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Comorbidity in Pediatric Bipolar Disorder

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Synopsis

A growing literature shows the pervasiveness and importance of comorbidity in youth with bipolar disorder (BPD). For instance, up to 90% of youth with BPD have been described to manifest comorbidity with attention deficit hyperactivity disorder. Multiple anxiety, substance use, and disruptive behavior disorders are the other most commonly reported comorbidities with BPD. Moreover, important recent data highlights the importance of obsessive compulsive and pervasive developmental illness in the context of BPD. Data suggests that not only special developmental relationships are operant in context to comorbidity, but also that the presence of comorbid disorders with BPD results in a more severe clinical condition. Moreover, the presence of comorbidity has therapeutic implications for the treatment response for both BPD and the associated comorbid disorder. Future longitudinal studies to address the relationship and the impact of comorbid disorders on course and therapeutic response over time are required in youth with BPD.

Keywords

bipolar disorder; comorbidity; treatment

Pediatric onset bipolar disorder (BPD) seldom occurs in the absence of comorbid conditions. The co-occurrence of additional disorders complicates both the accurate diagnosis of BPD and its treatment. BPD is one of the most debilitating psychiatric disorders, estimated to cost Americans 45 billion dollars per year. It is not so infrequent as previously reported, with rates of bipolar spectrum disorder reaching an estimated 4%. Youth with BPD are amongst the most impaired population and the presence of comorbidity compounds disability, complicates treatment, and appears to worsen the prognosis in this population. Comorbid disorders may have a significant impact on various indices of BPD correlates. Knowledge of their comorbid presence with BPD could be informative in determining course, prognosis, and functional and therapeutic outcomes. Early identification and appropriate management

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may lead to improved functioning, prevention of impending emergence of comorbid disorders (Oppositional defiant disorder/Conduct disorder [ODD/CD], Substance use disorders [SUD]), and attenuation of the untreated course of BPD[27,163]. On the other hand, if comorbidity is not appropriately acknowledged then misattribution of impairing symptoms could lead to inappropriate therapeutic interventions, unnecessary exposure to neuroleptics, worsening of symptoms, delayed diagnosis, and misuse of mental health resources.

Recognition of comorbidity is important as it has therapeutic implications such as 1) increased risk of mood destabilization that is inherent to the therapeutic options for the comorbidity, as is the case with anti-anxiety, antidepressant, or anti-ADHD medications that have manicogenic potential, 2) atypical response (efficacy and tolerability) to psychotropics associated with certain disorders like Pervasive developmental disorders (PDD), or 3) less than expected anti-manic response to thymoleptic agents in the presence of certain comorbid disorders (for instance Attention deficit hyperactivity disorder [ADHD], Obsessive – Compulsive disorder [OCD]).

Comorbid disorders may be challenging to diagnose due to overlapping symptoms and developmentally sensitive complicated patterns of symptom development. Several methods have been applied to scientifically understand comorbidity. Structured diagnostic interviews (for instance, Schedule for Affective Disorders and Schizophrenia-Epidemiological Fifth Version [K-SADS-E][6] are helpful in clinically parsing out the comorbid conditions as they comprehensively assesses the spectrum of psychopathologies described in DSM including past and present severity of symptoms. Diagnoses are considered positive only if the diagnostic criteria are met to a degree that would be considered *clinically meaningful*. "Clinically meaningful" means that the data collected from the structured interview indicated that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. For a given disorder the overlapping non-specific symptoms are considered for the diagnosis if the respective cardinal symptoms are present and the disorder is cause for significant impairment. Furthermore, although DSM criteria do not permit comorbid presence of certain disorders and assigns diagnoses based on hierarchy, in order to fully characterize the clinical picture a non-hierarchical diagnostic approach is taken to assess for comorbid disorders. Thus the approach taken by structured interview objectively and comprehensively documents symptom presentation and minimizes diagnostic biases.

Perhaps the most compelling scientific method to examine comorbidity is familial risk analysis which addresses uncertainties regarding complex phenotypes in probands by examining the transmission of comorbid disorders in families[55,56]. Therapeutic response has also provided evidence of the existence of separate conditions. For instance, in a review of clinical records in manic children, Biederman et al. (1998) reported that whereas mood stabilizers significantly improved mania-like symptoms, antidepressants and stimulants did not and conversely, tricyclic antidepressants and not mood stabilizers were associated with improvement of ADHD symptoms[14]. Finally, attributes of comorbidity can also be addressed by applying neurobiological probes to seek the existence of underlying changes commensurate with each comorbid disorder, either disorder, or neither disorder indicating a unique subtype with distinct neurobiological attributes. The emerging proton magnetic resonance spectroscopic (^{1}HMRS) imaging intervention research in youth with BPD is suggesting a profile of cerebral metabolites in a specific region of the brain which may facilitate the understanding of neurochemical correlates of BPD in the context of comorbidity. For instance, the ^{1}HMRS profile of cerebral metabolites in the anterior cingulate cortex region of the brain in children with ADHD appears to have a significantly

higher ratio of glutamate plus glutamine to myo-inositol-containing compounds than does the profile of children with comorbid BPD and ADHD[129].

Present studies addressing comorbidity generally rely either on cross-sectional observations or on recall of disorders over the whole life course. Both of these approaches pose limitations. Longitudinal studies are required that offer the best possibility for observing the developmental progression of the emergence of comorbid conditions.

Treatment guidelines for pediatric BPD indicate that the treatment plan must include treatment for each comorbid disorder, which may become a complex process of trial and error to find the most effective combination of medications[105]. These guidelines further recommend that in the absence of treatment trials specifically studying a population of children with BPD and specific comorbid disorders, clinicians should use psychopharmacological and psychosocial treatments which are generally recommended for each comorbid disorder when that disorder occurs as the primary problem. Though certain comorbid disorders associated with BPD respond to anti-manic agents (disruptive behavior disorders [DBD], PDD), there are frequently co-occurring disorders (ADHD, anxiety disorders, depression) with typical onset prior to the emergence of mania that require treatment with agents that have manicogenic potential. Available empirical evidence and clinical acumen dictates that treatment of comorbid conditions can be addressed only after the symptoms of BPD are stabilized[181]. Decision to treat the comorbid disorders following stabilization of mania should be guided by clinically determining the level of impairment associated with the disorder. As a rule, medications with lower manicogenic potential are preferred in this population.

Comorbid conditions frequently associated with pediatric onset BPD include ADHD, disruptive behavior disorders, substance use disorders, anxiety disorders (including panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder), and pervasive developmental disorders (Figure-1). In the following sections we will address the characteristics and management of frequently occurring comorbid disorders in children and adolescents with BPD.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Systematic studies of pediatric populations with BPD show that the rates of comorbid ADHD range from 60 to 90%[71,168,171]. While a high prevalence of ADHD is reported in youth with BPD, a modest rate (22%) of comorbid BPD is reported in pediatric populations with ADHD[12]. Although the rates of ADHD in youth with BPD are universally high, the age at onset modifies the risk for comorbid ADHD. ADHD comorbidity is more often associated with early onset BPD (< 18 years)[34,147]. Rates of ADHD in adolescents with BPD are reported to be greater in childhood onset BPD (• 12 years) than in adolescent onset BPD (> 13 years)[18,54]. Sachs et al. (2000) reported that, among adults with BPD, a history of comorbid ADHD was only evident in those subjects with onset of BPD before the age 19 years.

Although the adult literature on the subject has been less extensive, similar findings have been documented. The National Comorbidity Survey Replication epidemiological study documented significantly higher rates of BPD in the adult population with ADHD compared with adults without ADHD (19.4% vs. 3.1%)[96]. Consistent with the documented association of comorbid ADHD almost exclusively with early-onset BPD, a relatively low lifetime prevalence (9.5%) of comorbid ADHD is reported in an adult research population with BPD[133]. Similarly, Winokur et al. (1993) reported childhood hyperactivity in 21.3% of their adult BPD population (N=189) and in 19% of their first-degree adult relatives with BPD. ADHD comorbidity with BPD is over-represented in males and in its presence, BPD adults

had the onset of their mood disorder approximately 5 years earlier, had shorter periods of euthymia, were more frequently depressed, and had a greater burden of additional comorbid psychiatric disorders, especially anxiety disorders and SUD[133].

