



Published in final edited form as:

*J Psychiatr Res.* 2022 July ; 151: 667–675. doi:10.1016/j.jpsychires.2022.04.008.

## Long Term Outcomes of Pediatric Bipolar-I Disorder: A Prospective Follow-Up Analysis Attending to Full Syndromatic, Subsyndromal and Functional Types of Remission

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### Abstract

**Objective:** To examine patterns of remission of pediatric bipolar I (BP-I) disorder attending to syndromatic, symptomatic, and functional outcomes from childhood to adolescent and young adult years.

**Methods:** We analyzed data from a six-year prospective follow-up study of youths aged 6-17 years with BP-I disorder. Subjects were comprehensively assessed at baseline and subsequently at four, five, and six years thereafter. Assessments included structured diagnostic interviews and measures of psychosocial and educational functioning. Patterns of remission were calculated attending to whether syndromatic, symptomatic, and functional remission were achieved.

**Results:** Kaplan-Meier failure functions revealed that the probability of functional recovery from pediatric BP-I disorder was very low. Of the 88 youths assessed, only 6% (N=5) of the sample were euthymic with normal functioning during the year prior to their last follow-up assessment (average follow-up time =  $5.8 \pm 1.8$  years).

**Conclusions:** These results provide compelling evidence of the high level of persistence of pediatric BP-I disorder. Symptomatic and functional remission were uncommon and most subjects continued to demonstrate high morbidity into late adolescence and early adulthood.

### Keywords

bipolar disorder; persistence; pediatric; adolescent; young adult

## Introduction:

Pediatric bipolar I (BP-I) disorder is recognized as a prevalent and highly morbid disorder. Epidemiological surveys of pediatric bipolar disorder range from 0-5%, with differences attributed to varying definitions of bipolar disorder, whether 'full' or 'subthreshold' cases are included and which geographic regions are studied.<sup>1-7</sup> Pediatric bipolar disorder is associated with high levels of morbidity in clinical and epidemiologic studies.<sup>8-11</sup> Despite some disagreements, research from multiple centers across the world show that data from family studies, longitudinal studies, studies of high-risk offspring of BP parents, treatment studies and biomarker studies all support the validity of pediatric bipolar disorder.<sup>12-32</sup> Moreover, adult bipolar researchers document that most adults with BP disorder have an onset of their disorder in childhood and adolescence.<sup>33</sup> Despite the large body of evidence supporting its validity,<sup>34</sup> ongoing controversy regarding the diagnosis remain<sup>29</sup> and parents of affected children require longitudinal information to help them predict and plan for the future.

Although one of the key features supporting the validity of a psychiatric disorder is course,<sup>35</sup> the literature assessing the longitudinal course of pediatric BP-I disorder is limited. Two other research sites have extensively studied the longitudinal course of pediatric bipolar disorder. The seminal study by Geller and colleagues focused on the persistence and remission of the full disorder.<sup>36</sup> This first significant long-term follow-up report of pediatric BP-I disorder reported that 44% of participants with BP-I disorder in childhood continued to meet full diagnostic criteria for BP-I disorder in adulthood,<sup>36</sup> strongly supporting continuity of pediatric BP-I disorder. In this study, BP-I disorder was defined with modified diagnostic criteria, and the persistence of subsyndromal states was not attended to. While this manuscript was pioneering as the first to focus on course of pediatric BP-I disorder, the focus on full syndromal persistence of manic symptomatology did not address the possibility of continued affective instability in the form of subsyndromal forms of bipolar (BP) disorder or functional impairment. Persistence of subsyndromal forms of BP disorder themselves are associated with significant functional impairment and their presence would not constitute full remission.<sup>37,38</sup> As discussed by Post et al, "the functional impairment, comorbidity, and symptomatic burden of bipolar spectrum disorders in childhood are comparable to those of full-fledged bipolar I and II disorder in adulthood." Even brief periods of manic symptoms are associated with severe impairment.<sup>39-43</sup>

The Course and Outcome of Bipolar Youth (COBY) and the Geller et al<sup>34, 39</sup> studies used different definitions of mania, although they describe a similar group of children with high levels of morbidity. The COBY study, in contrast, included BP spectrum diagnoses, reporting on both subsyndromal states of mania and episodes of depression. This study noted high rates of relapse and recovery (63% and 82%, respectively) and frequent shifts in polarity. Persistence of subsyndromal states and episodes of depression were reported in high rates in youth with BP-I disorder, bipolar II (BP-II) disorder, and bipolar disorder not otherwise specified (BPD-NOS) in a four-year time span.<sup>44</sup> Delbello et al<sup>45</sup> evaluated the course of adolescent onset bipolar disorder (N=71) over 12-months with baseline and 4, 8 and 12 month follow-ups, attending to syndromic, symptomatic and functional outcomes. Over this time period, consistent with the COBY findings,

most of the adolescents experienced syndromic recovery, but rates of symptomatic and functional recovery were much lower. Assessing functional outcome in remitted subjects is also essential in establishing the longitudinal course of pediatric BP-I disorder. BP youth and adults may experience remission in the form of absence of symptoms, but remain functionally impaired. The COBY study is one of few studies reporting on specific psychosocial outcomes in BP in youths. These authors found that even with symptomatic remission, participants still had impairment across domains of interpersonal relationships with family and friends, school/work, recreation and life satisfaction.<sup>46</sup>

As initially described by Keck and colleagues<sup>47</sup> many years ago, a comprehensive view of patterns of remission and persistence of BP disorder should evaluate all manifestations of the disorder. They argued that in addition to the full threshold disorder, subsyndromal and functional residual states should be considered when reporting of the course of BP disorder. Yet this very important perspective has had limited study. In a longitudinal study of adult patients with BP disorder, these authors operationalized outcome by defining three different levels of recovery: syndromic, symptomatic, and functional. *Syndromic remission* occurs when a subject no longer meets full criteria for mania or depression. *Symptomatic remission* refers to having no or minimal symptoms of mania or depression. *Functional remission* refers to the return to premorbid levels of function. This study highlights the importance of assessing functional outcomes in subjects with symptomatic remission as a marker of persistence. A useful method of establishing course over a long period of time of remission is survival analysis. Kaplan-Meier statistics estimate the cumulative percentage of BP disorder cases that would remit over time since onset of the first episode. Using this method and applying the varied definitions of remission, the probability of syndromic remission, symptomatic remission and functional remission can be assessed and compared.

