). Full recovery was defined as 8 consecutive weeks with PSR score ≤ 2 (minimal/no mood symptoms). Recurrence was defined as PSR ≥ 5, with 1-week duration for mania/hypomania and 2-weeks for depression. PSR reliability for percentage of time meeting full DSM-IV criteria for a mood episode yielded ICC = 0.85; without mood symptoms ICC = 0.82. Reliability for PSR mood disorder ratings over COBY course = 0.8 (Kendall's W).

At intake, presence of lifetime (past/current) physical and/or sexual abuse was obtained using the PTSD section of the K-SADS-PL. Questions for evaluating physical abuse were: *"When your parents got mad at you, did they hit you?", "Have you ever been hit so that you had bruises or marks on your body, or were hurt in some way?"* Inclusion criteria were bruises/injuries sustained on more than one occasion. Questions for evaluating sexual abuse were: *"Did anyone ever touch you in your private parts when they shouldn't have?", "Has someone ever touched you in a way that made you feel bad?", "Has anyone who shouldn't have ever made you undress, touch you between the legs, make you get in bed with him/her, or make you play with his private parts?*", *"Was Child, Youth and Family Services ever involved with your family?"*. Inclusion criteria were isolated/repeated incidents of genital fondling, oral sex, vaginal or anal intercourse.

During follow-up, presence of lifetime physical and sexual abuse was assessed regularly using the Traumatic Events Screen (TES), 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 TES documented severe events, including being victim of a violent crime (including physical/sexual assault) and experiencing physical/sexual abuse, among others. Abuse by a caregiver was coded as physical/sexual abuse; abuse by a significant other as intimate partner violence. The events in the TES are answered: yes/no. Events were ascertained at each follow-up separately for parents and participants, and a summary score was determined. In general, if parent/participant endorsed an event, the summary score was considered positive. If an event was reported, the interviewer recorded the total number of occurrences, dates of the first, second and most recent event. If there was discrepancy between informants, further clarification was obtained. If parent reported an event as traumatic, but participant indicated he/she did not perceive this as traumatic, the event was not given a positive score. Correlations between summary scores and parent/participant reports indicate summary scores depended more heavily on participants' than parents' reports (Spearman correlations = 0.95 and 0.72, respectively). Spearman correlation between parents' and participants' reports was 0.59.

SES was ascertained using the 4-factor Hollingshead Scale at intake and during follow-up (Hollingshead, 1975). Participants' psychosocial functioning was assessed at intake via the Children's Global Assessment Scale (CGAS) (< age 22) (Shaffer et al., 1983), and over follow-up via the Global Assessment of Functioning (GAF) (> age 22) (Jones et al., 1995); psychosocial functioning in specific domains was assessed over follow-up using the A-LIFE Psychosocial Functioning Scale (PSF) (Keller et al., 1987). Interpersonal relationships were evaluated over the past 6 months, both for family and friends, and rated according to quality from 1 (very good: had several special friends/family members that he/she saw regularly and frequently and felt close to) to 5 (very poor: had no special friends/family members and practically no social contacts). The parent was interviewed at intake about personal psychiatric history using the Structured Clinical Interview for DSM-IV (SCID-IV) (First, 1996), and psychiatric status of first/second degree relatives was ascertained using an enhanced version of the Family History Screen (Weissman et al., 2000). Each participant and parent completed the Conflict Behavior Questionnaire (CBQ) to assess family conflict (Robin and Foster, 1989) and Family Adaptability and Cohesion Evaluation Scale-II (FACES-II) (Olsen et al., 1985) to assess family environment. The Life Events Checklist (LEC) assessed for the presence of negative and positive life events, and impact on the participant's wellbeing, over the last 12 months at each assessment (Johnson and McCuthcheon, 1980).

2.3. Statistical analyses

Given the differences in the nature of childhood vs. adulthood abuse and the potential differences in risk factors, COBY participants who did not have a follow-up assessment before age 18 were excluded from the analyses of childhood abuse unless they reported abuse that occurred before age 18.

To identify the strongest predictors of childhood abuse risk, Cox proportional hazards regression modeled age of first abuse (right-censoring at age 18) implementing Least Absolute Shrinkage and Selection Operator (LASSO) for feature selection (Hastie et al., 2009). Briefly, a LASSO is a modified form of linear or generalized linear regression that penalizes overfit models via a regularization parameter that proportionally shrinks predictor magnitude coefficients toward zero, and for less important predictors, coefficients shrink to zero. Thus, predictor selection is implicitly performed, as less important variables are removed from the model without potential biases of other variable selection techniques, such as multiple comparisons and collinearity between predictor variables. Multiple imputation was used to impute missing values (five iterations); LASSO was separately implemented within each imputation iteration (lambdas selected via three-fold cross-validation within each iteration), and results were pooled across the five iterations (van Buuren S, 2011). Lastly, the stability of LASSO results was assessed by bootstrapping (Hastie et al., 2015; Schomaker and Heumann, 2018), the process described above (1000 iterations with multiple imputation and pooled LASSO uniquely implemented within each iteration) and computing the percent of iterations in which each predictor was retained (higher percentages indicate more stable, and consistently influential predictors). Predictor variables entered into the analysis were chosen based on the literature, including demographic, clinical, and family history factors, and hypothesized interactive effects between predictors including: social support as a protective factor, family history of substance abuse as a risk factor among low SES families, and more negative life events associated with abuse risk in families with worse family functioning. All baseline models controlled for age at intake.

Follow-up prediction models similarly identified factors preceding new onset physical/sexual abuse (as well as non-event censored cases). These models were useful for identifying changes that occurred in close temporal proximity (as per last follow-up interview) to first instance of abuse, including all clinical symptomatology (diagnosis, and relevant

clinical variables) and any demographic changes occurring during the prior follow-up period.

3. Results

3.1. New onset abuse during follow-up

For this analysis, to ensure that past/intake predictors preceded the abuse, we excluded participants with abuse history prior to intake (n = 75). This analysis includes 279 participants (44% female, 83% White) with BD-I (57%), BD-II (7%), and BD-NOS (35%). Of these, 42/279 (15%) reported new onset abuse during follow-up (62% physical, 26% sexual; 12% both), of which 20 (48%) had one instance of abuse and 22 (52%) had two or more. Sociodemographic and clinical characteristics of the included sample are noted in **Table 1**.

a) Past/intake predictors for new onset abuse during follow-up, should be placed AFTER Table 1, where the results are presented.

Physical abuse. LASSO selection of the Cox proportional hazards regression predictor variables for physical abuse showed participants with more severe depressive symptoms (HR = 1.29, 95% of iterations) and those with an interaction between low SES and family history of SUD were at higher risk for physical abuse over follow-up (inverted HR = 1.19, 85% of iterations) than participants without presence of those factors (**Fig. 1**). Notably, 79% of participants who suffered physical abuse had family history of SUD, and in 65% of those cases, at least one of the family members with SUD was a parent.

Sexual abuse. The strongest predictor of sexual abuse selected by LASSO was female sex (HR = 2.41, 97% of iterations) (**Table 2**).

Table 1
Sociodemographic and clinical characteristics of the included participants.

Demographics at intake	Mean (SD) or N (%)
Age	12.14 (3.11)
Sex (Female)	124 (44.44)
Race (White)	231 (82.80)
SES	3.43 (1.19)
Living Situation	
Both Biological Parents	127 (45.52)
One Biological Parent	130 (46.59)
Other (e.g., grandparents)	22 (7.89)
Maternal Age at Child's Birth	27.05 (5.90)
Lifetime (past, intake, follow-up Categorical diagnosis)	**N (%)**
Bipolar Disorder	
BD-I	193 (69.18)
BD-II	41 (14.70)
BD-NOS	45 (16.13)
Age of BD Onset	8.99 (3.73)
ADHD	193 (69.18)
DBD	181 (64.87)
Anxiety Disorders	204 (73.12)
PTSD	46 (16.49)
SUD	110 (39.43)
Psychosis	95 (34.05)
Suicidal Ideation and/or Attempts	213 (76.34)
Family History	**N (%)**
Depression	246 (88.17)
Mania	166 (59.5)
ADHD	133 (47.67)
Conduct Disorder	98 (35.13)
Schizophrenia	19 (6.81)
Psychosis	48 (17.2)
Anxiety	214 (76.7)
SUD	191 (68.46)
Suicidality	146 (52.33)

Abbreviations: ADHD= Attention Deficit Hyperactivity Disorder; BD= Bipolar Disorder; DBD= Disruptive Behavior Disorder (including Conduct Disorder [CD] and/or Oppositional Defiant Disorder [ODD]); PTSD= Post traumatic Stress Disorder; SES= Hollingshead Socioeconomic Status; SUD= Substance Use Disorder.

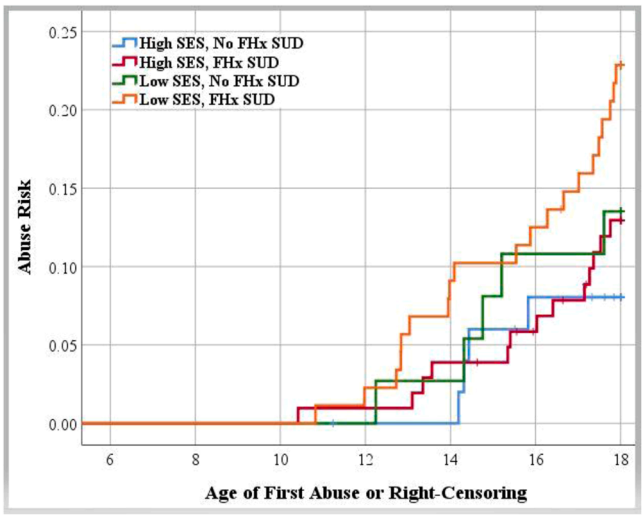

Fig. 1. LASSO Evaluated socioeconomical status and family history of substance use disorders predicting risk for new onset physical/sexual abuse
Abbreviations: FHx = Family History; LASSO = Least Absolute Shrinkage and Selection Operator;SES = Socioeconomic Status, SUD = Substance Use Disorder.
Note: Unlike in the prediction models, SES was dichotomized in the plot above to improve interpretability. Models evaluated through LASSO.