In an analysis of prepubertal children with BPD and ADHD, Wozniak et al. (1995) demonstrated correlates of both conditions. Affected children had high rates of major depression, psychosis, multiple anxiety disorders, impaired psychosocial function, and hospitalization, consistent with BPD. Similarly, phenotypic features of ADHD and associated neuropsychiatric correlates (that is, high rates of learning disabilities and need for educational services) have striking homology to the presentation of ADHD in the context of comorbidity with BPD, suggesting that ADHD may be a bona fide disorder when comorbid with BPD[14]. As ADHD and mania diagnostically share nonspecific symptoms (distractibility, motoric hyperactivity, and talkativeness), there is a risk of unintentional over-diagnosis. Several studies have addressed this issue[128]. Biederman et al. (1996) showed that the majority of children with the combined condition continued to meet criteria of both mania and ADHD after removing overlapping symptoms suggesting that BPD and ADHD comorbidity is not a methodologic artifact due to shared diagnostic criteria. Although limited information is available regarding the potential for different rates of comorbidity with BPD among the DSM-IV subtypes of ADHD, the rates of BPD are reported to be highest among youth with combined-type ADHD (26.5%), but also elevated among hyperactive-impulsive (14.3%) and inattentive (8.7%) youth[51]. Wilens and his colleagues (2003) examined a research population of adults with ADHD where nearly half the population also met the criteria for BPD (47%); the vast majority were BPD-II (88%). Although ADHD adults with comorbid BPD shared the prototypic characteristics of both the disorders, they had higher rates of combined type ADHD, with a greater number of DSM-IV ADHD symptoms (especially attentional symptoms), a higher prevalence of anxiety disorders, and poorer global functioning[171].

While the mechanisms that mediate the association between BPD and ADHD are not entirely clear, other data suggest that subforms of these disorders share genes in common[50]. Children of bipolar parents have an elevated risk for ADHD and relatives of ADHD children have an increased risk for BPD[52]. The transmission of these disorders has been studied in families ascertained through pediatric BPD patients, ADHD boys[52] and ADHD girls[53]. In each of these reports, the pattern of transmission supported the hypothesis that early onset BPD may be a developmental subtype of BPD.

In BPD youth with ADHD whose mood is well stabilized, ADHD symptoms often become the second most severe presenting complaint[181]. If the symptoms of inattentiveness, distractibility, talkativeness, and impulsivity are not recognized as comorbid ADHD then they may be inappropriately treated as residual symptoms of mania. Conversely, identification of mania in youth with ADHD has therapeutic implications as failure to recognize comorbidity could lead to administration of anti-ADHD medications that could exacerbate the mania.

The response to lithium has been reported to be less robust in the presence of ADHD comorbidity in youth with BPD[154,161] suggesting that this subgroup of BPD may constitute a unique genetic subform with a differential treatment response. Chart review evaluating treatment outcome of youth with BPD treated over a 4-year period showed that mood stabilizers selectively improved manic symptoms, whereas stimulants had no effect[10]. Furthermore, in youngsters with BPD comorbid ADHD could be addressed selectively with the anti-ADHD armamentarium, but only after mood stabilization.

The stimulants have been reported to be efficacious in treating comorbid ADHD without precipitating (hypo)mania in mood stabilized BPD youth in two controlled trials. A controlled trial of stimulants as an adjunctive therapy for ADHD in BPD youth with manic symptoms stabilized on divalproex found mixed amphetamine salts to be safe and efficacious for the treatment of ADHD in the context of BPD[149]. More recently, Findling et al. (2007) reported that in youth stabilized with a stable dose of at least one mood stabilizer, concomitant treatment with methylphenidate improved ADHD in a dose dependent manner without destabilization of mood. Furthermore, in an open trial of the non-stimulant anti-ADHD agent bupropion in adults with predominately mood stabilized bipolar II disorder and ADHD, we previously reported a significant improvement in ADHD without activation of mania[174]. These aggregate data suggest that treatment for BPD needs to precede ADHD treatment; and that in general, stimulants and non-stimulants may be cautiously introduced.

OPPOSITIONAL DEFIANT DISORDER

High rates with bidirectional overlap of comorbid ODD and BPD are reported by various studies. Rates of ODD in the BPD population range from 47% – 88%[61,72] and conversely, 20% of children with ODD are reported to have comorbid BPD[76]. A recent meta-analysis reported ODD as the second most common comorbidity after ADHD, with a weighted rate of 53% among samples of children and adolescents with BPD[105].

The diagnosis of ODD in the context of BPD is challenging as nosologically ODD shares overlapping symptoms with mania without any symptom specific to ODD that could diagnostically differentiate it from mania. Because ODD is so frequently comorbid with pediatric BPD, the understanding of the relationship of ODD with BPD ranges from ODD being a secondary disorder as a consequence of bipolar illness or being a prodrome or early manifestation of BPD, to ODD representing a “true independent” comorbid psychopathological phenomenon. However, many children with disruptive behavior disorders do not go on to develop BPD[12], suggesting that different forms of disruptive behavior disorders may exist, one that could be prodromal to BPD and another form that is not. More work is needed to further evaluate this issue.

A clinical inquiry summarized 8 reviews on ODD treatments of children and found improved behavior with a 20– 30% decrease in disruptive or aggressive behaviors with parenting interventions and behavioral therapy including cognitive-behavioral therapy (CBT), social problem-solving skills training, and parent management training involving the child and / or parent for 12–25 sessions[57].

Though treatment of ODD is primarily behavioral in nature, when comorbid with other medication-responsive psychiatric conditions (BPD, ADHD), pharmacological treatment of the comorbid disorder often reduces overall symptoms of the ODD. While there is currently no data available on the treatment of ODD in the context of BPD comorbidity, an emerging body of literature points to the role of thymoleptic agents in the treatment of DBD (CD, ODD, and DBD-NOS) including ODD in youth with significant aggression. Evidence suggests that pharmacotherapy may be effective in youth with DBD, especially those experiencing problematic aggression, but response of the DBD per se to these thymoleptics is understudied. Multiple studies have examined the safety and efficacy of atypical antipsychotics (risperidone, olanzapine, quetiapine, and aripiprazole) in treating aggression in children with DBD. Atypical antipsychotics have generally been significantly more efficacious than placebo in treating aggression in DBD youth.

To date, risperidone is the most extensively studied atypical antipsychotic for DBD. Several trials indicate that risperidone can be useful for DBD, especially the aggressive features, in both short term and long term use[5,40,60,167]. Short- and long-term efficacy and tolerability of

risperidone as pharmacotherapy for DBDs in children with sub-average intelligence has been demonstrated in over 1,300 children and adolescents in the literature[5,40,60,143,152,167]. In two short-term (6-week) controlled trials Aman and colleagues (2005) studied the role of low dose risperidone (mean dose 1.16 and 0.98 mg/day) in borderline intellectual functioning ((IQ of 36–84) DBD youth (N=223; ages 5–12) and reported an acceptable tolerability profile with significant improvement in aggression and behaviors associated with DBD[5,152]. As the five long-term (1–3 year) follow-up trials suggest, a low dose of risperidone (mean dose ranged from 1.38–1.92 mg/day) was equally well tolerated and effective in controlling the DBD and aggressive behaviors in this population[40,60,143,144,167]. Low dose risperidone (0.02 mg/kg/day) is also reported to be well tolerated and efficacious in treating DBD behaviors in youth with normal intelligence as suggested by short and long-termtrials[79,143].

However, a post-hoc analysis of the data from the controlled trial of risperidone in DBD conducted by Aman and colleagues[5] examined 24 candidate affective symptoms extracted from the 64 item Nisonger Child Behavior Rating Form[15]. These symptoms reflected the bipolar symptoms of explosive irritability, agitation, expansiveness, grandiosity, and depression. Risperidone was also effective in treating these putative symptoms of mania. This analysis raises the question of whether studies which examine the effects of anti-manic agents on DBD may include subjects with comorbid bipolar spectrum illness, and, further, whether the improvement in DBD is a function in part of the improvement in BPD.

Quetiapine is the other most studied atypical antipsychotic for DBD in youth. In youth with DBD and ADHD who fail to respond to OROS methylphenidate monotherapy (at 54 mg/day dose), the addition of quetiapine (at a mean dose 329 mg/day) has been shown to be effective in controlling symptoms of ODD and aggression[107]. Open-label and placebo-controlled studies suggest that divalproex is efficacious for the treatment of mood lability and explosive temper in children and adolescents with DBD[46,47]. Further prospective studies addressing the course and treatment of ODD when comorbid with BPD are warranted.