The main aim of this study was to combine data from the four-, five-<sup>32, 58</sup> now six-year follow-up assessments to extend the findings and further examine patterns of persistence and remission of pediatric BP-I disorder attending to syndromic, symptomatic and functional definitions of remission in a longitudinal sample of youth transitioning into late adolescence and early adulthood. We hypothesized that a high level of persistence of pediatric BP-I disorder, as well as its subsyndromal states, would continue into late adolescence and early adulthood and that full functional remission would be rare.

## Methods

### Participants

We recruited 105 youths of both sexes, 6-17 years of age, and their first-degree relatives in a longitudinal follow-up study of BP-I disorder. Detailed study methodology was reported previously.<sup>48,58</sup> Potential probands were ascertained from the Clinical and Research Programs in Pediatric Psychopharmacology at the Massachusetts General Hospital, responses to advertisements in the community, and referrals from local clinicians. All probands met full diagnostic criteria for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) BP-I disorder with active symptoms at the time of ascertainment. This study excluded potential probands with a full-scale intelligence quotient (IQ) <70 or whose BP-I disorder was due solely to a medication reaction. For those younger

than 18 years of age, parents or guardians signed written informed consent forms; children older than 7 years of age signed written assent forms. All subjects 18 years of age and older signed written informed consent. Subjects were followed up after four, five, and six years. All study procedures were reviewed and approved by the subcommittee for human subjects of our institution.

### Diagnostic Procedures

Psychiatric assessments of subjects younger than 18 years of age were made with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (K-SADS-E).<sup>49</sup> Psychiatric assessments of subjects 18 years of age or older were made with the Structured Clinical Interview for DSM-IV (SCID)<sup>50</sup> supplemented with modules from the K-SADS-E to cover childhood disorders.

Diagnoses for subjects younger than 12 years of age were determined by a structured diagnostic interview with the parent about the subject. Diagnoses for subjects 12 years of age or older were determined by a structured diagnostic interview with the parent about the subject and by a structured diagnostic interview with the subject about him/herself. Endorsement of a diagnosis by either the parent or the subject resulted in a positive diagnosis.

Extensively trained and supervised psychometricians with undergraduate degrees in psychology conducted all structured interviews. At the baseline clinical assessment, raters were blind to the study assignment and whether the subject was a proband or a sibling. Different raters conducted the assessments at baseline and the four-, five-, and six-year follow-ups. All diagnoses were reviewed by a sign-off committee of experienced board-certified child and adolescent psychiatrists or clinical psychologists. The committee members were blind to the subjects' ascertainment group, ascertainment site, and data collected from other family members. Based on 500 interviews, the median kappa coefficient between raters and clinicians was 0.99. Median kappa coefficients for individual diagnoses have been previously reported.<sup>49</sup>

Subjects were diagnosed with BP-I disorder if they met DSM-IV criteria according to assessments completed with the K-SADS-E. The DSM-IV criteria required subjects to meet criterion A for a distinct period of extreme and persistently elevated, expansive, or irritable mood lasting at least one week, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance. To ensure that the criterion B symptoms were concurrent with the criterion A mood disturbance, subjects were directed to focus on the worst or most impairing episode of mood disturbance while being assessed for the presence of the confirmatory criterion B symptoms. In addition, the onset of the first episode, the number of episodes, the offset of the last episode, and the total duration of the illness were recorded. Once the most impairing episode of mood disturbance, lasting at least one week, combined with the confirmatory criterion B symptoms was established, the question was asked, "How many episodes has your child had since the first?" Subjects meeting criteria for BP-II disorder or BPD-NOS were excluded from this study.

Subjects were diagnosed with subthreshold mania if they met criterion A for a period of four days or longer and/or had at least two (three if the mood is irritable only) of the seven criterion B symptoms and associated impairment. Subjects were diagnosed with subthreshold depression if they met criterion A for a period of at least one week and/or had at least three of the seven criterion B symptoms and associated impairment.

Raters also assigned a severity designation (mild, moderate, or severe) for all past and current diagnoses according to assessments with the K-SADS-E. All severity designations were reviewed by the same diagnostic sign-off committee of experienced board-certified child and adolescent psychiatrists or clinical psychologists.

### Other Subject Characteristics

Socioeconomic status (SES) was measured using the five-point Hollingshead scale.<sup>56</sup>

Overall level of current (last month) functioning and lifetime functioning was measured using the DSM-IV Global Assessment of Functioning (GAF).<sup>57</sup>

### Group Assignment

Subjects were categorized as having persistent or remitted BP-I disorder based on diagnoses from their last follow-up assessment. One-year prevalence was defined as positive if the proband met the criteria for a given disorder in the year prior to the date of their follow-up.

**Persistence** of probands at last follow-up was described as syndromatic or symptomatic persistence. Syndromatic persistence is defined as full diagnostic criteria for mania met in the past year. Symptomatic persistence is defined as subthreshold diagnostic criteria for mania or full or subthreshold diagnostic criteria for major depressive disorder (MDD) met in the past year.

**Remission** of probands at last follow-up was described as euthymic with and without impaired functioning. Euthymia with *impaired* functioning is defined as absence of full or subthreshold diagnoses of mania or MDD in the past year and a GAF score <65. Euthymia with *normal* functioning, referred to as “functional remission” is defined as absence of full or subthreshold diagnoses of mania or MDD in the past year and a GAF score ≥ 65.

### Statistical Analysis

Demographics were compared between those lost to follow-up and those who returned for follow-up using Student's t-tests, Pearson's chi-square tests, and Wilcoxon rank-sum tests. Baseline predictors of persistent BP-I disorder and clinical correlates of persistent BP-I disorder at follow-up were individually analyzed using logistic, exact logistic, or multinomial logistic regression models depending on the distribution. The probability of remission of BP-I disorder was analyzed using Kaplan-Meier failure functions. We used the age of offset to compute the time to remission for those who remitted and the age at last assessment as the time of censoring for those who persisted. All analyses were two tailed and performed at the 0.05 alpha level using Stata<sup>®</sup> (Version 16). Descriptive statistics are presented as mean ± standard deviation (SD) or absolute numbers and percentages. Effect sizes are presented

as odds ratios (OR) with 95% confidence intervals (CI). For this study, ORs 1.5 are considered clinically meaningful.