Table 2
LASSO selected predictors of risk for abuse (Physical and/or Sexual).

	Physical Abuse		Sexual Abuse	
	Pooled HR[1]	% of Iterations Selected	Pooled HR	%of Iterations Selected
Past and intake predictors for new onset abuse during follow-up				
Sex (Female vs. Male)	—	—	2.41	97%
DRS	1.29	95%	—	—
SES x Family History of SUD Interaction	0.84	85%	—	—
Predictors ascertained during follow-up that preceded new onset abuse				
Current Age[2]	1.42	100%	—	—
Sex (Female vs. Male)	—	—	4.33	100%
Change in Living Status	—	—	2.76	100%
Interpersonal Relationship with Friends	0.72	100%	0.70	100%
Current DBD	1.39	100%	—	—
SES x Family History of SUD Interaction	0.86	100%	—	—

1, 2Hazard ratios were standardized for continuous predictors. Abbreviations: DBD= Disruptive Behavior Disorder (including Conduct Disorder [CD] and/or Oppositional Defiant Disorder [ODD]); DRS= Depression Rating Scale of the Kiddie Schedule for Affective Disorders and Schizophrenia in School-Aged Children; HR= Hazard Ratios; LASSO = Least Absolute Shrinkage and Selection Operator; SES=Socioeconomic Status; SUD= Substance Use Disorders.

After bootstrapping the LASSO models, the above predictors (more severe depressive symptoms, low SES, family history of SUD, female sex) were retained in 85% or more of the bootstrap iterations, indicating stable predictor selection.

b) Predictors ascertained during follow-up preceding new onset abuse.

Physical abuse. Older age (HR = 1.42, 100% of iterations), comorbid Disruptive Behavior Disorder (DBD; including Conduct Disorder [CD] and/or Oppositional Defiant Disorder [ODD]) (HR = 1.39, 100% of iterations), and the interaction between low SES and family history of SUD (HR = 0.86, 100% of iterations) predicted new onset physical abuse. Good interpersonal relationships with friends was associated

with significantly lower risk for physical abuse (HR = 0.72, 100% of iterations) (Table 2).

Sexual abuse. Models initially included a trichotomous predictor indicating whether participants lived with both, one, or no biological parents. After finding that LASSO selected living with both biological parents as a significant protective factor (HR = 0.8), this was replaced with a more longitudinally-informative predictor including *any changes* in living status that occurred prior to the abuse. Changes in living status were associated with increased risk of sexual abuse during the next follow-up period (HR = 2.76, 100% of iterations). Nearly all these instances of sexual abuse involved child living with biological mother along with a non-biologically related father (e.g., boyfriend, husband) who moved into the household. Female sex was associated with increased sexual abuse risk during the next follow-up period (HR = 4.33, 100% of iterations). Good interpersonal relationships with friends were associated with decreased sexual abuse risk (HR = 0.70, 100% of iterations) (Table 2).

After bootstrapping the LASSO models, the above predictors (older age, DBD, low SES and family history of SUD interaction, living status changes, female sex) were retained in 100% of the bootstrap iterations, indicating extremely stable predictor selection.

After observing that depression at intake, but not during follow-up, was predictive of physical abuse risk, a sensitivity analysis reimplemented the follow-up LASSO using only factors that were also available at intake to assess whether depression is a retained risk factor. Depression was retained by LASSO (26% of bootstrap iterations). Rerunning this model after reintroducing interpersonal relationships during follow-up as a predictor resulted in the retention of this variable instead of depression in 100% of bootstrap iterations. Thus, depression's role as a predictor of future abuse risk may be explained by the absence of protective factors (i.e., interpersonal relationships).

Estimated 5-year-risk was evaluated to illustrate cumulative risk of physical/sexual abuse given presence/absence of LASSO-identified risk and protective factors (Fig. 2).

The above analyses were also completed with the included participants (n = 279) plus the initially excluded participants who had physical/sexual abuse history prior to intake (n = 75). Abuse history was a significant abuse predictor during follow-up (HR = 1.99, 100% of iterations; HR = 1.66, 100% of iterations, respectively). Moreover, if past abuse was present, participant SUD increased physical abuse risk (HR = 1.54, 31% of iterations) in the upcoming follow-up period. All other predictors noted in the above analyses (older age, DBD, low SES and family history of SUD interaction, living status changes, female sex, protective relationship with friends) were similar and remained significant.

4. Discussion

To our knowledge, this is the first study among youth with BD to prospectively examine lifetime (past/intake and follow-up) risk factors for new onset physical/sexual abuse, specifically those that temporally precede new onset abuse.

Fifteen percent (42/279) of youth with BD reported new onset abuse during follow-up (62% physical, 26% sexual; 12% both). More severe depression at intake, low SES in families with history of SUD, older age and more DBD symptoms predating abuse were associated with

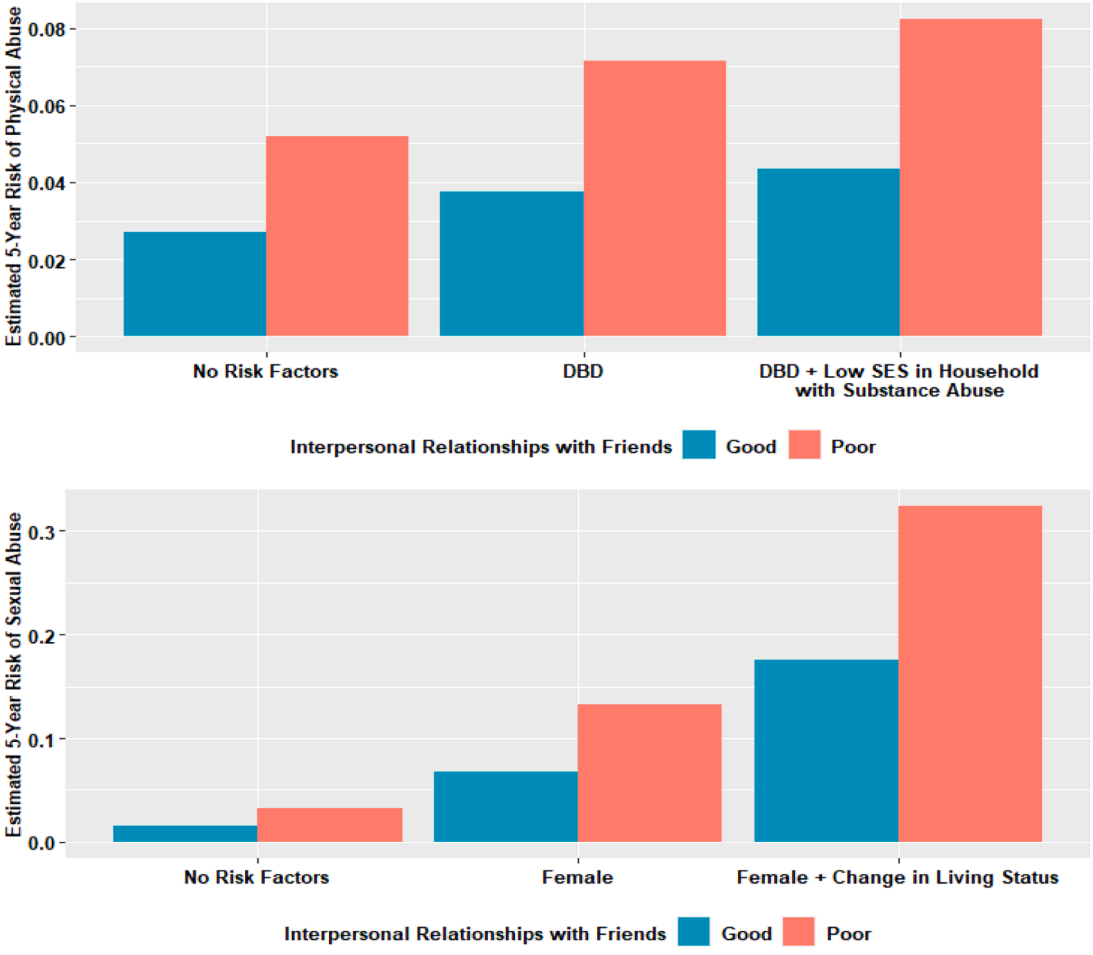

Fig. 2. Estimated additive 5-year risk of physical/sexual abuse. Abbreviations: DBD=Disruptive Behavior Disorder (including Conduct Disorder [CD] and/or Oppositional Defiant Disorder [ODD]); SES=Socioeconomic Status. Note: For the risk estimates above, assessment age was held constant at the mean value=14.5.

increased risk for first physical abuse. About 79% of the participants who experienced new onset physical abuse had family history of SUD, and in 65% of those cases, at least one of the family members with SUD was a parent. Being female and not living with both biological parents (specifically living status changes) in the follow-up period preceding the abuse were associated with increased risk for first sexual abuse. Living with the biological mother and the presence of a non-biologically related father increased risk for sexual abuse three-fold. However, good interpersonal relationships with friends prospectively evaluated during follow-up was associated with decreased risk for both physical and sexual abuse.