CONDUCT DISORDER

In a comprehensive literature review, Geller[70] concluded that: “Available data strongly suggest that prepubertal-onset BPD is a non-episodic, chronic, rapid-cycling, mixed manic state that may be comorbid with attention-deficit hyperactivity disorder (ADHD) and conduct disorder (CD) or have features of ADHD and/or CD as initial manifestations.” This observation is supported by a body of research documenting a bi-directional overlap between CD and BPD in children. As both CD and BPD are highly impairing conditions, their co-occurrence heralds a particularly severe clinical picture and raises important clinical questions. From a diagnostic standpoint, the question remains as to whether antisocial behaviors in a child with BPD such as stealing, lying or vandalizing, should be attributed to the disinhibition of mania with its attendant impulsivity, irritability and grandiosity or to comorbid CD. From a treatment standpoint in such a child, the question further remains as to whether the symptoms of CD will diminish when the symptoms of BPD are adequately treated.

The association between CD and mania is consistent with the well documented comorbidity between CD and major depression[7] and the frequently bipolar nature of juvenile depression[69,160]. Moreover, pediatric onset BPD is frequently mixed (dysphoric) and commonly associated with “affective storms,” with prolonged and aggressive temper outbursts[30,41]. These irritable outbursts often include threatening or attacking behavior towards family members, children, adults, and teachers, behaviors that overlap with CD. For example, McGlashan et al.[126] reported that juvenile onset BPD may be particularly

explosive and disorganized and that children with mania tended to have more trouble with the law and more "psychotic assaultiveness" than adults with BPD. Kovacs[104] reported that some youngsters with mania showed serious acting out behaviors including burglary, stealing, vandalism and a history of school suspensions. Although these aberrant behaviors are consistent with the diagnosis of CD, they may be due to the behavioral disinhibition that characterizes BPD. Thus, it is not surprising that youth with BPD frequently meet diagnostic criteria for CD. High rates of CD (69%) are reported in youth with BPD[104] and the comorbid presence of BPD and CD in youth heralds a more complicated course with high rates of hospitalization (42%)[108]. Furthermore, CD is reported to be severe in the presence of comorbid BPD[130].

Epidemiologic studies report high rates of comorbidity between BPD and DBD[111,146]. There seems to be an increase in the risk for BPD with a higher number of CD symptoms[146] and a nearly 7-fold increase in the risk for BPD in individuals with antisocial personality disorder[22]. The risk of CD is three fold higher in younger bipolar individuals (< 30 years) with comorbid SUD than those without SUD (52% vs. 14.8%)[29].

Comorbid CD in BPD youth might confuse the clinical presentation of childhood BPD and possibly account for some of the documented failure to detect bipolarity in children. Isaac[86] examined a group of adolescents found to be the most problematic, crisis prone, and treatment resistant in a special educational day school and treatment program. These authors found that two-thirds of these youngsters satisfied DSM-III-R criteria for BPD, which had often been misdiagnosed as ADHD and CD. Most of the remaining youngsters showed significant bipolar features but did not fully satisfy DSM-III-R criteria for BPD. Considering the heterogeneity of BPD and that of CD, these findings may have important implications in helping to identify a subtype of BPD with early onset characterized by high levels of comorbid CD[104] and a subtype of CD with high levels of dysphoria and explosiveness.

In a large, well characterized, prospective sample of children referred with ADHD[9], ADHD children with comorbid BPD and CD reported higher familial and personal risk for mood disorders than youth with ADHD and CD alone, who were found to have higher personal risk for antisocial personality disorder. This suggests that the presence of BPD in some CD children could be clinically meaningful, at least in the context of ADHD. Further analysis of structured interview-derived data from a large sample of consecutive, clinic-referred children and adolescents, showed again a large and symmetrical overlap between BPD and CD[10]. Examination of the clinical features, patterns of psychiatric comorbidity and functioning in multiple domains showed that children with CD and BPD had similar features of each disorder irrespective of comorbidity with the other disorder. These findings further supported the hypothesis that children satisfying diagnostic criteria for BPD and CD suffer from both disorders, rather than one being misdiagnosed as the other, even outside the context of comorbid ADHD. These authors also documented that psychiatric hospitalizations among CD probands were almost entirely accounted for by those with comorbid BPD. This finding is consistent with the notion that CD plus BPD probands, along with other symptoms of CD, engage in a disorganized type of aggression associated with BPD. Since many children in psychiatric hospitals with the diagnosis of CD commonly have a profile of severe aggressiveness, it is likely that these children required psychiatric hospitalizations because of the manic picture and not necessarily due to the CD.

Further evidence that a subtype of CD linked to BPD could be identified derives from pilot familial risk analyses[13,183]. These results suggest that relatives of BPD probands were at an increased risk for BPD but not CD. On the other hand, relatives of CD probands had an increased risk for CD but not for BPD, while relatives of CD plus BPD probands had an elevated risk for both disorders[183]. Among relatives in this latter group, BPD and antisocial

disorders showed significant cosegregation, i.e., relatives with one disorder were highly likely to have the other. As a result of this cosegregation, CD plus BPD was significantly elevated among relatives of CD plus BPD probands but was rare among the relatives of the other proband groups. Probands with the combined condition of CD and BPD also had high rates of non-BPD conduct/antisocial disorders among the relatives, suggesting a genetic loading with two sub-types of CD: with and without BPD. These results provide compelling evidence that subtypes of CD and of BPD can be identified based on patterns of comorbidity with the other disorder suggesting that, their cooccurrence may correspond to a distinct familial syndrome[13,51–53,183].

The delineation of a subgroup of manic CD children would have important clinical implications. It could lead to improvement in our efforts to ameliorate the guarded outcome of some CD youth. Since BPD may respond to specific pharmacological treatments, correctly identifying those CD children with BPD may afford the opportunity to introduce these medications in the treatment of antisocial and aggressive youth.

There is limited evidence from various trials of atypical antipsychotics in youth with BPD on the possible role of thymoleptics in managing CD when comorbid with BPD. In our open-label short-term (8-week) trials of risperidone (N=30) and ziprasidone (N=21) in children and adolescents aged 6–17 years with BPD, these atypical antipsychotics were associated not only with significant improvement in symptoms of pediatric BPD, but also with improvement in the severity of comorbid CD (a CGI rating of much or very much improved) in the subset of BPD youth with comorbid CD[16,17]. Likewise, a similar response of comorbid CD to open-label short-term trial (8-week) of risperidone (N=16) and olanzapine (N=15) is recorded in a younger population of preschool-age children (4–6 years) with BPD[17]. The promising role of atypical antipsychotics in treating comorbid CD in youth with BPD as suggested by these open trials requires further validation by conducting controlled studies that apply specific measures to assess the response of CD.

As discussed earlier under the role of thymoleptic agents in the DBD population, potential pharmacotherapy for CD with marked aggression includes mood stabilizers, typical and atypical anti-psychotics - the very medications most commonly recommended for the treatment of BPD. The anti-manic agent lithium has been found to be an effective anti-aggressive agent in youth with CD as reported by various studies conducted in ambulatory and hospitalized youth with CD[27,151]. A small literature suggests that typical antipsychotic medications such as haloperidol and molindone are helpful in decreasing aggression in youth with CD[26,28,77]. However, typical antipsychotic treatment was associated with range of problematic adverse effects. This led to the use of the atypical antipsychotic agents in treating CD with aggressive features.

In an open-label short-term (8-week; N=17) followed by long-term (18-week; N=9) trial of quetiapine (at median dose 150 mg/day) in children aged 6–12 years with the primary diagnosis of CD, quetiapine was found to be effective in treating aggression and conduct problems by week 8; the benefit was sustained during long-term treatment with quetiapine in children who responded to an acute therapeutic trial of quetiapine[63,64]. In this trial, no subject developed extra-pyramidal symptoms or discontinued the trial due to adverse events, suggesting that short and long-term treatment with quetiapine was safe and well tolerated. More recently, in a controlled trial, quetiapine 294 (±78) mg/day was reported to be superior to placebo in treating adolescents with CD (N=9/10) on clinician-assessed measures of global severity but failed to separate from placebo on parent-assessed specific measures of aggression and conduct behaviors; this discrepancy could be attributed to small sample size, leading to diminished statistical power to detect differences[38].

There is preliminary evidence on the role of olanzapine in treating aggression with CD from a retrospective chart review of adolescents with CD (N=23) who were treated with olanzapine (mean dose of 8±3.2 mg/day) for an extended period of time (6–12 months)[120]. Treatment with olanzapine resulted in improvement of aggression but was also associated with a modest weight gain (4.6±3 Kg). These aforementioned empirical evidence from clinical trials exclusively conducted in CD populations in addition to the previous discussion of trials conducted in DBD populations strongly suggest the role of atypical antipsychotics in managing behaviors related to CD and aggression.