## Results:

Of the 105 probands with BP-I disorder enrolled at baseline, 88 (84%) returned for at least one follow-up assessment. There were no significant differences between those who returned for at least one follow-up (N=88) and those who were lost to follow-up (N=17) in baseline age (Returned:  $9.9 \pm 3.5$  years vs. Lost to follow-up:  $10.7 \pm 3.1$  years,  $p=0.35$ ), sex (Returned: 77% male vs. Lost to follow-up: 94% male,  $p=0.18$ ), age at onset of BP-I disorder (Returned:  $5.2 \pm 3.6$  vs. Lost to follow-up:  $6.3 \pm 3.2$ ,  $p=0.25$ ), or baseline GAF score (Returned:  $40.3 \pm 5.7$  vs. Lost to follow-up:  $37.4 \pm 7.3$ ,  $p=0.06$ ). There was a statistically significant difference in SES (Returned:  $1.7 \pm 0.8$  vs. Lost to follow-up:  $2.7 \pm 1.1$ ;  $p<0.001$ ) between the two groups. Those who returned for follow-up came from a higher SES bracket.

Returning probands had an average follow-up time of  $5.8 \pm 1.8$  years. At follow-up, returning probands had an average age of  $15.7 \pm 4.1$  years and an average age at BP-I disorder onset of  $5.2 \pm 3.6$  years of age. The average duration of BP-I disorder at follow-up was  $8.9 \pm 4.6$  years with an average of  $63.9 \pm 112.2$  episodes of mania (median=20.5, interquartile range [IQR]=67.5). Six probands had outlying numbers of episodes ( $>275$ ). When these probands were excluded, the average number of episodes was  $37.9 \pm 50.4$  (median=16.5, IQR=35).

As shown in Figure 1, 6% (N=5) of returning probands with BP-I disorder at baseline were euthymic with normal functioning (i.e. functional remission) and 18% (N=16) were euthymic with impaired functioning during the year prior to their last assessment. The other 76% (N=67) of probands either continued to meet full diagnostic criteria for BP-I disorder (N=42, 48%) (i.e., syndromatic persistence) or continued to have persistent subthreshold BP-I disorder (N=10, 11%) or full (N=10, 11%) or subthreshold (N=5, 6%) MDD (i.e., symptomatic persistence).

### Psychiatric Comorbidity at Baseline

As shown in Table 1, those with syndromatic and symptomatic persistent mania had a significantly higher rate of ADHD at baseline compared to those with functional remission. The two groups did not differ in rates of any other psychiatric disorder.

### Baseline Predictors of Persistent BP-I Disorder

As shown in Table 2, there were no statistically significant baseline predictors of syndromatic and symptomatic persistent BP-I disorder (all  $p>0.05$ ). However, there were a handful of characteristics with clinically meaningful ORs including SES, prepubertal onset, and family history of BPD, ODD, and cigarette smoking (all ORs  $>1.5$ )

### Clinical Correlates of Persistent BP-I Disorder at Follow-up

At follow-up, those with current GAF scores <65 (OR=5.25, 95% CI=1.26, 21.94), one psychiatric comorbidity versus none (OR=8.40, 95% CI=1.60, 44.10), two or more psychiatric comorbidities versus none (OR=21.43, 95% CI=4.65 98.70), ADHD (OR=4.33, 95% CI=1.54, 12.19), and ODD (OR=7.57, 95% CI=2.52, 22.78) were at statistically significantly increased odds of having persistent BP-I disorder (all  $p < 0.05$ ) (Figure 2). The rates of psychiatric comorbidity at follow-up are presented in Table 1. Further, all correlates examined at follow-up had clinically meaningful ORs.

### Probability of Remission of BP-I Disorder

Figure 3 presents the probability of three levels of remission over time. The first level was functional remission (i.e. euthymia with normal functioning), the second was symptomatic remission (i.e. euthymia with impaired or normal functioning), and the third was syndromatic remission (i.e. symptomatic persistence or euthymia with impaired or normal functioning). As shown, the probability of functional remission over time was the lowest and the probability of syndromatic remission was the highest.

### Discussion:

The objective of this six-year longitudinal follow-study was to extend the findings from previous four- and five- year follow-up studies conducted by our group<sup>48</sup> to investigate the longitudinal course and persistence of pediatric BP-I disorder as well as its subsyndromal states into late adolescence and early adulthood. In addition, in this study, we have combined findings from 3 follow-up periods to analyze probability of remission, attending to functional outcomes as well as symptomatic and syndromatic outcomes. Consistent with our hypothesis that pediatric BP-I disorder and subsyndromal states would persist at a high rate, 48% of the probands returning for the six-year follow-up continued to meet full diagnostic criteria for BP-I disorder (i.e. syndromatic persistence). The majority (28%) of the remaining 52% of cases met for symptomatic persistence. The minority (24%) of youths returning for the six-year follow-up did not meet criteria for full or subthreshold BP-I disorder or MDD and were considered euthymic, but only 6% were euthymic with normal functioning and considered to have functional remission. Although functional recovery is key to full remission, continuity of mania is central to this study, as depicted in our survival analysis curves which depict remission with and without functional recovery. Given the multiple comorbidities, there are multiple potential reasons for low functional recovery in our cohort which merit further study.

These findings are consistent with results from our four- and five-year follow-up studies examining the longitudinal course of pediatric BP-I disorder in youth.<sup>48,58</sup> Our four-year follow-up study revealed that 73.1% of youth diagnosed with BP-I disorder continued to meet full diagnostic criteria for BP-I disorder at follow-up.<sup>48</sup> Among the remaining 26.9% of cases, the majority of youths (20.5%) met diagnostic criteria for subsyndromal BP-I states: subthreshold BP-I disorder (6.4%), full or subthreshold depression without mania (5.1%), or euthymia but with continued treatment for a mood disorder (9.0%).<sup>48</sup> Similar results were found at the time of the five-year follow-up: 50% of youths continued to meet

full diagnostic criteria for BP-I disorder and the majority of the remaining non-persistent cases (31%) met diagnostic criteria for subthreshold BP-I disorder (13%) or full (13%) or subthreshold (5%) depression.<sup>58</sup>