COBY is the only study to also evaluate the abuse prevalence among youth with BD prospectively, reporting that 15% (62% physical, 26% sexual; 12% both) of participants with no prior abuse history experienced first abuse instance in their lives during the follow-up. Two epidemiological studies among children of general population that used prospective measures to evaluate abuse, reported prevalence of abuse among children of 7% and 20% respectively (Newbury et al., 2018; Shaffer et al., 2008). Importantly, our study adds to the literature by identifying abuse risk factors ascertained prospectively and temporally preceding new onset abuse. As such, our study may provide new perspectives on risk assessment and prevention that might enable identification of vulnerable youth with BD to potentially mitigate risk and decrease vulnerability to ongoing victimization.

While low SES and family history of SUD at intake and during follow-up were independent risk factors for new physical abuse onset, their interaction most potently predicted physical abuse. Other adult/youth BD studies also report that low SES and separately, family psychopathology, are associated with both types of abuse (Leverich et al., 2002; Romero et al., 2009). Community studies also find low SES and family instability (common among families with psychopathology), is associated with physical abuse risk (Sidebotham et al., 2006). These findings emphasize the need for identification and referral of parents of youth with BD for SUD treatment, as well as connection with case management and social services for low resourced families. We found older age during follow-up increased risk for first physical abuse, although other studies among youth with BD have not reported such association (Marchand et al., 2005). In community studies, younger age has been associated with maltreatment and may be partially explained by the increased vulnerability at younger ages (Zeanah and Humphreys, 2018). Other community studies indicate older age might be a risk factor for certain types of abuse (i.e., sexual) associated with increasing peer interactions during adolescence (Finkelhor et al., 2009). However, perpetrator information was not available in COBY.

We found that severe depression at intake is associated with increased risk for first physical abuse. Of note, childhood trauma has been associated with depression later in life, partly explained by the cognitive dimension of depression and resulting difficulties in emotion regulation (Huh et al., 2017). Retrospective studies have also reported an association between severe depression and physical abuse (Agnew--Blais and Danese, 2016; Daglas et al., 2014; Daruy-Filho et al., 2011), but others have found that only manic symptom severity was associated with abuse (Du rocher Schudlich, 2015). In line with this, a study among general population parents and risk for new onset abuse in their children, reported that parents with comorbid SUD and depression were found to be risk factors for new onset abuse among their children (Chaffin et al., 1996). Our findings were further explored, showing that such risk of depression was potentially related with some of the core symptoms of depression (e.g., isolation, low self-esteem…) that impact interpersonal relationships, and might place this youth in a vulnerable position, related with lack of protective factors (i.e., interpersonal relationships). In a longitudinal study among adults with BD, social support appeared to be associated with less depression at follow-up; findings were consistent with a mediational model suggesting that self-esteem may be one of the mechanisms whereby social support influences depression over time (Johnson et al., 2000). Retrospective studies have also reported an association between severe depression and risk for abuse (Agnew-Blais and Danese, 2016; Daglas et al., 2014; Daruy-Filho et al., 2011; Haussleiter et al., 2020; Saito et al., 2019). Of note, depression not only increases the risk for abuse, but abuse during childhood also increases the risk to develop depression later in life (Huh et al., 2017; Vares et al., 2015), which may be also partly explained by the cognitive dimension of depression and the resulting difficulties in emotion regulation resulting from trauma. Moreover, in a metanalytic review of the literature for child abuse, child's social competence was moderately related to child's physical abuse (Stith et al., 2009). Several studies have found a positive correlation between social isolation and abuse (Hazler and Denham, 2002), which can be embedded by specific aspects related with social support such as higher levels of belonging, availability of individuals who will engage in joint activities and provide physical and emotional support. Further, self-esteem might buffer an individual against downturns in self-evaluation. To our knowledge, this is the first study that uses a temporal sequence among youth with BD to analyze risk factors for abuse, so we are not able to compare this finding.

Comorbid DBD also predicted physical abuse during follow-up. Other studies show comorbidity in youth with BD is associated with physical abuse (Cazala et al., 2019; Du rocher Schudlich, 2015; Marchand et al., 2005). Youth/adults with other disorders manifested by behavior problems (e.g., Attention Deficit Hyperactivity Disorder) are also at elevated risk for physical abuse (Black et al., 2001a; Fuller-Thomson et al., 2014).

Additionally, when including participants with past abuse history ($n = 75$), we observed that participants with past abuse history and SUD diagnosis were at greater risk for physical abuse in the upcoming follow-up period. Literature among BD youth and adults have also reported that SUD has been associated with abuse (Brown et al., 2005; Du rocher Schudlich, 2015; Maniglio, 2013a). The significance of such association has a complex nature and the effects of early-abuse in the brain could partially explain this relationship; abuse survivors may tend to use substances as a coping strategy in order to alleviate painful internal states (Roesler and Dafler, 1993). Further, SUD has been associated with increased risk for maltreatment in adolescent community samples (Thornberry et al., 2014), perpetuating this daunting cycle and placing these youth at increased risk for revictimization. The relationship of how individuals with past abuse and comorbid SUD are at increased risk for recurrent physical abuse among BD youth should be further studied.

For sexual abuse, we found females had more than four times the risk for sexual abuse than males both at intake and follow-up. Other studies in BD youth/adults (Conus et al., 2010; Maniglio, 2013b; Marchand et al., 2005), as well as community studies, have similarly reported higher rates of sexual abuse among females than males (Black et al., 2001b). Not living with both biological parents over follow-up was also associated with subsequent risk of first sexual abuse. In fact, prospectively evaluated *changes* in living status, specifically, living with a biological mother and a stepfather/mother's boyfriend moving into the house, nearly tripled the risk of subsequent new onset sexual abuse among females. In the BD literature, having single or divorced parent(s) has been associated with abuse, but has not previously been demonstrated as a temporally precedent risk factor (Conus et al., 2010; Marchand et al., 2005; Rucklidge, 2006). Prospective studies including community samples also found that living in single-parent families and having a biologically unrelated father posed increased risk for any type of abuse (Sidebotham et al., 2006; White et al., 2015). Similar to our findings, community studies have reported that female sex and not living with both biological parents, parents with low educational level and unemployment, or single parent households were associated with lifetime abuse (Schick et al., 2016).

Good relationships with friends during follow-up were associated with lower risk for physical/sexual abuse. This holds special importance since sequelae of abuse include psychosocial impairment, suicidality, and comorbid psychopathology (Carr et al., 2018a). To the best of our knowledge, there are no other BD studies reporting protective factors for

abuse, although in community studies, social support and having good friends is associated with decreased risk for both types of abuse (Finkelhor, 2007; Flemming et al., 1997; Sidebotham et al., 2006). In a longitudinal study among adults with BD, positive relationships with friends was inversely associated with severity of depression over time, and predicted a better illness course (Johnson et al., 2000). The above findings highlight the importance of fostering supportive relationships among youth with BD in order to not only mitigate risk of first onset physical and/or sexual abuse, but also potentially contribute to improvement in their mood episodes and, thus, decrease their ongoing risk for victimization.

4.1. Limitations

The results presented above need to consider the following limitations. First, participants were mostly White, and recruited from clinical settings, limiting the generalizability of the results. Nonetheless, similar clinical course and morbidity of youth with BD has been observed in non-clinical populations (Lewinsohn et al., 2000). Second, COBY did not recruit a control group, so conclusions cannot be drawn on abuse predictors among youth with BD relative to controls. Third, although prospective data on abuse and follow-up variables were gathered longitudinally, these data were assessed retrospectively at each follow-up period encompassing an average of 7-months. While all reports of abuse are retrospective, we limited the time interval between assessments to minimize retrospective recall. Fourth, severity/frequency of abuse, perpetrator information, parents' abuse history, other forms of abuse (e.g., emotional abuse, neglect), or interventions/services for abuse were not systematically assessed. Finally, abuse was not further corroborated with other sources of information (e.g., CPS) due to confidentiality.

4.2. Conclusions

To summarize, this is the first study to prospectively evaluate risk factors both at intake and over follow-up temporally preceding new onset physical and/or sexual abuse among youth with BD. Our study broadens prior research scope on this population by establishing temporal precedence of risk factors for new onset abuse through longitudinal analyses, instead of using cross-sectional associations. These results have several clinical implications, including the importance of providers identifying high risk individuals and circumstances (i.e., those with above noted predictors of female sex, severe depression, DBD, not living with both biological parents, low SES in families with SUD) that may inform strategies to diminish abuse risk.