SUBSTANCE USE DISORDERS

In recent years, a focus on mood disorders in SUD youth has emerged as a major clinical and public health concern, particularly given the implications for reduction of SUD, delinquency, and mood symptoms with treatment[145]. In epidemiological and clinically based studies, SUD is one of the most common comorbidities found in BPD in adolescents and adults[125,159,179]. McElroy et al. reported that drug and alcohol use disorders were found in 39% and 32% of BPD adults, respectively. In terms of linking SUD to early-onset adult BPD, Dunner and Feiman[48] showed that BPD onset prior to adulthood was strongly and specifically related to SUD development in young adults. Similarly, McElroy and colleagues showed a retrospective association between early onset BPD, mixed symptoms and comorbidity, and SUD.

A smaller but growing literature suggests that juvenile-onset BPD is a risk factor for SUD[177]. An excess of SUD has been reported in the literature in adolescents with BPD or prominent mood lability and dyscontrol and BPD is over-represented in youth with SUD[19,169,170]. A high prevalence of SUD (40%) is reported in an inpatient adolescent population with BPD[169]. In a five-year follow-up study of 54 inpatients adolescent with BPD, Strober et al. reported an increase in the rates of SUD from 10% at baseline (mean age 16 yrs) to 22% at follow-up and described a mixed presentation with highly relapsing course in the presence of comorbidity with SUD[162].

We previously documented that adolescents with SUD referred to a psychiatric ambulatory care clinic were more likely than those without SUD to have comorbid BPD[170]. Preliminary prospective findings from our longitudinal study of ADHD youth signaled that youth with early-onset BPD, independent of ADHD, were reported to be at risk for SUD[19] and were also found to be at higher risk for early initiation and higher rates of cigarette smoking[172]. Similarly, clinically referred adolescents with BPD are at heightened risk for the development of SUD, independent of the status of CD, as compared to non-BPD psychiatric adolescents[176].

More recently, we reported the baseline findings of an ongoing, controlled longitudinal family-based study of SUD in BPD adolescents[175] where we evaluated specifically the relationship between SUD and the age at onset of BPD (child vs. adolescent onset) and the presence of comorbid CD. Participating youth (N=105 BPD and 98 non-mood disordered controls; mean age of 13.6 +/− 2.5 years) did not differ by group (BPD vs. controls) for any clinical characteristics or demographics. Nicotine dependence was found in 23% of BPD and 4% of controls whereas full SUD was found in 34% of BPD youth compared to 4% of controls. BPD youth with SUD had higher rates of additional comorbidities and poorer overall functioning than youth with BPD without SUD and controls. Comorbidity with ADHD, conduct, or anxiety disorders did not account for the high risk of SUD in BPD[175].

We previously reported that the onset of BPD in adolescence was more pernicious in terms of SUD onset than if the BPD began prepubertally[176] (Figure-3). We further evaluated the relationship between the developmental effect of BPD onset and the onset of SUD.

Interestingly, we replicated our previous findings in that youth with the onset of their BPD in adolescence were at higher risk for cigarette smoking and SUD compared to those with the onset prepubertally[175].

Because CD is an important comorbidity of both BPD and predictor of SUD, we very recently examined the contribution of CD on later development of SUD. We found that while CD increases the risk for SUD in BPD, the risk of SUD in BPD was not substantially changed with or without CD[173]. Thus we can conclude that juvenile BPD is a risk factor for SUD irrespective of the status of CD, ADHD, or other comorbid psychopathology. Youth with the onset of their BPD during adolescence were at particularly high risk for SUD and the severity and course of both the disorders is worse when comorbid.

Mechanism of SUD Risk in BPD

The reasons that juvenile BPD is a risk factor for SUD in particular, and that adolescent- vs. child-onset BPD confer a differential risk for SUD remain unclear. Given the prominent genetic influences in both BPD and ADHD (as individual disorders and perhaps co-segregating), it remains unclear if SUD in BPD youth represents a subtype of BPD and/or SUD, or if a vulnerability to SUD development exists in these youth. For instance, we previously speculated that the development of BPD may be particularly predictive of the development of SUD during adolescence, considering that adolescence is a time of vulnerability for the development of SUD[33,176].

Among disturbances reported in BPD youth, severe affective and self-regulation problems may predispose them to seek drugs of abuse[120]. By nature of their intrapsychic distress and behavioral disinhibition, these youth may try to modulate their irritable and labile mood with substances of abuse; such has been described in adults[99]. We recently examined this issue and found evidence that youth with BPD tended to initiate substances of abuse to attenuate mood relative to non-mood disordered adolescents who reported using substance more often to get high[113].

Genes and Adolescent SUD

Child- and adolescent-onset BPD may be etiologically distinct with a variable course and outcome including the risk for SUD. It may also be that adolescent-onset BPD and adolescent-onset SUD may represent variable expressivity of a shared risk factor[37,49]. In order to better understand these competing influences, family studies are necessary. To this end, we examined the parents of our adolescents with and without BPD (and/or SUD) as part of our NIH funded longitudinal study. We found the parents of proband youth with BPD (without SUD) and BPD & SUD were more likely to develop BPD than the parents of controls (omnibus test ^{2}=10.18, p=0.006); we also found no differences between the two bipolar groups. Parents of proband youth with BPD and with BPD & SUD were more likely than relatives of controls to develop SUD (omnibus test ^{2}=14.69, p<0.001); however, we found no differences between the parents of the two proband bipolar groups. Within the parents of proband youth with BPD & SUD, we found higher risk of SUD in parents with BPD than in those without BPD (^{2}=8.39, p=0.004) leading us to speculate that BPD and SUD are prevalent in the first-degree relatives of adolescents with BPD, adults with BPD were more likely to manifest SUD, and that BPD and SUD cosegregated. Interestingly, recent work from our group with a candidate gene for BPD – namely the dopamine transporter protein[127] - has also been found to be associated with the development of early – onset SUD.

Diagnostic and Treatment Considerations

The first consideration that clinicians should have in mind in the establishment of a specific treatment plan for adolescents with co-occurring mental and substance-related disorders is the determination of the level of care needed. When treating dually diagnosed disorders such as BPD and SUD, clinicians should consider a simultaneous approach. Given limited, albeit important, data on the effects of medication treatment reducing SUD in BPD, both psychosocial and medication strategies should be considered simultaneously in these comorbid adolescents. There is evidence that pharmacological interventions are effective for youth with SUD and BPD. Two studies, including one randomized controlled study, have reported that mood stabilizers, specifically lithium and valproic acid, significantly reduced substance use in bipolar youth[45,68]. A controlled, 6-week study of treatment with lithium in youth with affective dysregulation and substance dependence Geller et al.[68] reported a clinically significant decrease in the number of positive urines as well as a significant increase in overall global functioning.

In a 5-week open trial of valporic acid in adolescent outpatients with marijuana abuse/dependence and “explosive mood disorder” (mood symptoms were not classified using the DSM IV) Donovan et al.[45] reported significant improvement in their marijuana use and their affective symptoms. The use of atypical neuroleptics as mood-stabilizing agents in comorbid SUD-BPD remains understudied, albeit compelling, and further work in this area is needed.

ANXIETY DISORDERS

The presence of anxiety disorders in individuals who suffer from BPD has been under-recognized and understudied. One reason for this lack of recognition could be the notion that it is counterintuitive to suggest that BPD, which is characterized by high levels of disinhibition, could coexist with anxiety, which is characterized by fear and inhibition. However, in the first paper to demonstrate the high frequency of BPD in an outpatient pediatric psychopharmacology clinic (16%), 56% of the children with BPD suffered from 2 or more lifetime anxiety disorders (multiple anxiety disorders) comorbidly. Furthermore, a recent detailed analysis of the comorbidity between pediatric BPD and anxiety disorders in a clinically referred population revealed that 76% of youth with BPD have one or more anxiety disorders comorbid with their BPD[81]. In a community sample Lewinsohn et al.[111] reported that a third of non-referred BPD adolescents had comorbid anxiety disorders, a significantly higher rate than that found in those without a history of BPD. Because the anxiety disorders are heterogeneous (eight are included in the DSM-IV[1]) and as most studies lump them, uncertainties remain as to which anxiety disorders are associated with BPD. Various clinical and epidemiological studies in adult and pediatric populations have identified a wide range of anxiety disorders associated with BPD with rates ranging between 12.5% and 76%[11,52,54,58,81,88,111,121–123,137,164,175,184] (Figure-4).