Similar findings have also been reported in a longitudinal study that followed youths with BP disorder at numerous intervals for up to eight years.<sup>36</sup> At the eight-year follow-up point, 44.4% of now adult subjects with pediatric onset BP-I disorder continued to meet full criteria for a manic episode.<sup>36</sup>

Additionally, the findings of the current study are in accord with those of the COBY longitudinal follow-up study of youth with BPD, which demonstrated that 50% of youths experienced at least one syndromal recurrence and that, for 60% of the 2 year follow-up time period, youths experienced syndromal or subsyndromal symptoms.<sup>14,41</sup> Delbello et al<sup>45</sup> similarly reported low rates of symptomatic and functional recovery. Youth with subthreshold BP disorder are reported to experience impairment at the same severity level as youths with full BP disorder.<sup>38,43</sup> Subthreshold pediatric BP disorder has a highly impairing and morbid clinical picture compared with non-BP control youth.<sup>38</sup> Subthreshold BPD was also associated with a high level of morbidity and disability in adults.<sup>59</sup> The documented high level of morbidity associated with both subsyndromal states as well as full BP-I disorder highlights the importance of attending to the persistence of subsyndromal states as well full BP-I disorder in longitudinal follow-up.

Taken together, the consistent findings from these 4 studies from 4 separate sites with differing methodologies demonstrate the validity of a high level of persistence of pediatric BP-I disorder as well as its associated subsyndromal states throughout childhood, adolescent, and into early adulthood years. These findings are further supported by 'top down' studies of adults with bipolar disorder. Perlis et al report that with retrospective questioning 37% of adults with bipolar disorder report an adolescent onset of their disorder and 28% report a pre-adolescent onset.<sup>33</sup> Further support that children and adolescent onset bipolar patients go on to populate adult clinics are the findings that 9.5% of adults with bipolar disorder report comorbid ADHD, and these adults had earlier onset, chronicity, and high rates of comorbidity, a phenotype similar to the children identified with bipolar disorder. Notably, these adults had more impairing illness as indicated by lower GAF, more suicide attempts, more legal problems and more violence.<sup>60</sup> Bipolar disorder is among the most severe psychiatric disorders. These studies support the validity of this severe mood disorder onsetting in childhood but are also a call to action for early identification and aggressive intervention in pediatrics with psychotherapies, natural treatments and pharmacotherapy to mitigate later course and outcome.

Given the morbidity of bipolar disorder at any age, predictors of persistence from childhood onto later years would be a helpful clinical finding. Unfortunately, there were no baseline demographic characteristics that were statistically significant predictors of persistent mania. Among the factors studied, SES did have a clinically meaningful odds ratio, suggesting that youths of lower SES have increased odds of having persistent mania. The role of lower SES in persistence was also reported in the Delbello et al<sup>45</sup> and COBY studies.<sup>62</sup> This is

expected given the large literature which confirms the importance of social determinants of health in all psychiatric and medical illness.<sup>62</sup>

The very young average age onset in our cohort reflects the information provided by the parents of these children when asked about the onset of their child's symptoms when interviewed with the KSADS diagnostic interview. While not statistically significant, the odds ratios for both preschool age of onset and severe impairment were also clinically meaningful, indicating that those with very early onset and those with severe impairment at baseline were at increased odds of having persistence of mania at follow-up. This finding suggests the need to expand the limited literature addressing the diagnosis and treatment of preschool youth with bipolar disorder, as well as a call to action to develop safe and effective treatments for this group.<sup>63</sup> There were no other baseline bipolar characteristics (duration, number of episodes, number of symptoms) that were clinically meaningful or statistically significant predictors of persistence.

Examining family history of psychopathology as predictive, the odds ratios for family history of BP-I disorder, oppositional defiant disorder, and cigarette smoking were clinically meaningful, but not statistically significant, suggesting that youth with a family history of BP-I, ODD, or cigarette smoking are at increased odds for having persistent pediatric BP-I disorder. Family history of all other psychiatric disorders (MDD, ADHD, conduct disorder/antisocial personality disorder, multiple anxiety disorders, or substance use disorders) were not clinically meaningful or statistically significant predictors of persistence.

Youth with a one-year prevalence of at least one comorbid disorder at follow-up were at significantly increased odds of having persistence of mania. Examining individual comorbid psychiatric disorders at follow-up, while one-year prevalence of ADHD and ODD were the only statistically significant psychiatric correlates of persistent BP-I disorder at follow-up, all other disorders examined (conduct disorder/antisocial personality disorder, multiple anxiety disorders, substance use disorders, and cigarette smoking) had clinically meaningful odds ratios. The presence of these comorbidities further compromises the persistent clinical course of youth with BP-I disorder, but their presence may also confound accurate diagnosis of the complex clinical picture. Further, questions abound as to the course of these comorbidities (do they remit when bipolar disorder remits?) and how to safely treat this comorbidities.

As highlighted by Keck and colleagues<sup>47</sup>, assessment of functioning is an important feature of longitudinal outcome studies. At follow-up, those with current GAF scores <65 were at significantly increased odds of having persistence of mania BP-I disorder. In addition, when combining data from three waves of follow-up and attending to the probability of three levels of remission over time, the probability of syndromatic remission was the highest (no longer meeting full criteria for BP-I, but continuing to have depression or subsyndromal mania), but the probability of functional remission (no mania, no depression and normal functioning) over time was very low and unlikely. These findings are consistent with those from the COBY study which parsed functioning into domains including family/ friend relationships, school/work, recreation and life satisfaction. These findings indicate that, even in cases of symptomatic remission, up to 20% remain functionally impaired.<sup>61</sup> High rates of

persistence of any symptoms and persistence of poor functioning when symptoms do abate, indicate the long-term nature of this highly disabling disorder.