Authorship Contributions

Conception and design of the study: M. Andreu-Pascual, B. Birmaher, T.Golstein. Statistical expert: J. Merranko. Analysis, acquisition and/or interpretation of data: J. Merranko, M. Andreu-Pascual, B. Birmaher, T. Goldstein, M. Kay Gill, H. Hower, J.Levenson, S. Yen, M. Strober, D. Hafeman, B. Goldstein, R.Diler, N.D. Ryan, L.Weinstock, M. Keller, D. Axelson. Drafting the manuscript: M. Andreu-Pascual, J. Merranko, T. Goldstein, B. Birmaher

Revising the manuscript critically for important intellectual content: M. Kay Gill, H. Hower, J.Levenson, S. Yen, M. Strober, D. Hafeman, B. Goldstein, R.Diler, N.D. Ryan, L.Weinstock, M. Keller, D. Axelson. Approval of the version of the manuscript to be published: M. Andreu-Pascual, T. Goldstein, J. Merranko, M. Kay Gill, H. Hower, J. Levenson, S. Yen, M. Strober, D. Hafeman, B. Goldstein, R.Diler, N.D.Ryan, L.Weinstock, M. Keller, D. Axelson, B. Birmaher. Agreement to be accountable of all aspects of the work in ensuring that questions related to the accuracy of the paper are appropiately investigated and resolved: M. Andreu-Pascual, J. Merranko, M. Kay Gill, H. Hower, J. Levenson, S. Yen, M. Strober, D. Hafeman, B. Goldstein, R. Diler, N.D. Ryan, L. Weinstock, M. Keller, D. Axelson, B. Birmaher, T. Goldstein

Role of the Funding Source

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CRediT authorship contribution statement

Maria Andreu-Pascual: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **John Merranko:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **Mary Kay Gill:** Data curation, Supervision, Validation, Visualization, Writing – review & editing. **Jessica C. Levenson:** Data curation, Supervision, Validation, Visualization, Writing – review & editing. **Danella Hafeman:** Data curation, Supervision, Validation, Visualization, Writing – review & editing. **Heather Hower:** Data curation, Supervision, Validation, Visualization, Writing – review & editing. **Shirley Yen:** Data curation, Funding acquisition, Supervision, Validation, Visualization, Writing – review & editing. **Michael Strober:** Data curation, Funding acquisition, Supervision, Validation, Visualization, Writing – review & editing. **Benjamin I. Goldstein:** Data curation, Data curation, Supervision, Validation, Visualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Writing – review & editing. **Rasim Diler:** Data curation, Supervision, Validation, Visualization, Writing – review & editing. **Neal D. Ryan:** Data curation, Supervision, Validation, Visualization, Writing – review & editing. **Lauren M. Weinstock:** Data curation, Supervision, Validation, Visualization, Writing – review & editing. **Martin B. Keller:** Data curation, Funding acquisition, Supervision, Validation, Visualization, Writing – review & editing. **David Axelson:** Data curation, Supervision, Validation, Visualization, Writing – review & editing. **Boris Birmaher:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Tina R. Goldstein:** Conceptualization, Investigation, Methodology, Project administration, Resources, Software.

Declaration of Competing Interest

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5.3 ETHICAL CONSIDERATIONS

Each university's Institutional Review Board approved the study before enrollment, and informed consent and assent were obtained from the participants and participant´s caregivers at intake (See below). COBY research staff administered semi-structured interview assessments to participants and parents.

Inform consent was obtained before initiation of the assessment from participant caregiver or directly from the participant if 14 years or older. The study procedures were explained in age-appropriate language to younger participants and verbal assent was obtained before the assessment. At age 18, if participant no longer lived with parents or parents were unwilling to participate, participants chose whether to include parents or secondary informants' reports. 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.

Institutional Review Board (IRB) approval and ethics

University of Pittsburgh | Institutional Review Board Office of Research Protections

APPROVAL OF SUBMISSION (Expedited)

Date:	August 11, 2021
IRB:	MODCR19080331-003
PI:	Boris Birmaher
Title:	Course and Outcome for Bipolar Disorders in Youth and Predicting Adult Outcomes
Funding:	Name: National Institute of Mental Health , Funding Source ID: RO1 MH059929; RO1 MH112544

The Institutional Review Board reviewed and approved the above referenced study. The study may continue as outlined in the University of Pittsburgh approved application and documents.

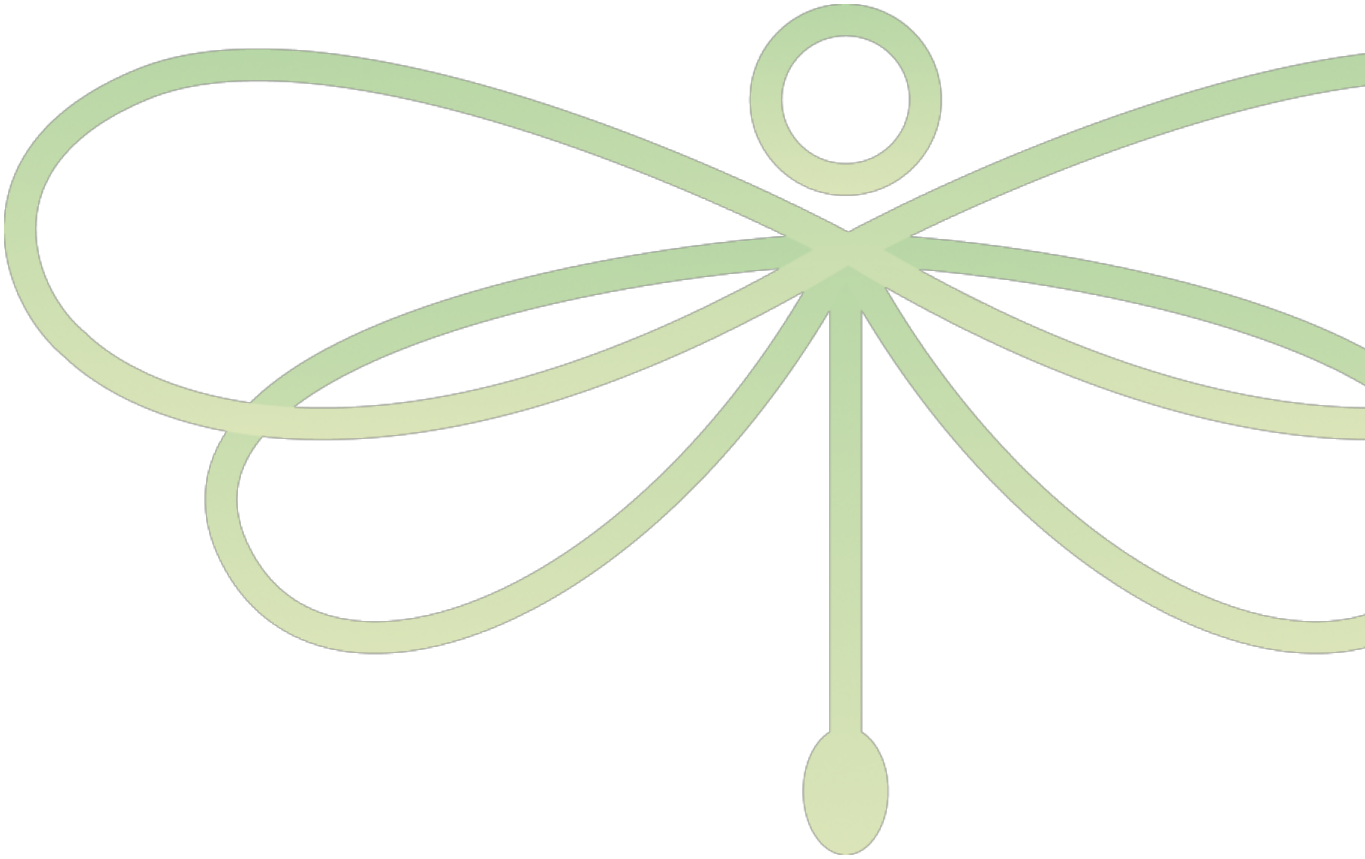
Approval Documentation

Review type:	Modification and Continuing Review
Approval Date:	8/11/2021
Expiration Date:	8/10/2022
Expedited Category	(9) Convened IRB determined minimal risk
Finalized Documents:	• 18 Year Old Addendum Consent for Ongoing Follow-up, Category: Consent Form; • 18 Year Old Full Consent for Continued Participation, Category: Consent Form; • Addendum Consent for X-Ray , Category: Consent Form; • Neuroimaging Consent, Category: Consent Form; • Parent Consent for Ongoing Follow-up, Category: Consent Form;

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Continuing review (CR) can be submitted by clicking “Create Modification/CR” from the active study at least 5 weeks prior to the expiration date. Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

6. DISCUSSION



DISCUSSION

The present work represents 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 physical and/or sexual abuse); and allowing for the first time in the pediatric BD literature to analyze time-varying risk factors for prospectively examined physical and/or sexual abuse among this youth, specifically new onset, including past, intake and follow-up predictors that precede close in time first instance of abuse.

6.1. Main Findings regarding the effects of trauma on the longitudinal course and outcomes of youth with BD.

There were two important findings for the first study. 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.

6.2 Prevalence of TE among youth with BD

In a recent meta-analysis, the lifetime prevalence of TEs among adults with BD ranged from 8-77% (29), while the prevalence of TEs among BD youth in some longitudinal studies has been reported around 40% (48, 49). 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 (80), while concurrent/retrospective studies have reported the prevalence of abuse among BD youth around 11-24% (46, 51). The higher 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 8.7 years, 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.

6.3 TEs presence and clinical outcomes

Similar to prior literature, TEs presence among BD youth in our study was associated with poorer clinical and psychosocial outcomes (47, 48, 107), and TEs increased as youth aged (50). Consistent with BD youth studies, we replicated the finding that participants with TEs have significantly greater psychiatric comorbidities, such as SUD and PTSD (46). 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 (108, 109), 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 (32, 35), with very few studies including BD youth (49, 52). 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 (52). 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 (110, 111). 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.

6.4 Clinical BD course after abuse occurrence

Consistent with the adult BD literature (112), 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 (46), others have reported that abuse exposure among BD youth was not associated with poorer symptomatic and functional outcomes (51). 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 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 (58, 113, 114). 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 (46, 115), 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 and abuse 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 (54). Moreover, the early adversity sensitization (EAS) hypothesis suggests that early-TEs could have enduring effects on the catecholamine-stress-response (55), hyper-reactivity of corticoid systems (56), and functioning of prefrontal cortex and hippocampus (57). This could potentially lower the threshold for future mood episodes, leading to worsened BD course (58). 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 (59). 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, that could therefore precipitate BD symptoms (60).

6.5 New onset comorbid disorders among BD youth exposed to abuse

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 (46, 80, 116). 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 (117, 118). 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 (119). Specific mechanisms that mediate SUD onset among abuse-exposed BD youth should be further studied.