Among various anxiety disorders, a specific association of certain anxiety disorders more than others has been suggested in youth with BPD[20,164]. A preponderance of investigators have suggested that a particular link exists between panic disorder and BPD in adults[35,75] and children[20]. Data from adult studies report a lifetime prevalence of panic disorder in 21%–33% of individuals with BPD[35,75,98] and conversely, lifetime BPD in 6%–23% of individuals with panic disorder[21,137]. MacKinnon et al.[115,116] utilize family genetic methodology in 57 families to argue that panic disorder with BPD is a genetic subtype of BPD. Savino et al.[148] systematically explored the intra-episodic and longitudinal comorbidity of 140 adults with panic disorder and reported comorbidity with BPD in 13.5% of the patients with panic disorder. They also note that an additional 34.3% met features of “hyperthymic temperament”, a possible bipolar spectrum condition. Biederman et al. reported high rates of panic disorder (52%) among youth with BPD[11] consistent with the

observation by Birmaher et al.[20] suggesting that the association between BPD and panic disorder in children and adolescents might be unique and specific. However, recent emerging literature indicates high prevalence of various anxiety disorders - including but not limited to panic disorder - in pediatric[81,88,122] and adult[31,65,123] populations with BPD, that challenges the notion of specific link between BPD and panic disorder. Thus, more information is needed as to whether the association between BPD and anxiety disorders in youth is limited to a single anxiety disorder or is more extensive and includes other anxiety disorders as well.

In the presence of high levels of anxiety, adults with BPD experience greater symptom severity, increased risk for suicide and alcohol abuse, higher frequency of a polypharmacy regimen, more severe adverse effects, poor treatment response, and higher rates of non-remission with poor course and functioning[58,67,136,185]. Olvera et al.[134] found that children with BPD and multiple anxiety disorders displayed manic symptoms at an earlier age and were more likely to have been hospitalized for their illness.

Improving the understanding of the relationship between anxiety disorders and BPD in youth has important treatment implications. Masi et al.[122] reported high rates of pharmacologic hypo/mania in youth with anxiety disorders with mean age of onset of for anxiety disorders preceding that for BPD. This finding suggests caution when considering antidepressant pharmacotherapy in a pediatric population with multiple anxiety disorders. Considering that treatments for BPD with traditional mood stabilizers do not generally treat anxiety disorders, and that treatment of anxiety disorders with SSRIs can aggravate the BPD, the pharmacological approach to bipolar children with comorbid anxiety disorders needs to be defined. As BPD and anxiety disorders respond to different treatments, identification of the comorbid state is essential for proper treatment and for achieving optimal functioning.

No systematic data is available which examines treatment of anxiety disorders in the context of bipolar comorbidity. Trials of pediatric anxiety disorders exclude children with BPD by protocol design and similarly, children with a BPD diagnosis are typically excluded from the trials of treatment for both depression and anxiety.

To-date, only one open-label trial has assessed response of co-occurring panic attacks and generalized anxiety disorder in adults with BPD, reporting significant decrease in or remission of anxiety symptoms with divalproex therapy[25]. Corroborative evidence for anti-anxiety effect of mood stabilizers comes from various open-label and controlled trials in adult population with anxiety disorders that suggest valproate to be effective in treating panic disorder and Posttraumatic stress disorder (PTSD)[8,36,59,114,124,135,140]. Anti-anxiety response of certain mood stabilizers could be specific to certain anxiety disorder(s). For instance, carbamazepine, though effective in treating certain symptoms of PTSD, it is found to be ineffective in treating other anxiety disorders in adults namely panic disorder and OCD[87,112,157,165,180].

Obsessive – Compulsive Disorder

Descriptions of OCD symptoms in bipolar patients date back to the 19th century[131]. Most data on comorbid OCD and BPD are not based on systematic studies[74,142], but are documentation from naturalistic studies. In adults, evidence of a higher-than-expected overlap between OCD and BPD first came from the ECA study, where 23% of those with BPD also met criteria for OCD[146]. Subsequent studies have consistently found the overlap between OCD and BPD at rates as high as 15–35%[35,138,175]. When comorbid with BPD, OCD in adults has a more episodic course, often featuring higher rates of sexual and religious obsessions, lower rates of checking rituals, and greater frequency of concurrent

major depressive episodes and panic disorder. They also exhibit increased rates of suicidality, more frequent hospitalizations and more complex pharmacological interventions than those without BPD[32,35,138,139]. A recent survey conducted among the French Association of OCD patients provides corroborating evidence for this comorbidity in subjects giving retrospective childhood reports. While reporting a high prevalence of comorbid lifetime bipolarity, they also noted that many of these subjects had a juvenile onset of their OCD[80,102].

While the available literature suggests substantial impact on clinical presentation, global functioning, and treatment decisions when BPD and OCD co-occur in young patients[121] the nature of this relationship is not clearly delineated. For example, the agitation, racing thoughts and feelings of distress which can be associated with severe OCD could mimic a bipolar picture; conversely, the manic symptom of increase in goal directed activity ("mission mode" behavior) or repetitive, unwanted hypersexual thoughts in a child or adolescent with BPD could mimic an OCD presentation. In one of the two studies that addresses this comorbid presentation Masi et al.[121] reported that in comparison to OCD, comorbid OCD and BPD youth were significantly more impaired, had earlier age of onset of OCD and had more frequent existential, philosophical, odd and/or superstitious obsessions, indicating that comorbidity with BPD may have a clinically relevant influence on the symptom expression of the OCD. Half of the comorbid population in this study had type II BPD and one-third experienced pharmacologic hypomania. This high risk of (hypo) manic switches reported with antidepressant treatment in pediatric OCD is suggestive of a bipolar diathesis[44,100].

In other study of youth ascertained for family genetic study of BPD and OCD we previously[92] documented a significant and symmetrical bidirectional overlap between BPD and OCD (21% of the BPD cohort and 15% of the OCD cohort satisfied criteria for both BPD and OCD). In the presence of comorbid BPD, youth with OCD more often presented with the symptom of hoarding/saving, experienced a higher prevalence of other comorbid disorders especially ODD, major depressive disorder (MDD), and psychosis, suffered from poorer psychosocial functioning, and required hospitalization at a greater frequency. Higher prevalence of comorbidity with multiple anxiety disorders, especially General anxiety disorder (GAD) and social phobia, was observed in youth with comorbid OCD and BPD than when either disorder occurred in youth without reciprocal comorbidity. Limited family genetic data suggests a genetic linkage between OCD and BPD. Coryell[39] reported an equal incidence (2.3%) of BPD in families of probands with OCD and in families with BPD. Similarly, an increased incidence of obsessional traits has been reported in the offspring of bipolar probands[101].

Though no systematic data to date are available that address the therapeutic response of BPD in the presence of comorbid anxiety disorder, Joshi et al.[90] conducted a secondary data analysis to examine the antimanic response of BPD youth to olanzapine in the context of comorbidity status with OCD and GAD and concluded that in children and adolescents with BPD the comorbid presence of lifetime OCD, but not GAD, is associated with poor antimanic response (Figure-5). This suggests that certain anxiety disorders when comorbid with BPD may have a larger mediating effect on BPD treatment outcome than others.

Conversely, the presence of BPD with anxiety disorders may have a negative effect on the treatment outcome of the anxiety disorder. For instance, compared to OCD youth without comorbid BPD, children and adolescents with comorbid OCD and BPD have been reported to show poor response to psychotropic medications and are more frequently on a combined pharmacy regimen[119]. Non-pharmacological treatments such as CBT have been found to be

useful and should be instituted when possible, along with any of the pharmacological alternatives to SSRIs.

Posttraumatic Stress Disorder

Individuals who work with trauma victims make the clinical observation that mood swings are common in this group. Although considerable literature implicates psychosocial stresses in the onset and recurrence of BPD[24,84,106], there is paucity of research on the association of PTSD with BPD. While Breslau et al. reported that 40–76% of children had been exposed to a traumatic event by age 17[23,73], the estimated lifetime prevalence of the full syndromatic PTSD in the general population is between 1 and 14%, and its prevalence in children is around 6%[73]. By contrast, reported rates of PTSD comorbidity in patients with BPD have varied widely from 7% to 50%.

Rates of SUD are substantially higher in youths who had a lifetime diagnosis of PTSD before age 18 compared to youths who had never experienced a trauma[108]. Given the increasing recognition of SUD in BPD and PTSD, we further examined the relationship of BPD, SUD, and PTSD in an older group of adolescents with BPD. We found significantly more PTSD in adolescents with BPD compared to non-mood disordered controls. Sixteen percent of youth with BPD had broad PTSD compared to 4% of controls. Moreover, a higher risk of SUD was found in BPD adolescents with PTSD. While exploratory in nature, interesting temporal patterns emerged suggesting a pattern of onset of BPD first, followed by substance use, trauma, PTSD and then the onset of full SUD. These data highlight the high risk of PTSD in BPD adolescents that appears to be related to SUD in these youth[155].