The findings of this study should be considered in the context of methodological limitations. This study used an epidemiologic version of the KSADS in a referred clinical sample in an academic medical center. Validated interview schedules vary in their structure, vary in their cross-sectional and retrospective reporting and are limited in the detail they can provide.<sup>65-67</sup> Studies with weekly mood ratings provide more nuance and detail and may be especially useful in capturing the severity and frequency of subsyndromal symptoms that predominate the course of bipolar disorder. Because our diagnostic data relied on the KSADS interview conducted by highly trained and highly supervised psychometricians. We do not know if other types of assessment would have led to similar or different result<sup>51-55</sup> However, all clinical diagnoses of BP-I, regardless of age, were confirmed with a clinical assessment by an expert clinician [JW] prior to inclusion.<sup>67</sup> For subjects 12 years of age or older, diagnoses were determined if either the parent or the subject endorsed a diagnosis, while only endorsement by a parent was considered for subjects under the age of 12. In a previous study examining the correspondence between maternal and child self-reports for pediatric BPD, the majority (N=59) of 98 pairs of parents and children were concordant.<sup>68</sup> In addition, the similarities between discordant and concordant reports in symptomatology of mania and depression, rates of comorbidities, treatment needs, and other clinical correlates suggest that a mother-based diagnosis of mania should not be discounted in discrepant cases in which the youth fails to endorse the diagnosis. Based on these findings, we determined that parental reports are valid.

Due to the lengthy nature of this follow-up study, a portion of the sample ascertained at baseline was not assessed at the six-year follow-up. However, there were few significant differences (SES and baseline GAF score) between those who were lost to follow-up and those who returned for follow-up. Additionally, this sample included clinically referred youths and was primarily Caucasian, meaning the findings of this study may not generalize to a non-referred population or to other ethnic groups. This study did not include diagnosis of Disruptive Mood Dysregulation Disorder (DMDD), which was added to DSM-5 as an alternative option to combat a perceived overdiagnosis of childhood bipolar disorder. Children meeting criteria for mania or hypomania for 1 day, however, are excluded from this diagnosis, and therefore this diagnosis would not apply to this cohort.<sup>69,70</sup> Trauma and bipolar may co-occur with a complicated bidirectional relationship. Childhood trauma increases the risk for earlier onset and a more difficult course, however, trauma may also occur as a result of the disinhibition, poor judgement and vulnerability associated with bipolar disorder.<sup>71-73</sup> Although trauma and adversity play a bidirectional role in bipolar disorder, this longitudinal report is unable to review of the role of trauma. Unfortunately, while medications can have a positive or negative effect on persistence and course, we do not have this clinical detail to report or correlate with clinical outcomes.

Lastly, we defined persistence or remission based on diagnoses occurring in the past year, although previous studies conducted by other investigators defined remission as the loss of the full syndrome for an eight-week period.<sup>14,36,41</sup> Our definitions differ from the DSM, which characterizes a full year of euthymia as recovery, rather than remission,

and considers 8 weeks to be the minimum period for symptomatic recovery. While lower-duration remission is important, as our follow-up periods were approximately year-long, we unfortunately do not have shorter duration remission information, which limits our ability to compare with prior studies. While additional research must be done to establish a standard for the best definition of persistence and remission of pediatric BP-I disorder, we consider the definition that was used in this study to be a strength of our methodology as it considers a clinically significant period of time.

Despite the limitations of this study, these findings provide further support of a high level of persistence of pediatric BP-I disorder as well as its subsyndromal states. These results further contribute to the growing body of literature providing evidence for the high level of persistence and morbidity of pediatric BP-I disorder into late adolescence and early adulthood. The findings from this follow-up study highlight the clinical importance of early identification of and effective interventions for pediatric BP-I disorder and related subsyndromal states and disorders.

### Acknowledgements:

This research was partially supported by NIMH 5R01MH66237-5 [JW], the Prechter Foundation, and the Pediatric Psychopharmacology Council Fund.

### Disclosure of Interest:

Dr. Janet Wozniak receives research support from PCORI and Demarest Lloyd, Jr. Foundation. In the past, Dr. Wozniak has received research support, consultation fees or speaker's fees from Eli Lilly, Janssen, Johnson and Johnson, McNeil, Merck/Schering-Plough, the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH), Pfizer, and Shire. She is the author of the book, "Is Your Child Bipolar" published May 2008, Bantam Books. Her spouse receives royalties from UpToDate; consultation fees from Emalex, Noctrix, Disc Medicine, Avadel, HALEO, OrbiMed, and CVS; and research support from Merck, NeuroMetrix, American Regent, NIH, NIMH, the RLS Foundation, and the Ellison Baszucki Donor Fund. In the past, he has received honoraria, royalties, research support, consultation fees or speaker's fees from: Otsuka, Cambridge University Press, Advance Medical, Arbor Pharmaceuticals, Axon Labs, Boehringer-Ingelheim, Cantor Colburn, Covance, Cephalon, Eli Lilly, FlexPharma, GlaxoSmithKline, Impax, Jazz Pharmaceuticals, King, Luitpold, Novartis, Neurogen, Novadel Pharma, Pfizer, Sanofi-Aventis, Sepracor, Sunovion, Takeda, UCB (Schwarz) Pharma, Wyeth, Xenoport, Zeo.

Dr. Mai Uchida receives research support from the NIMH under Award Number 1K23MH122667-01.

Dr. Gagan Joshi is supported by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) under Award Number K23MH100450. In the last year he has received research support from the Demarest Lloyd, Jr. Foundation as a primary investigator (PI) for investigator-initiated studies. Additionally, he receives research support F. Hoffmann-La Roche Ltd. as a site PI for multi-site trials. In the past three years, he has received research support from Pfizer and the Simons Center for the Social Brain. In addition, he has received honorarium from the Governor's Council for Medical Research and Treatment of Autism in New Jersey and from NIMH for grant review activities. Finally, he received speaker's honorariums from the American Academy of Child and Adolescent Psychiatry, The Israeli Society of ADHD, the Canadian Academy of Child and Adolescent Psychiatry, and the University of Jülich.

In the past year, Dr. Stephen V. Faraone received income, potential income, travel expenses continuing education support and/or research support from, Akili Interactive Labs, Arbor, Genomind, Ironshore, KemPharm/Corium, Ondosis, Otsuka, Rhodes, Shire/Takeda, Sunovion, Supernus, Tris, and Vallon. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, has received support from: Alcobra, Aveksham, CogCubed, Eli Lilly, Enzymotec, Impact, Janssen, KemPharm, Lundbeck/Takeda, McNeil, Neurolifesciences, Neurovance, Novartis, Pfizer, and Vaya. He also receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health; Oxford University Press: Schizophrenia: The Facts; and Elsevier: ADHD: Non-Pharmacologic Interventions. He is also Program Director of [www.adhdinadults.com](http://www.adhdinadults.com). Dr. Faraone is supported by the European Union's Horizon

2020 research and innovation programme under grant agreement No 667302 and NIMH grants U01 MH109536-01, 1R01MH116037-01A1 and 1R01AG06495502.