6.6 Main findings regarding the risk factors preceding new onset abuse among BD youth

Our findings provide further evidence of the substantial risks of abuse among youth with BD; when excluding participants who already reported abuse, fifteen per cent (42/279) of this youth with BD reported new onset childhood abuse within the 12 years of the study follow-up (62% physical, 26% sexual; 12% both).

The most potent past and intake risk factors for new onset physical abuse were more severe depressive symptoms at intake and an interactive effect such that the families with low SES and with history of SUD were at greater risk. About 79% of the participants who experienced new onset physical abuse had family history of SUD, and in 65% of those cases, at least one of the family members with SUD was a parent. Being female was the most potent past risk factor for sexual abuse among this youth. For physical abuse in particular: older age, more disruptive behavior symptoms, and the interactive effect of low SES in families with SUD, were predictors for physical abuse in the upcoming follow-up period. For sexual abuse, being female and not living with both biological parents (specifically living status changes) in the preceding follow-up period to the abuse were found to be the strongest near-term risk factors for first sexual abuse. Living with the biological mother and the presence of a non-biologically related father increased risk for sexual abuse three-fold. However, good interpersonal relationships with friends prospectively evaluated during follow-up, were associated with decreased risk for both

physical and/or sexual abuse. When including participants who experienced past abuse, all the above remained significant, plus past history of physical/sexual abuse respectively increased abuse in the next follow-up period.

6.7 New onset abuse prevalence in COBY

Prevalence of lifetime abuse has been reported ranging from 21-30% in other samples of youth with BD, as well as previously documented in COBY when using retrospective measures (with 3-30% for physical abuse, 10-29% for sexual abuse, and 6-11% for both) (31, 45, 46, 48, 49, 51, 80, 81).

Nonetheless, our study further evaluated the prevalence of new onset abuse prospectively. To our knowledge, COBY is the only study to also evaluate the abuse prevalence among youth with BD prospectively, reporting that 15% (62% physical, 26% sexual; 12% both) of participants with no prior abuse history experienced first abuse instance in their lives during the follow-up. Two epidemiological studies among children of general population that used prospective measures to evaluate abuse, reported prevalence of abuse among children of 7% and 20% respectively (99, 120). Unlike most of the studies on child abuse that use Child Protective services reports, our study used both youth reports and caregiver's reports. Other studies have reported that the prevalence of physical and sexual abuse is 4 to 6 times higher if they use self-reports than if they used social services records (70, 121). Importantly, our study adds to the literature by identifying abuse risk factors ascertained prospectively and temporally preceding new onset abuse. As such, our study may provide new perspectives on risk assessment and prevention that might enable identification of vulnerable youth with BD to potentially mitigate risk and decrease vulnerability to ongoing victimization.

6.8 Past, intake and follow-up risk factors for physical abuse

While low SES and family history of SUD at intake and during follow-up were independent risk factors for new physical abuse onset, their interaction most potently predicted physical abuse. Other adult/youth BD studies also report that low SES and separately, family psychopathology, are associated with both types of abuse (32, 82). Community studies also find low SES and family instability (common among families with psychopathology), is associated with physical abuse risk (93). Further, in a recent study among students, results indicate that parents have a significant influence in their offspring mental health, having the strongest associations with depression and aggression parents with SUD and parents who regularly argued (122). These findings emphasize the need for identification and referral of parents of youth with BD for SUD treatment, as well as connection with case management and social services for low resourced families.

We found older age during follow-up increased risk for first physical abuse, although other studies among youth with BD have not reported such association (47). In community studies, younger age has been associated with maltreatment and may be partially explained by the increased vulnerability at younger ages (72, 189). Other community studies indicate older age might be a risk factor for certain types of abuse (i.e., sexual) (190), starting to rise at age 9 and peaking in adolescence, when peer interactions start to increase, decreasing family interactions, that might place them at higher risk for abuse. However, information about the perpetrator was not available in COBY, so we are not able to conclude that this is what explains these findings. Further, BD age of onset could contribute, since mean age at COBY sample is 12 years old, it is possible that some of the youngest population has not been included yet in the study.

We found that severe depression at intake was associated with increased risk for first physical abuse. Of note, childhood trauma has been associated with depression later

in life, partly explained by the cognitive dimension of depression and resulting difficulties in emotion regulation (123, 124), explaining that depressed subjects with childhood abuse experiences, have changes in their hippocampus related to stress. Given that hippocampus plays a role in the acquisition and consolidation of episodic-declarative memory, this can partially explain cognitive symptoms of depression that could be putatively attributed to hippocampal and prefrontal cortex disfunctions, pointing that cognitive distortions have a role in the upcoming depressive symptoms. Traumatic events have played a role in the etiology of depression, a considerable body of the literature suggests that childhood abuse is associated with severity and course of depression and anxiety (125). Retrospective studies have also reported an association between severe depression and physical abuse (28, 48, 107), but others have found that only manic symptom severity was associated with abuse (46). In line with this, a study among general population parents and risk for new onset abuse in their children, reported that parents with comorbid SUD and depression were found to be risk factors for new onset abuse among their children (191). Our findings suggesting that BD youth with more severe depressive symptoms at intake are at higher risk for first physical abuse, were further explored; showing that such risk of depression was potentially related with some of the core symptoms of depression (e.g., isolation, low self-esteem, inability to defend themselves…) that impact interpersonal relationships, and might place this youth in a vulnerable position to experience abuse, related with lack of protective factors (i.e., interpersonal relationships). In a longitudinal study among adults with BD, social support appeared to be associated with less depression at follow-up; findings were consistent with a mediational model suggesting that self-esteem may be one of the mechanisms whereby social support influences depression over time (192). Retrospective studies have also reported an association between severe depression and risk for abuse (28, 48, 107, 164, 167). Of note, depression

not only increases the risk for abuse, but abuse during childhood also increases the risk to develop depression later in life (123, 124), which may be also partly explained by the cognitive dimension of depression and the resulting difficulties in emotion regulation resulting from trauma. Moreover, in a metanalytic review of the literature for child abuse, child's social competence was moderately related to child's physical abuse (87). Several studies have found a positive correlation between social isolation and abuse (193), which can be embedded by specific aspects related with social support such as higher levels of belonging, availability of individuals who will engage in joint activities and provide physical and emotional support. Further, self-esteem might buffer an individual against downturns in self-evaluation. To our knowledge, this is the first study that uses a temporal sequence among youth with BD to analyze risk factors for abuse, so we are not able to compare this finding.

BD youth with comorbid DBD also predicted physical abuse during follow-up. Other studies show comorbidity in youth with BD is associated with physical abuse (45-47). Youth with other disorders manifested by behavior problems (e.g., Attention Deficit Hyperactivity Disorder) are also at elevated risk for physical abuse (90, 126), chronically abused children are found to be more aggressive in community studies (194) which might pose a particular additional challenge for parenting. Some studies have studied the interplay between youth with BD and parenting challenges that coexists with DBD symptoms (127). The course of the BD among youth is variable, and both depression and mania tend to highly coexist with irritability, emotion dysregulation and maladaptive coping strategies, which adds on to the complex nature of adolescence among these youth, placing them as particularly vulnerable to experience abuse.

6.9 Past, intake and follow-up risk factors for sexual abuse

Moreover, for sexual abuse, we found females had more than four times the risk for sexual abuse than males both at intake and follow-up. Other studies in BD youth/adults (47, 51, 128), as well as community studies, have similarly reported higher rates of sexual abuse among females than males (129, 130, 170), gender issues and cultural biases might be related with the higher vulnerability of girls compared to boys. Risk factor studies among normative youth have reported that female gender was the strongest risk factor for sexual abuse, together with not living with both biological parents (195). Profiles of abuse depend on a wide variety of characteristics and are imbedded culturally, and the attitudes that society plays towards the victims (i.e.: sexual education, moral values like virginity or obedience) (196, 197) and the attitudes towards abuse reporters and social expectations that could strongly influence the disclosure.

Not living with both biological parents over follow-up was also associated with subsequent risk of first sexual abuse. In fact, prospectively evaluated *changes* in living status, specifically, living with a biological mother and a stepfather/mother's boyfriend moving into the house, nearly tripled the risk of subsequent new onset sexual abuse among females. In the BD literature, having single or divorced parent(s) has been associated with abuse, but has not previously been demonstrated as a temporally precedent risk factor (43, 47, 51). Prospective studies including community samples also found that living in single-parent families and having a biologically unrelated father posed increased risk for any type of abuse (88, 93). Similar to our findings, community studies have reported that female sex and not living with both biological parents, parents with low educational level and unemployment, or single parent households were associated with lifetime abuse (195).

6.2 Sensitivity analysis when including participants who already experienced abuse before intake

When we run a sensitivity analyses including participants with past abuse history, both physical/sexual abuse history predicted recurrent abuse in the next follow-up period. Literature among BD youth and adults have also reported that SUD has been associated with abuse (46, 80, 116). The significance of such association has a complex nature and the effects of early-abuse in the brain could partially explain this relationship; abuse survivors may tend to use substances as a coping strategy in order to alleviate painful internal states (119). Further, SUD has been associated with increased risk for maltreatment in adolescent community samples (94), perpetuating this daunting cycle and placing these youth at increased risk for revictimization. Past history of abuse has been reported as a significant risk factor for abuse among children investigated by social services among non-clinical populations (93), with some studies reporting increase risk after the index episode and declining overtime; suggesting that both biological factors and sustained sociodemographic factors may interplay. Finkelhor and colleagues, studied the risk of persistence of abuse from one year to the next, relating the persistence of abuse with violent families, alcohol use, unemployment and family disruption (198). Past abuse might point these families are vulnerable; the association between child victimization and family instability (Family history of SUD, unemployment…), has already been described, emphasizing the need of professionals to check on the wellbeing of the family when dealing with a child with abuse problems and try to best coordinate services to ameliorate this situation (191, 199).