Although many studies have looked at possible links between early traumatic events and development of psychopathology over the life span[78,94,97], few studies have examined the potential role of early traumatic life stresses on the development of BPD and PTSD. Emerging evidence suggests that trauma significantly compromises the course of BPD. Leverich et al.[110] evaluated 631 outpatients with BPD and reported that nearly half of the females (49%) and one-third of the males (36%) reported early sexual and physical abuse. Those who endorsed a history of child or adolescent physical or sexual abuse, compared with those who did not, had significantly higher rates of comorbid PTSD, a history of an earlier onset of bipolar illness, and a higher rate of suicide attempts. On the other hand Geller et al.[72] reported high rates (43%) of the symptom of hypersexuality (higher in pubertal versus prepubertal BPD population) and low rates (< 1%) of history of sexual abuse in their prepubertal and early adolescent BPD cohort, suggesting that the symptom of hypersexuality in pediatric BPD is etiologically unrelated to sexual abuse and more reflective of mania and puberty. Similarly, Garno et al.[66] studied 100 adult patients with BPD, and half (51%) reported a history of abuse while a quarter suffered from with comorbid PTSD (24%).

A report by Wozniak et al. raises the question as to whether a diagnosis of BPD may pose a risk factor for trauma. Using data from a large longitudinal sample of well-characterized boys with and without ADHD, these authors failed to find meaningful associations between ADHD, trauma, and PTSD. Instead, they identified early BPD as an important antecedent for later trauma. When traumatized children present with severe irritability and mood lability there may be a tendency to associate these symptoms to the trauma. On the contrary, these longitudinal results suggest that rather than a consequence, BPD may be an antecedent risk factor for later trauma (possibly because of the attendant reckless, disinhibited state). If confirmed, these results could help dispel the commonly held notion that mania-like symptoms in youths represent a reaction to trauma and would further suggest that children with BPD should be adequately treated and monitored closely to avoid trauma.

Though no empirical evidence is available for the treatment of comorbid BPD and PTSD, corroborative evidence comes from trials of mood stabilizers in adult population suggesting valproate to be effective in treating certain combat related (but not non-combat-related) PTSD symptoms[8,36,59,135,140]. Certain mood stabilizers have shown promise in treating specific symptoms of PTSD. Several open trials report that carbamazepine may be useful for treating PTSD symptoms of flashbacks, nightmares, and intrusive thoughts[112,157,180]. In a preliminary controlled trial lamotrigine exhibited potential efficacy in the treatment of PTSD symptoms of re-experiencing, avoidance, and numbing in adults[82].

PERVASIVE DEVELOPMENTAL DISORDERS

Recently, there has been immense interest in the overlap of BPD and autistic spectrum disorders. A limited literature exists on the diagnosis and treatment of comorbid BPD and PDD in children and adolescents. In the absence of systematic research on comorbid BPD and PDD, indirect evidence suggestive of comorbid BPD in pediatric populations with PDD comes from high rates of aggressive behaviors documented in children with PDD, a high incidence of BPD in family members of children with PDD, and from a small literature documenting the presence of BPD comorbidity in PDD populations.

High rates of aggressive behaviors and severe mood disturbances are documented in children with PDD[95,103,153,156]. There is considerable evidence suggesting that a subset of PDD youth with extreme disturbance of mood suffer from a symptom cluster that is phenomenologically consistent with the syndrome of BPD. In a study of a group of patients with Asperger's disorder who were followed into adolescence, Wing et al.[178] found that nearly one-half of the patients developed affective disorders. Conversely, high rates of PDD or PDD traits are reported in children and adolescents with BPD. Presence of significant PDD traits are reported to be as high as 62% in pediatric mood and anxiety disorder research populations[166].

In the first study using accepted operationalized criteria, our group assessed clinically referred children and adolescents (N=727) using a comprehensive diagnostic battery including structured diagnostic interview. We reported a bidirectional overlap: BPD occurred in 21% of PDD and PDD occurred in 11% of BPD youth[182]. There was striking homology in the clinical characteristics of PDD and BPD when clinical features were compared based on the presence or absence of reciprocal comorbidity. BPD and PDD irrespective of the reciprocal comorbidity were similar in phenotypic features including symptom profile, pattern of comorbidity, and measures of functioning. This work suggests that BPD and PDD are bona fide disorders when they co-occur in youth.

Recently we replicated our earlier findings and reported that one third of our clinically referred population of children and adolescents with PDD also received the diagnosis of BPD on structured diagnostic interviews[91]. Similarly we found consistently high rates of comorbid PDD (15%) in our research populations of children and adolescents with BPD irrespective of the aims for ascertainment - family genetic study or treatment trials of BPD[89,93]. In the presence of comorbid PDD, youth with BPD experience an earlier age at onset and increased severity of BPD with a poorer level of functioning[89,91,93]. Furthermore, PDD youth with a family history of BPD are more often high functioning and their mood disturbance is characterized by a severe cycling pattern, agitation, and aggression along with neurovegetative disturbances[43]. There is an accumulating body of literature from family genetic studies suggesting higher than expected incidence of BPD in first degree relatives of about one-third of the population with PDD[42,43,83].

Treatment response to psychotropics in youth with PDD is noted to be less robust with higher rates of adverse effects to both medication and placebo[2,4,141]. Thus, due to an

atypical response and higher susceptibility to adverse effects, it is advisable to initiate and titrate psychotropics at a lower dose and titrate upward in smaller increments in this population.

Though there is substantial evidence documenting the role of pharmacotherapy for the management of extreme mood difficulties, there is minimal published literature and no systematic data on the treatment of comorbid BPD in this population. Limited literature on the treatment of comorbid BPD in children with PDD suggests that first-generation antipsychotics (haloperidol, chlorpromazine, thioridazine) and traditional mood stabilizers (lithium, carbamazepine) are minimally effective for the treatment of mania[109]. On the contrary, in a recent secondary analysis of acute atypical antipsychotic monotherapy trials in BPD youth we reported acceptable tolerability and robust antimanic response to atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) in the presence of PDD comorbidity[89]. No difference was observed in the rate of anti-manic response and tolerability with the exception that PDD youth were more susceptible to the adverse effect of slurred speech and teary eyes. Furthermore, compared to other atypical antipsychotics, risperidone had a superior anti-manic response in BPD youth with comorbid PDD. However this study is limited by the retrospective nature of post-hoc analysis and lack of direct measures of PDD symptomatology.

There is evidence from the treatment trials of risperidone, aripiprazole, and ziprasidone that second-generation neuroleptics are well-tolerated and efficacious in treating symptoms of irritability and aggression in youth with PDD, a spectrum of symptoms suggestive of BPD. Controlled trials of risperidone consistently report favorable safety, tolerability, and efficacy profile for treating symptoms of irritability and aggression in youth with PDD[3,132,150]. Although risperidone is the only atypical antipsychotic that is FDA approved for the treatment of irritability and aggression in autistic children, weight gain associated with risperidone is a significant adverse effect that often limits continuation of treatment in this population. In contrast, results from recent short-term open trials with newer atypical antipsychotics - aripiprazole and ziprasidone-- show promise as a treatment for irritability in children with PDD, and are associated with negligible weigh gain[117,158]. Contrary to the encouraging response observed with the afore-mentioned atypical antipsychotics, the atypical antipsychotics quetiapine and olanzapine are noted to be ineffective in treating symptoms of irritability and aggression in this population[62,85,118].

Thus in choosing thymoleptic agent for the treatment of BPD in youth with comorbid PDD, consideration should be given to those anti-manic agents that are also shown to be efficacious in treating associated and core features of PDD. Furthermore, in this population due to higher susceptibility to adverse effects, it is advisable to initiate and titrate psychotropics at a lower dose. As afore-mentioned empirical evidence suggests, risperidone appears to be efficacious in treating both core and associated features of PDD and may be superior to other atypical antipsychotics as an anti-manic agent in youth with PDD. Youth should be closely monitored for adverse effects especially weight gain, as it remains a concern in short and long term therapy with risperidone.