Dr. Joseph Biederman is currently receiving research support from the following sources: AACAP, Feinstein Institute for Medical Research, Genentech, Headspace Inc., NIDA, Pfizer Pharmaceuticals, Roche TCRC Inc., Sunovion Pharmaceuticals Inc., Takeda/Shire Pharmaceuticals Inc., Tris, and NIH. Dr. Biederman and his program have received royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Biomar, Bracket Global, Cogstate, Ingenix, Medavent Prophase, Shire, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH. Through Partners Healthcare Innovation, Dr. Biederman has a partnership with MEMOTEXT to commercialize a digital health intervention to improve adherence in ADHD. Through MGH corporate licensing, Dr. Biederman has a US Patent (#14/027,676) for a non-stimulant treatment for ADHD, a US Patent (#10,245,271 B2) on a treatment of impaired cognitive flexibility, and a patent pending (#61/233,686) on a method to prevent stimulant abuse. In 2020: Dr. Biederman received an honorarium for a scientific presentation from Tris, and research support from the Food & Drug Administration. He receives honoraria from the Medlearning Inc and MGH Psychiatry Academy for tuition-funded CME courses.

In 2019, Dr. Biederman was a consultant for Akili, Avekshan, Jazz Pharma, and Shire/Takeda. He received research support from Lundbeck AS and Neurocentria Inc. Through MGH CTNI, he participated in a scientific advisory board for Supernus. He received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. In 2018, Dr. Biederman was a consultant for Akili and Shire. He received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. In 2017, Dr. Biederman received research support from the Department of Defense and PamLab. He was a consultant for Aevi Genomics, Akili, Guidepoint, Ironshore, Medgenics, and Piper Jaffray. He was on the scientific advisory board for Alcobra and Shire. He received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. In previous years, Dr. Biederman received research support, consultation fees, or speaker's fees for/from the following additional sources: AACAP, Abbott, Akili, Alcobra, Alza, APSARD, Arbor Pharmaceuticals, AstraZeneca, Avekshan, Boston University, Bristol Myers Squibb, Cambridge University Press, Celltech, Cephalon, The Children's Hospital of Southwest Florida/Lee Memorial Health System, Cipher Pharmaceuticals Inc., Eli Lilly and Co., Esai, EIMindA, Forest Research Institute, Fundacion Areces (Spain), Forest, Fundación Dr.Manuel Camelo A.C., Glaxo, Gliatech, Hastings Center, Ironshore, Janssen, Juste Pharmaceutical Spain, Magceutics, McNeil, Medgenics, Medice Pharmaceuticals (Germany), Merck, MGH Psychiatry Academy, MMC Pediatric, NARSAD, NIDA, New River, NICHD, NIMH, Novartis, Noven, Neurosearch, Organon, Otsuka, Pfizer, Pharmacia, Phase V Communications, Physicians Academy, The Prechter Foundation, Quantia Communications, Reed Exhibitions, Shionogi Pharma Inc, Shire, the Spanish Child Psychiatry Association, SPRITES, The Stanley Foundation, UCB Pharma Inc., Vaya Pharma/Enzymotec, Veritas, and Wyeth.

Ms. Maura DiSalvo, Ms. Abigail Farrell, Emmaline Cook and Dr. Carrie Vaudreuil have nothing to disclose.