6.11 Protective factors for physical and sexual abuse

Good relationships with friends during follow-up was associated with lower risk for physical/sexual abuse. This holds special importance since sequelae of abuse include psychosocial impairment, suicidality, and comorbid psychopathology (200). Poor social

support and social isolation have been largely related with increased risk of abuse in community studies (93, 201), as well as desistence of victimization has been associated with having good friends (198). To the best of our knowledge, there are no other BD studies reporting protective factors for abuse, although in community studies, social support and having good friends is associated with decreased risk for abuse (93). In a longitudinal study among adults with BD, positive relationships with friends was inversely associated with severity of depression over time, and predicted a better illness course (192). Future research should aim to expand how good quality of relationships protect against abuse in this youth (i.e., by providing specific help and protection, indirect role of friendship that enhances self-esteem and coping strategies, or simply because it implies lack of harmful relationships). Independently of the nature of this prediction, the above findings highlight the importance of fostering supportive relationships among youth with BD in order to not only mitigate risk of first onset physical and/or sexual abuse, but also potentially contribute to improvement in their mood episodes and, thus, decrease their ongoing risk for victimization.

6.12 STRENGHTS AND LIMITATIONS

The main strengths of this thesis are reported as follows: First, COBY sample represents one of the largest and longest samples of youth with childhood onset BD followed into adulthood. Second, both studies I and II did control for confounders such as sex, age, SES…Third, both studies evaluate not just the presence of past abuse or TEs, but we also evaluate presence during follow-up, allowing for the first time in the literature to prospectively evaluate TEs, abuse and clinical and sociodemographic changes. Forth, COBY had frequent assessments during follow-up (self-reports and collateral information) which means a great value for trauma and abuse literature, by minimizing

recall biases (97, 98, 131). Fifth, specifically, for study I, clinical severity and TEs rate were not studied before. Further, we considered temporal associations representing a novel contribution to the literature in terms of establishing mood changes before and after the abuse experience, and the new onset of psychopathologies related with abuse. Sixth, specifically, for study II, it represents the first study to prospectively evaluate risk factors for new onset abuse, allowing for the first time to establish stable predictors for abuse that precede first time abuse. Risk factor studies should use prospective studies since by definition the risk factor must be present prior to the outcome.

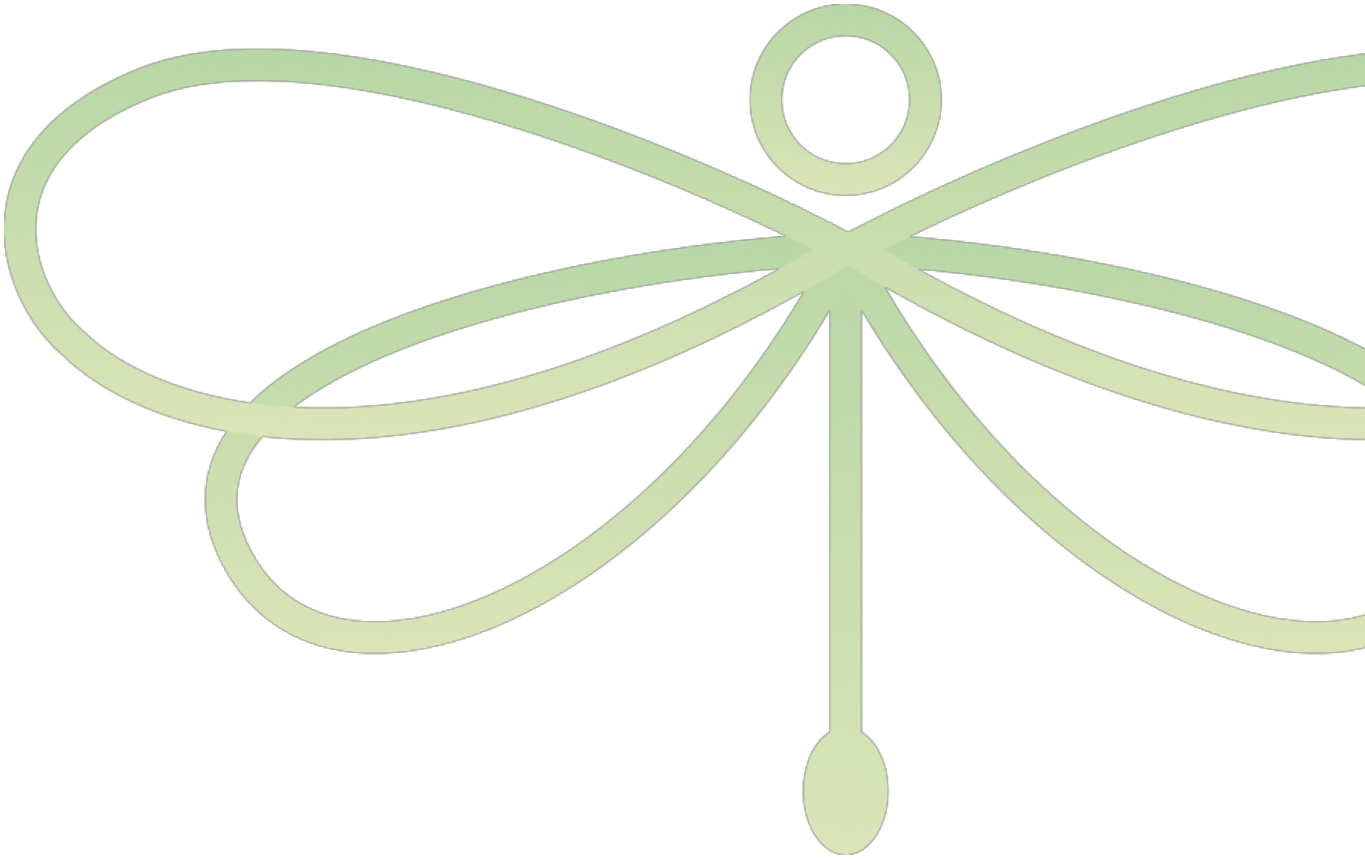
Nonetheless this thesis has a number of limitations that must be accounted. First, prospective data was gathered longitudinally in COBY and assessed retrospectively at every follow-up period encompassing an average of 7-months. While all reports of TEs and abuse are retrospective by nature, our design limited the interval between assessments to minimize retrospective recall. It is possible that conducting more frequent assessments would have increased the reliability of the study. Furthermore, could be that the 7-months window period that we used for prospective risk factor analyses would have been too broad to capture adequately any follow-up predicting changes in the next follow-up period. Second, as a longitudinal phenomenology study, COBY did not recruit a control group. Third, COBY participants were recruited from different clinical settings and thus might not be representative of general population who have not sought for treatment. Nonetheless, similar clinical course and morbidity of youth with BD has been observed in non-clinical populations (202). Fourth, participants were predominantly White; thus, findings might not be representative of a more culturally diverse sample. Fifth, all participants had a BD diagnosis at the time of study entry. Thus, it was not possible to

reliably ascertain whether some of the variables (i.e., abuse, TEs…) occurred before/after the BD diagnosis.

Specifically, for study I, some limitations must be accounted. First, 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. Second, emotional abuse and neglect were not ascertained with the TES. Third, 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.

Particularly for study II, some of the limitations include: severity and/or frequency of abuse, perpetrator information, parents' abuse history, parenting strategies that might involve abuse, other forms of abuse, or interventions/services for abuse were not systematically assessed. Abuse was not further corroborated with other sources of information (e.g., CPS) due to confidentiality.