Summary

The diagnosis and treatment of BPD needs to address psychiatric comorbidity given its ubiquitous nature. ADHD comorbidity is particularly associated with very early onset BPD, whereas the risk of SUD comorbidity is much higher for adolescent-onset versus child-onset BPD. Onset of pediatric BPD is generally either prior or simultaneous to the onset of SUD and severity of both the disorders is worse in the comorbid state. A higher than expected prevalence of anxiety disorders is documented in individuals with BPD. In the presence of

an anxiety disorder, individuals with BPD experience greater symptom severity, poorer treatment response, and poorer course and functioning. Hypersexuality in pediatric BPD is etiologically unrelated to sexual abuse and more reflective of dysregulation related to mania and puberty. BPD may be an antecedent risk factor for later trauma and subsequent PTSD and not merely represent a reaction to the trauma. There is an accumulating body of literature that suggests that a subset of PDD youth with extreme disturbance of mood suffer from a symptom cluster that is phenomenologically consistent with the syndrome of BPD and this is equally substantiated by family genetic studies that document a higher than expected incidence of BPD in first degree relatives of youth with PDD.

In general, the presence of comorbid disorders with BPD results in a more severe clinical condition. Earlier onset BPD seems to be related to additional comorbidity and more severe episodes and cycle acceleration. Identifying and treating these co-occurring psychiatric conditions may help alleviate the severity of impairment and duration of mood episodes in BPD.

Knowledge of the impact of comorbid disorders on the therapeutic response in youth with BPD is growing rapidly. BPD response to lithium is less robust in the presence of ADHD comorbidity. Stimulants are safe and efficacious for the treatment of comorbid ADHD once mania is stabilized in youth with BPD. Treatment of BPD with lithium or valporic acid results in attenuation of active SUD. In youth with BPD, the comorbid presence of lifetime OCD, but not GAD, is associated with poor antimanic response. Response to psychotropics in PDD youth with mood dysregulation is noted to be less robust with higher susceptibility to adverse effects.

The scientific interface between BPD and comorbidities remains unclear. Comorbidity may represent an important genetic and clinical subtype with distinct psychopathology, familiality, and cognitive, neural, and genetic underpinnings. Future longitudinal studies addressing the impact of comorbidity on the clinical presentation, course, and response to treatment along with studies examining the cognitive correlates, genetic-candidate genes, and neurobiological overlap would assist in further clarifying the relationship of BPD with its comorbidities.

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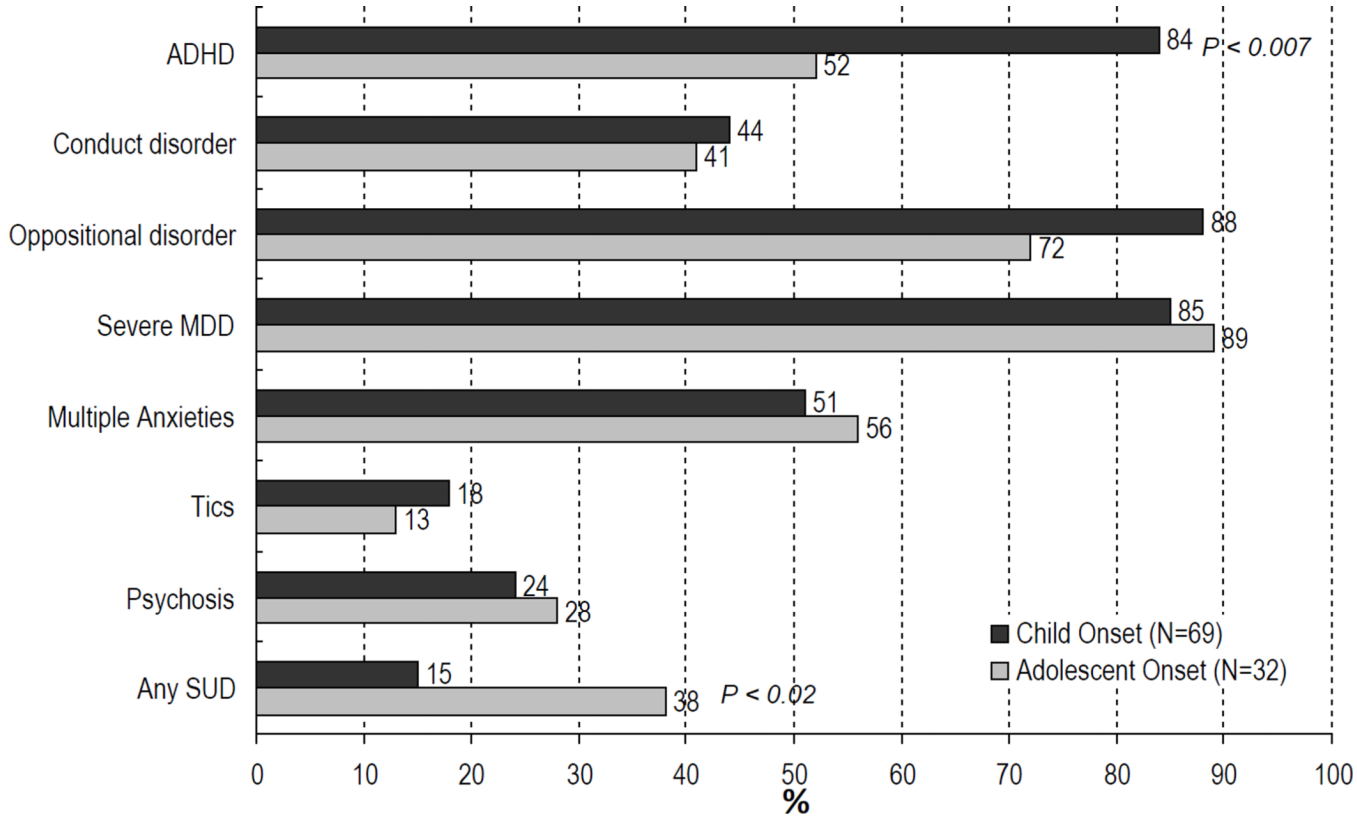

Figure-1.
Rates of Psychiatric Comorbidity in Bipolar Youth Stratified by Age at Onset of BPD

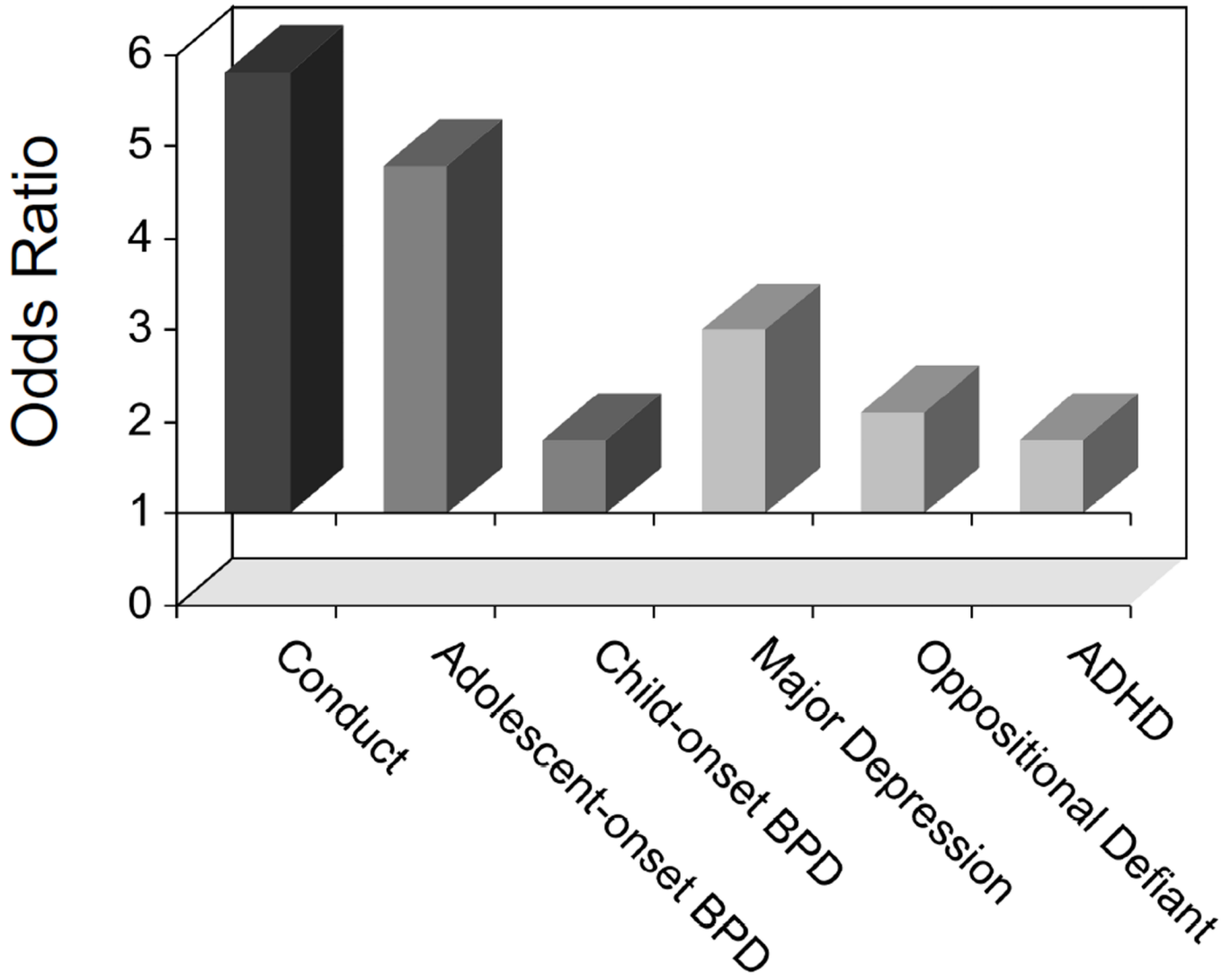

Figure-2.
Risk of SUD in Psychiatrically Referred Adolescent Outpatient Population