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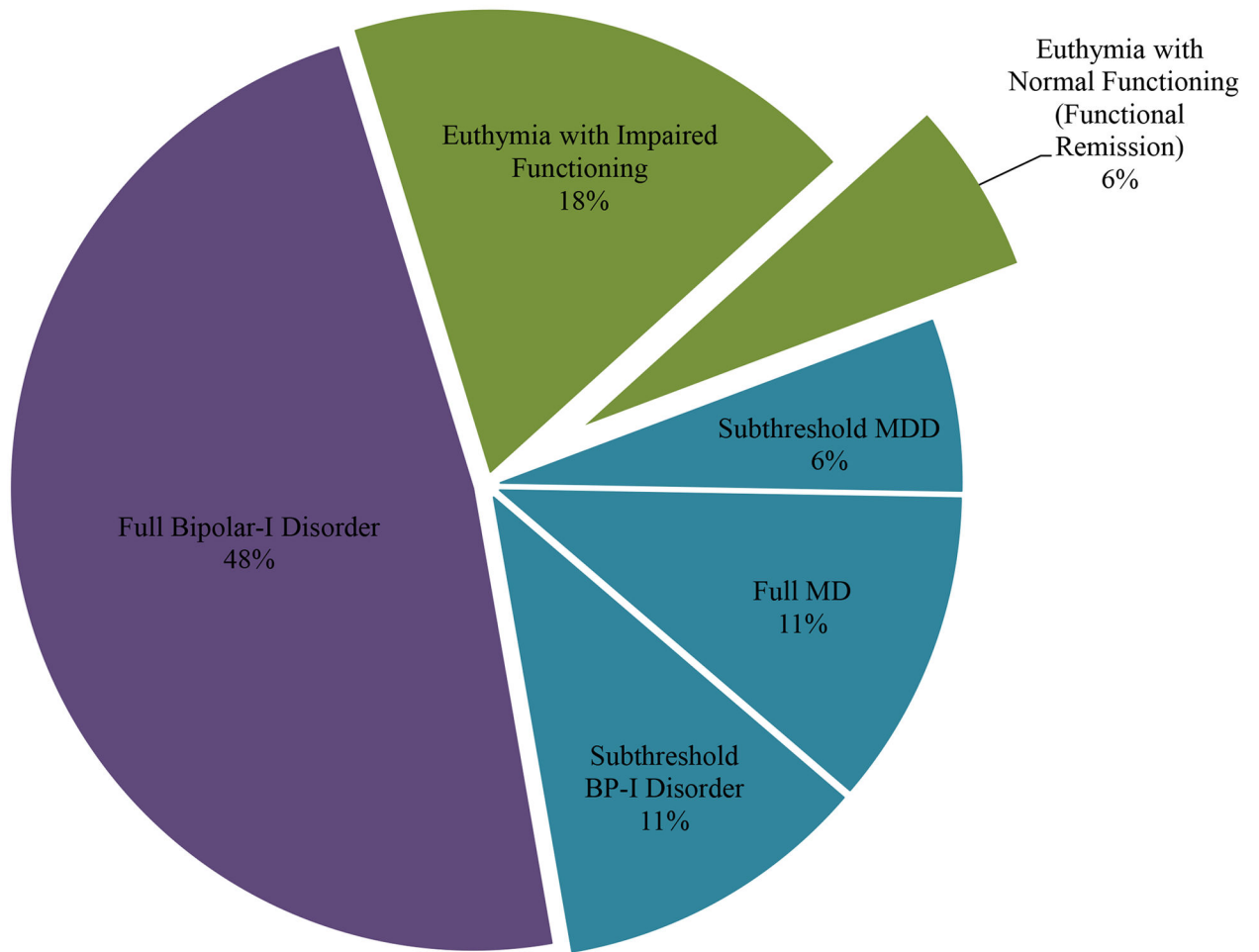
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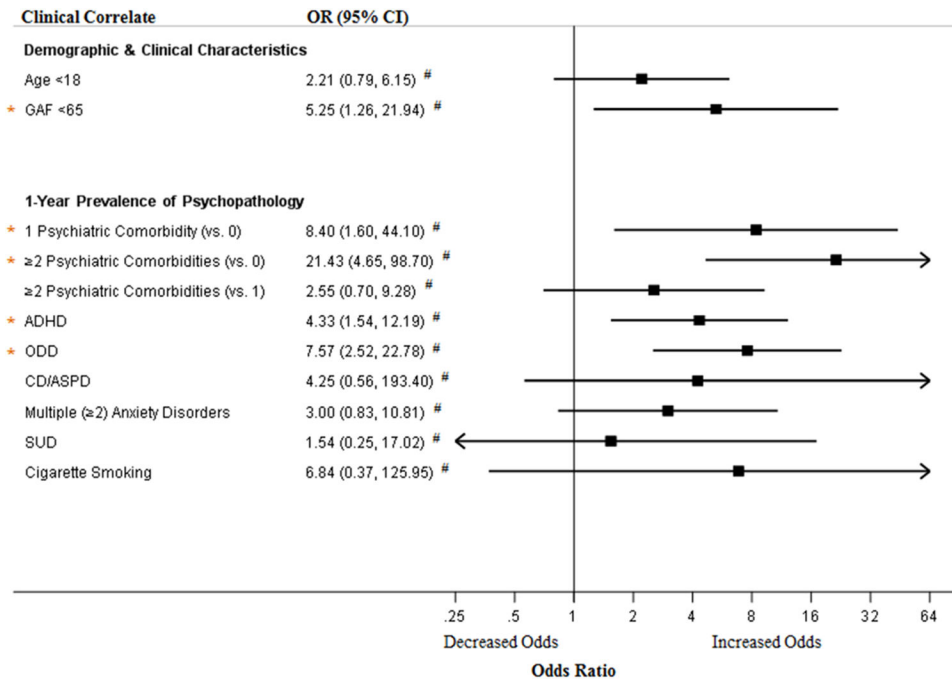
**Highlights:**

- Emerging evidence suggests that pediatric bipolar disorder persists over time
- In assessing longitudinal course of pediatric bipolar disorder, it is important to include “functioning” and “subthreshold” states.
- Lower SES, preschool age of onset and severe impairment at baseline increase the odds of having persistence of pediatric mania.

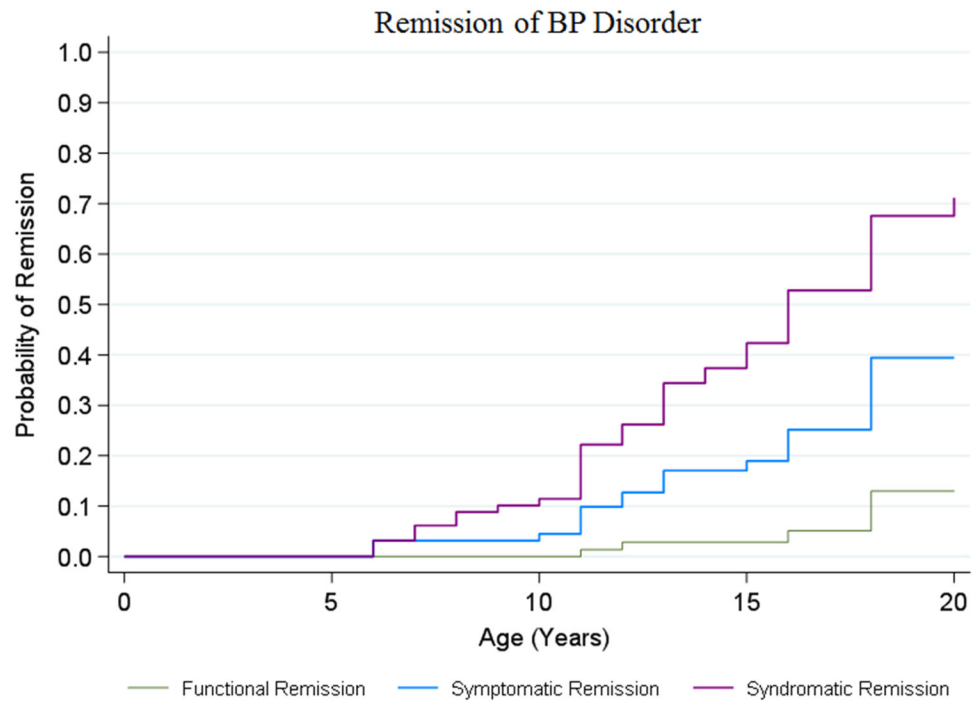
■ Euthymia   ■ Symptomatic Persistence   ■ Syndromatic Persistence



**Figure 1.**  
Heterogeneity of Remission and Persistence in Pediatric BP-I Disorder at Follow-up



**Figure 2.** Clinical correlates of persistent BP at follow-up. Odds ratios represent the odds of having persistent BP at follow-up; # Odds ratio is clinically meaningful (OR > 1.5); \* P<0.05



**Figure 3.**  
 Probability of Remission of BP Disorder.  
 Functional Remission = No BPD, No MDD, and GAF  $\geq$  65 (i.e. euthymia with normal functioning)  
 Symptomatic Remission = No BPD and No MDD (i.e. euthymia with impaired or normal functioning)  
 Syndromatic Remission = No full BPD (i.e. symptomatic persistence or euthymia with impaired or normal functioning)