7.CONCLUSIONS



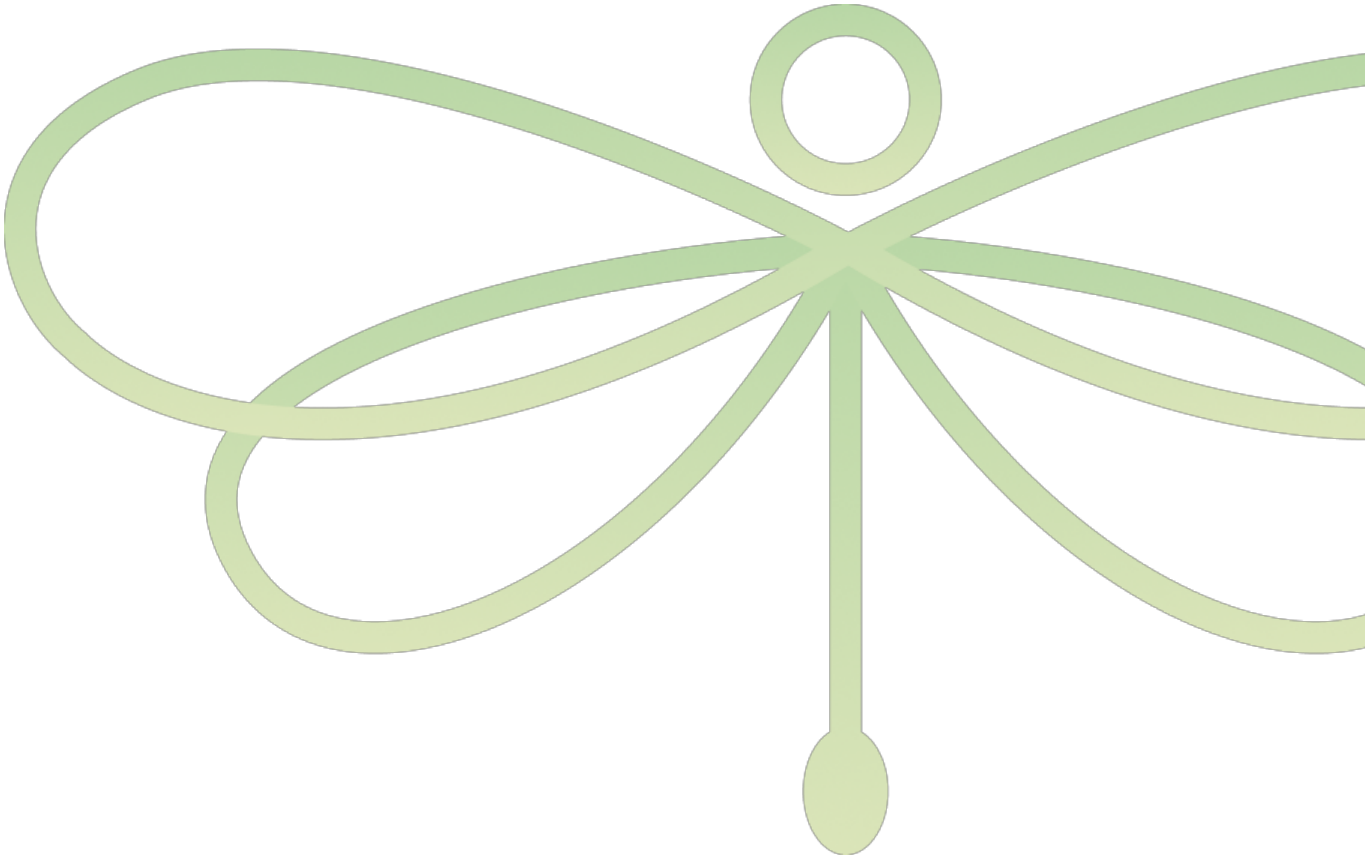
7.1 GENERAL CONCLUSIONS: CLINICAL, SOCIAL AND RESEARCH IMPLICATIONS

1. 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.
2. 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.
3. 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.
4. 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.
5. 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 (132). Read and colleagues based on a review of the literature in childhood abuse, recommend asking all patients if possible, during the initial assessment (not during crisis). Ask in the psychosocial context and provide clear examples of what is been asked. Provide validation once disclosed and check current safety, and provide further support, and check emotional state at the end of the session are some of the recommendations provided. Consideration of reporting to the authorities should be something important to bear in mind when abuse is disclosed.

6. Moreover, the second study represents the first study to prospectively evaluate risk factors both at intake and over follow-up temporally preceding new onset physical and/or sexual abuse among youth with BD. Our study broadens prior research scope among this population by establishing temporal precedence of risk factors for new onset abuse through longitudinal analyses, instead of using cross-sectional associations. These findings will serve for risk assessment and prevention, including frequent and thorough assessments of abuse, and involving other services such as CPS when appropriate.
7. Clinicians treating youth with BD should pay cautious attention not only to "static" variables, that are difficult to change but serve as high risk indicators, such as: female sex, single parent households, or age. But also, pay attention to certain variables that might be addressable wherein appropriate, such as: severity of depression, family substance use or DBD symptoms.
8. Depression at intake, and lack of protective factors were associated with increased risk for abuse. This brings the scope of the attention to efforts to treat and improve depression among BD children.
9. Identifying high risk individuals and circumstances such as low SES in families with SUD history and further changes in living status situations when a non-biologically related father moving into the household, should serve clinicians to inform strategies to diminish abuse risk.
10. Participants with past abuse history and SUD diagnosis were at greater risk for recurrent physical abuse. This association should serve clinicians to bring awareness and carefully evaluate those variables among BD youth.
11. Furthermore, good quality of relationships with friends has been shown to be a protective factor. Specific therapies enhancing quality of interpersonal skills and

focus part of the treatment in good quality of relationships may protect BD youth from experiencing abuse.

8.FUTURE DIRECTIONS



1. Although not specific for BD youth, more specific treatments for TEs such as Trauma-Focused-Cognitive-Behavioral Therapy, which is designed to improve family functioning and decrease interpersonal stress associated with TEs, should be considered (133). Trauma-Focus-Cognitive-Behavioral Therapy is designed to treat children ages 3-18 years old, based on three therapy components. First component involves emotional stabilization of the children, which includes providing a range of resources such as psychoeducation, parenting, relaxation skills, affective and cognitive regulation skills. Second component involves trauma narration and processing, in which children develop a narrative of the traumatic experience that allows them to process. Final component, includes integration phase, in which children are exposed to the reminders, using in vivo mastery, conjoint child-parent sessions, and finally enhancing safety moving forward. 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.
2. Other therapies such as Cognitive Behavioral Analysis System of Psychotherapy, integrative trauma focused and mentalization based therapy appears to have beneficial effects on subjects who had experienced traumatic experiences, and future clinical efforts should investigate their potential benefits over this youth.
3. Efforts to identify more vulnerable patients, mitigate their condition and interrupt their high vulnerability to ongoing victimization should be an important priority of intervention.
4. The brain continues to develop until mid-20's and trauma can have an impact in synaptic development. Anticipatory guidance on a safe and nurturing environment about the stresses of single parenting and safety of the parents themselves should

be further studied. Kairys reported some guidelines for primary care pediatricians to provide early detection and reporting which can be lifesaving (134).

5. Future research should aim to identify specific and more reliable dates for TEs and abuse. Moreover, a more comprehensive analyses would include severity of trauma and abuse, emotional abuse and neglect. Literature in the future should aim to include control groups.
6. Future studies should focus further in the proximal risk factors associated with abuse closer in time and should account for characteristics such as perpetrators, frequency of the abuse, and other relevant cultural and family information, which might reveal a more comprehensive approach to risk factors.

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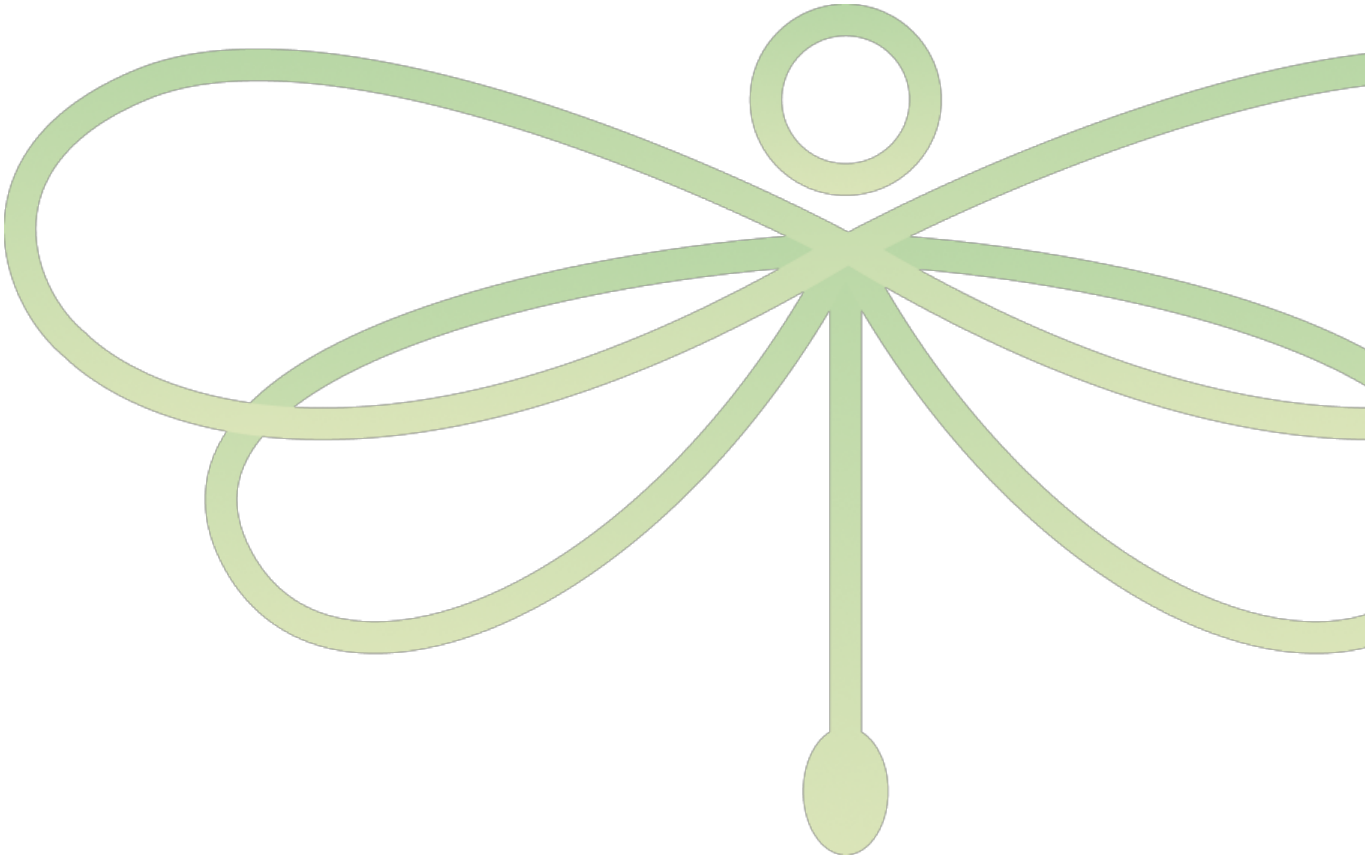