**Table 1.**

Psychiatric comorbidity at baseline and last follow-up assessment.

|                                            | <b>Patients in<br/>Remission at Last<br/>Follow-up<br/>Assessment<br/>N=21<sup>†</sup></b> | <b>Patients with<br/>Persistent<br/>BP-I Disorder at<br/>Last Follow-up<br/>Assessment<br/>N=67<sup>†</sup></b> | <b>P-Value</b> |
|--------------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------|
|                                            | <b>N (%)</b>                                                                               | <b>N (%)</b>                                                                                                    |                |
| Psychiatric Comorbidity at Baseline        |                                                                                            |                                                                                                                 |                |
| ADHD                                       | 14 (67)                                                                                    | 58 (89)                                                                                                         | 0.02           |
| ODD                                        | 17 (81)                                                                                    | 61 (91)                                                                                                         | 0.24           |
| CD                                         | 9 (43)                                                                                     | 37 (55)                                                                                                         | 0.32           |
| Multiple ( 2) anxiety disorders            | 13 (62)                                                                                    | 43 (64)                                                                                                         | 0.85           |
| SUD                                        | 3 (38)                                                                                     | 8 (53)                                                                                                          | 0.67           |
| Cigarette smoking                          | 1 (13)                                                                                     | 5 (33)                                                                                                          | 0.37           |
| Psychiatric Comorbidity at Last Assessment |                                                                                            |                                                                                                                 |                |
| ADHD                                       | 8 (38)                                                                                     | 48 (73)                                                                                                         | 0.005          |
| ODD                                        | 7 (35)                                                                                     | 53 (80)                                                                                                         | <0.001         |
| CD/ASPD                                    | 1 (5)                                                                                      | 12 (19)                                                                                                         | 0.18           |
| Multiple ( 2) anxiety disorders            | 4 (27)                                                                                     | 24 (52)                                                                                                         | 0.09           |
| SUD                                        | 2 (17)                                                                                     | 9 (24)                                                                                                          | 0.71           |
| Cigarette smoking                          | 0 (0)                                                                                      | 8 (21)                                                                                                          | 0.20           |

<sup>†</sup>Sample sizes vary. For ADHD, ODD, and CD/ASPD: Patients in remission at last follow-up assessment: N=20-21 and Patients with persistent BP-I disorder at last follow-up assessment=65-67. Not all patients had data available on anxiety disorders at last follow-up assessment, so Patients in remission at last follow-up assessment=15 and Patients with persistent BP-I disorder at last follow-up assessment=46 for multiple anxiety disorders at last assessment. For SUD and cigarette smoking, age was restricted to >12 years, so at baseline: Patients in remission at last follow-up assessment=8 and Patients with persistent BP-I disorder at last follow-up assessment=15 and at last assessment: Patients in remission at last follow-up assessment=12; Patients with persistent BP-I disorder at last follow-up assessment=38

**Table 2.**

Baseline predictors of persistent pediatric BP disorder.

|                                                 | Odds Ratio (95% CI) <sup>†</sup>     | P-Value |
|-------------------------------------------------|--------------------------------------|---------|
| <b>Demographic Characteristics</b>              |                                      |         |
| Age at Baseline (Continuous)                    | 0.95 (0.82, 1.09)                    | 0.43    |
| <b>SES</b> (Continuous)                         | <b>1.95 (0.91, 4.19)<sup>#</sup></b> | 0.09    |
| GAF Score (Continuous)                          | 0.99 (0.90, 1.07)                    | 0.74    |
| Age 12                                          | 0.69 (0.25, 1.93)                    | 0.48    |
| Male                                            | 1.08 (0.27, 3.80)                    | 1.00    |
| Caucasian vs. Non-Caucasian                     | 0.79 (0.02, 8.61)                    | 1.00    |
| <b>Bipolar Characteristics</b>                  |                                      |         |
| <b>Prepubertal Onset (&lt;5 years of age)</b>   | <b>2.47 (0.88, 6.89)<sup>#</sup></b> | 0.09    |
| Duration (Continuous)                           | 1.12 (0.95, 1.31)                    | 0.19    |
| Number of Episodes (Continuous)                 | 1.004 (0.99, 1.01)                   | 0.44    |
| Number of Symptoms (Continuous)                 | 1.38 (0.89, 2.14)                    | 0.15    |
| <b>Severe Impairment</b>                        | <b>1.69 (0.60, 4.71)<sup>#</sup></b> | 0.33    |
| <b>Family History of Psychopathology</b>        |                                      |         |
| Number of Disorders with Family Hx (Continuous) | 1.12 (0.87, 1.42)                    | 0.38    |
| <b>BPD</b>                                      | <b>2.37 (0.72, 7.86)<sup>#</sup></b> | 0.16    |
| MDD                                             | 1.08 (0.27, 3.80)                    | 1.00    |
| ADHD                                            | 0.65 (0.24, 1.74) <sup>#</sup>       | 0.39    |
| <b>ODD</b>                                      | <b>1.72 (0.62, 4.81)<sup>#</sup></b> | 0.30    |
| CD/ASPD                                         | 1.27 (0.41, 3.94)                    | 0.68    |
| Multiple ( 2) Anxiety Disorders                 | 1.27 (0.47, 3.39)                    | 0.64    |
| SUD                                             | 1.26 (0.44, 3.61)                    | 0.66    |
| <b>Cigarette Smoking</b>                        | <b>1.53 (0.56, 4.18)<sup>#</sup></b> | 0.40    |

<sup>#</sup> Clinically meaningful odds ratios (OR ≥ 1.5)

<sup>†</sup> Sample sizes vary. For ADHD, ODD, and CD/ASPD: Patients in remission at last follow-up assessment: N=20-21 and Patients with persistent BP-I disorder at last follow-up assessment=65-67. Not all patients had data available on anxiety disorders at last follow-up assessment, so patients in remission at last follow-up assessment=15 and patients with persistent BP-I disorder at last follow-up assessment=46 for multiple anxiety disorders at last assessment. For SUD and cigarette smoking, age was restricted to >12 years, so at last assessment: patients in remission at last follow-up assessment=12; patients with persistent BP-I disorder at last follow-up assessment=38