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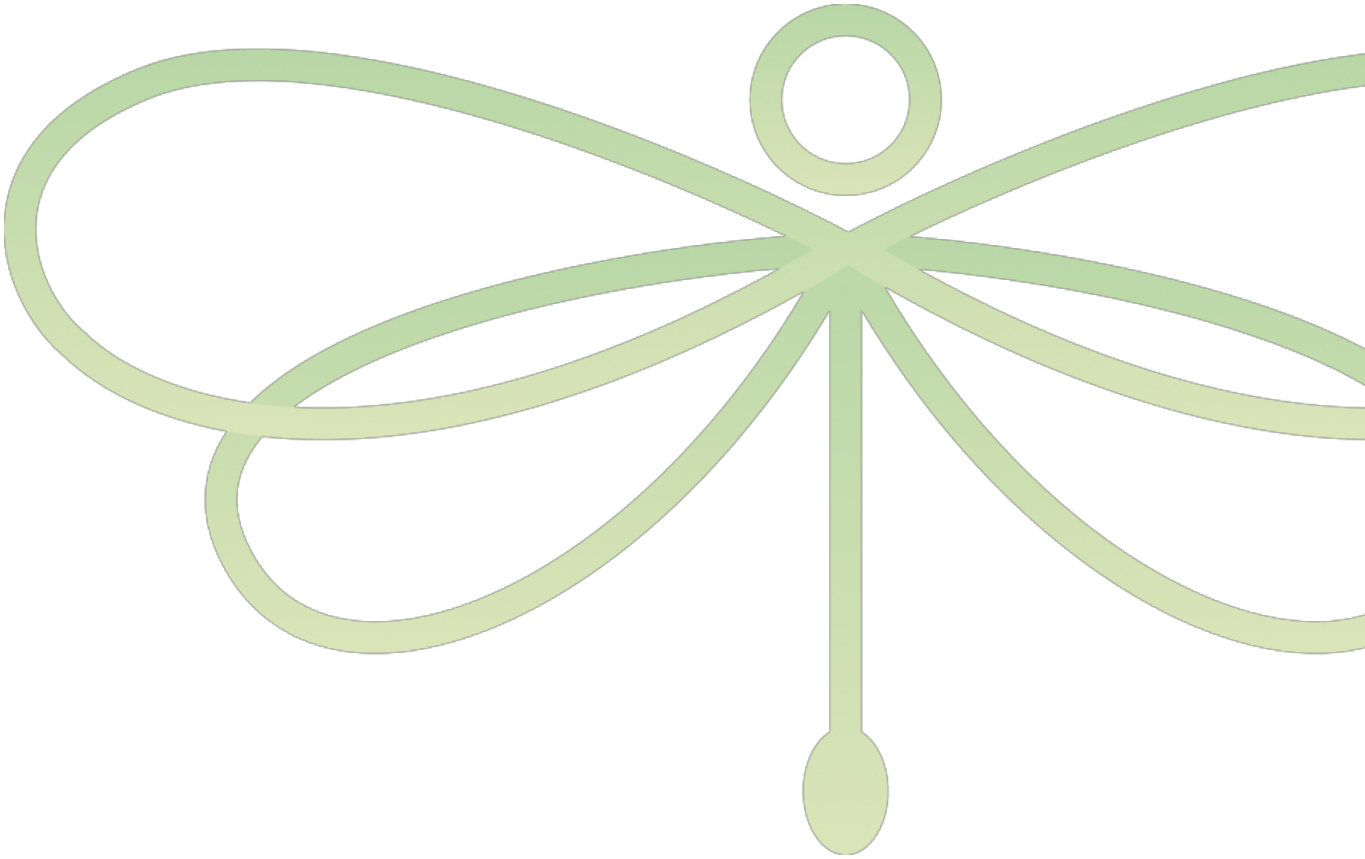
10. SUPPLEMENTARY MATERIAL



Supplement 1. Traumatic Events Scale

Information captured on this form represents events: since intake/ since last follow up

Probe: I am going to ask you about a number of bad things that often happen to people your age, and I want you to tell me if any of these things have ever happened to you. Be sure to tell me if any of these things have ever happened, even if they only happened one time.

0 = No Information, 1 = No, 2 = Yes. Record approximate dates in month/year format (e.g., 07/1999).

1. Car Accident

Have you ever been in a bad car accident? What happened? Were you hurt? Was anyone else in the car hurt?

Significant car accident in which child or other individual in car was injured and required medical intervention.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

2. Other Accident

Have you ever been in any other type of bad accidents? What about a biking accident? Other accidents? What happened? Were you hurt?

Significant accident in which child was injured and required medical intervention.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

3. Fire

Were you ever in a serious fire? Did your house or school ever catch on fire? Did you ever start a fire that got out of control? What happened? Did anyone get hurt? Was there a lot of damage?

Child close witness to fire that caused significant property damage or moderate to severe physical injuries.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

4. Witness of a Disaster

Have you ever been in a really bad storm, like a tornado or a hurricane? Have you ever been caught in floods with waters that were deep enough to swim in?

Child witness to natural disaster that caused significant devastation.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

5. Witness of a Violent Crime

Did you ever see someone rob someone or shoot them? Steal from a store or jump someone? Take someone hostage? What happened? Where were you when this happened? Was anyone hurt?

Child close witness to threatening or violent crime.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

6. Victim of Violent Crime

Did anyone ever mug you or attack you in some other way? What happened? Were you hurt?

Physical assault* Sexual assault*

Child victim of seriously threatening or violent crime.

*If perpetrated by a caretaker, code under Physical Abuse or Sexual Abuse. If perpetrated by significant other/spouse, code under Intimate Partner Violence.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

7. Confronted with Traumatic News

Have you ever gotten some really bad news unexpectedly? Like found out someone you loved just died or was sick and would never get better?

Learned about sudden, unexpected death of a loved one, or that loved one has life-threatening disease.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

Please use numbered coding below to indicate deceased relative's relationship to subject:

01: Biological Mother, 02: Biological Father, 03: Biological Sibling, 04: Maternal Grandmother , 05: Maternal Grandfather, 06: Maternal Aunt, 07: Maternal Uncle, 08: Paternal Grandmother
09: Paternal Grandfather, 10: Paternal Aunt, 11: Paternal Uncle, 12. Adoptive mother, 13: Adoptive Father 14: Adoptive Grandmother, 15: Adoptive Grandfather, 16:

Adoptive Aunt, 17: Adoptive Uncle, 18: Step Mother, 19: Step Father, 20: Foster Mother, 21: Foster Father, 88: Other

8. Witness to Domestic Violence

Some kids' parents have a lot of nasty fights. They call each other bad names, throw things, threaten to do bad things to each other, or sometimes really hurt each other. Did your parents (or does your mother and her boyfriend) ever get in really bad fights? Tell me about the worst fight you remember your parents having. What happened?

Child witness to explosive arguments involving threatened or actual harm to parent.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

9. Victim of Intimate Partner Violence

Some couples have a lot of nasty
fights. They call each other bad names, throw things, threaten to do bad things to each other, or sometimes really hurt each other. Do you ever get in really bad fights? Tell me about the worst fight you remember you have had. What happened?

Physical abuse*/Psychological, verbal aggression*

Intimate partner/significant other slapped, punched, shoved or threw potentially dangerous object at subject. Severe and/or persistant insulting, swearing, shouting or yelling, threatening to hit or throw something,

Include verbal/psychological aggression, dating violence and domestic violence in this category.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

10. Physical Abuse*

When your parents got mad at you, did they hit you? Have you ever been hit so that you had bruises or marks on your body, or were hurt in some way? What happened?

Bruises sustained on more than one occasion, or more serious injury sustained.

*If perpetrator is a significant other/spouse, code under Intimate Partner Violence.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

11. Sexual Abuse*

Did anyone ever touch you in your private parts when they shouldn't have? What happened? Has someone ever touched you in a way that made you feel bad? Has anyone who shouldn't have ever made you undress, touch you between the legs, make you get in bed with him/her, or make you play with his/her privates?

Isolated or repeated incidents of genital fondling, oral sex, or vaginal or anal intercourse.

*If perpetrator is a significant other/spouse, code under Intimate Partner Violence.

Parent/Child/Summary

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

12. Other

Is there anything else that happened to you that was really bad, or something else you saw that was really scary, that you want to tell me about?

Parent/Child/Summary

Please specify:

Date of First occurrence:

Date of second occurrence:

Date of most recent occurrence:

Total number of occurrences: Unknown/ Too many to count

Supplementary Table 1: Logistic Regressions of PTSD Risk as a Function of Traumatic Events Rate

Traumatic Event Cluster	Standardized Hazard Ratio	Wald χ^2	p-value
Any	2.19 (1.68, 2.85)	33.60	**<0.0001**
Witness Traumatic Event	1.10 (0.87, 1.38)	0.62	0.42
Accidents	1.45 (1.13, 1.85)	8.63	**0.0033**
Violence and Abuse	1.60 (1.25, 2.06)	13.37	**0.0003**
Confronted with Traumatic News	1.40 (1.09, 1.80)	6.94	**0.0084**
Other (divorce, separation, bankruptcy…)	1.57 (1.24, 1.99)	13.82	**0.0002**

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

Supplementary Table 2: Risk of new onset non-affective disorders in participants with vs. without history of abuse

Predicting New Onset Disorder Risk as a Function of Abuse History								
Disorder	**Eligible Sample Size**	**New Onset Rates**		**Kaplan-Meier Estimation**		**Cox Regression***		
		No Abuse History	**Abuse History**	**Log-Rank $\chi 2$**	**p-value**	**Hazard Ratio**	**$\chi 2$ Stat**	**p-value**
Substance Use Disorder	335	24.0%	49.7%	23.88	<0.0001	2.14 (1.47, 3.13)	15.53	<0.0001
Generalized Anxiety Disorder	312	21.0%	27.0%	1.62	0.2030	1.22 (0.76, 1.94)	0.67	0.4115
Disruptive Behavior Disorder	184	28.8%	27.3%	0.19	0.6636	0.82 (0.46, 1.44)	0.49	0.4823

**Models adjust for demographics and family history retained by LASSO.*