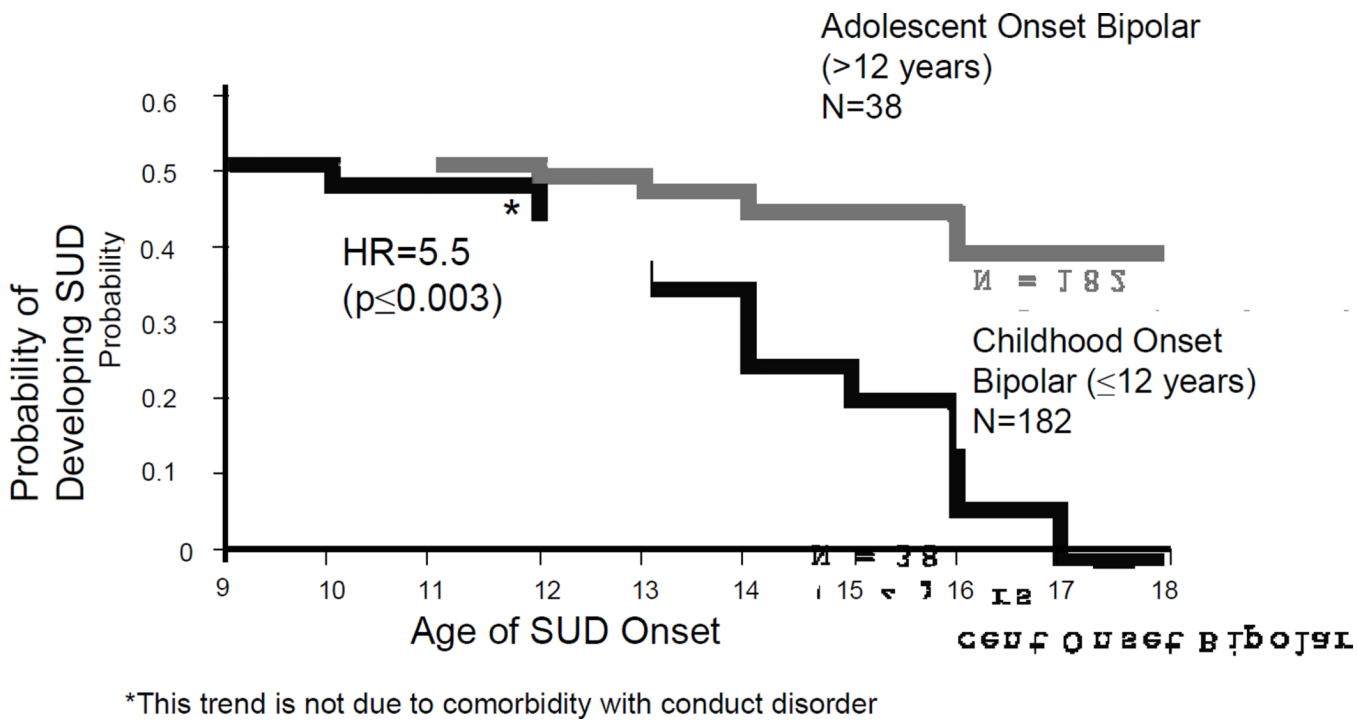

Figure-3.
Development of Substance Use Disorders in Child & Adolescent-Onset BPD Adolescent Onset Bipolar (>12 years) N=38

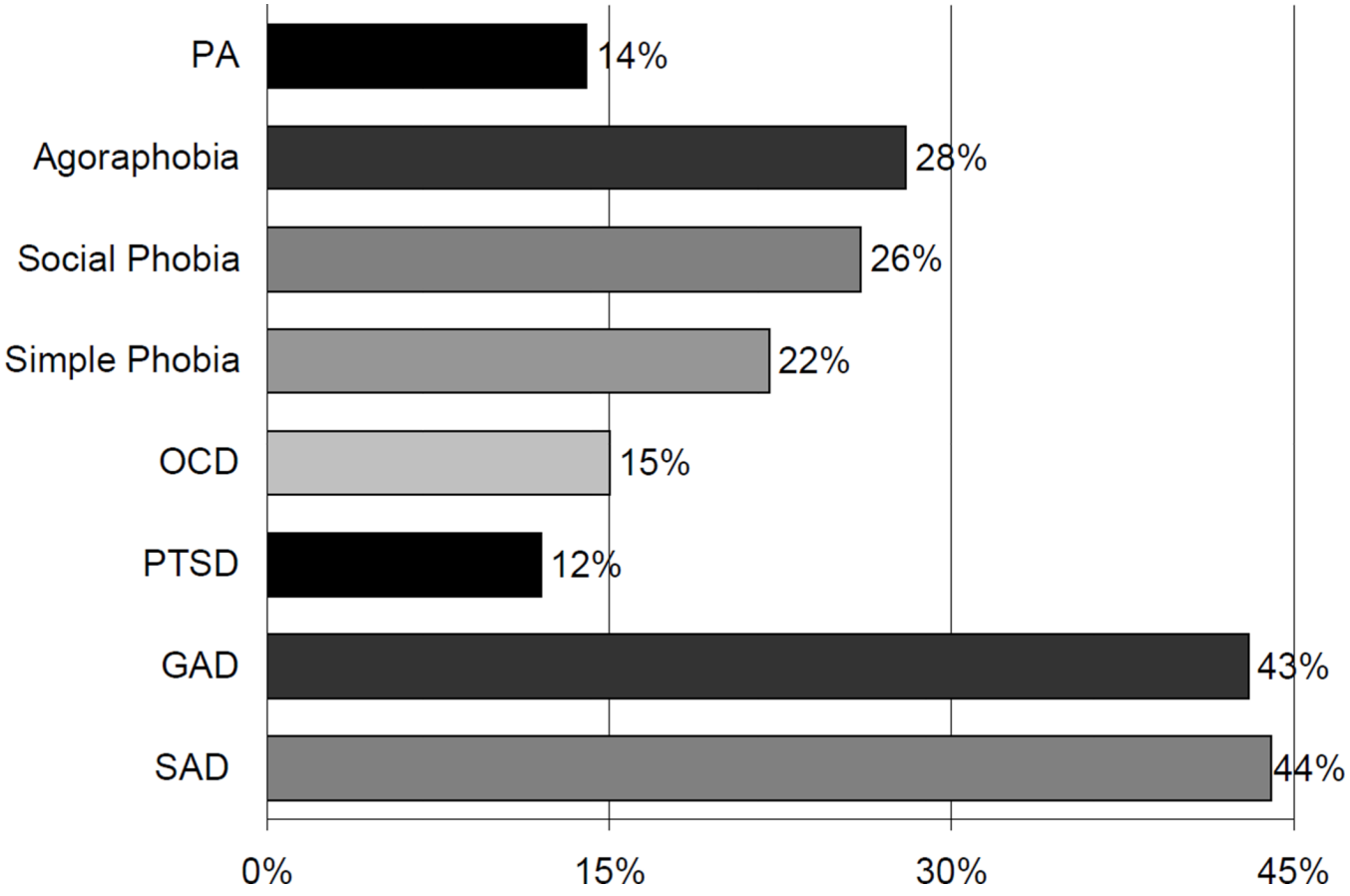

Figure-4.
Anxiety Disorders in Clinically Referred Youth with Bipolar Disorder

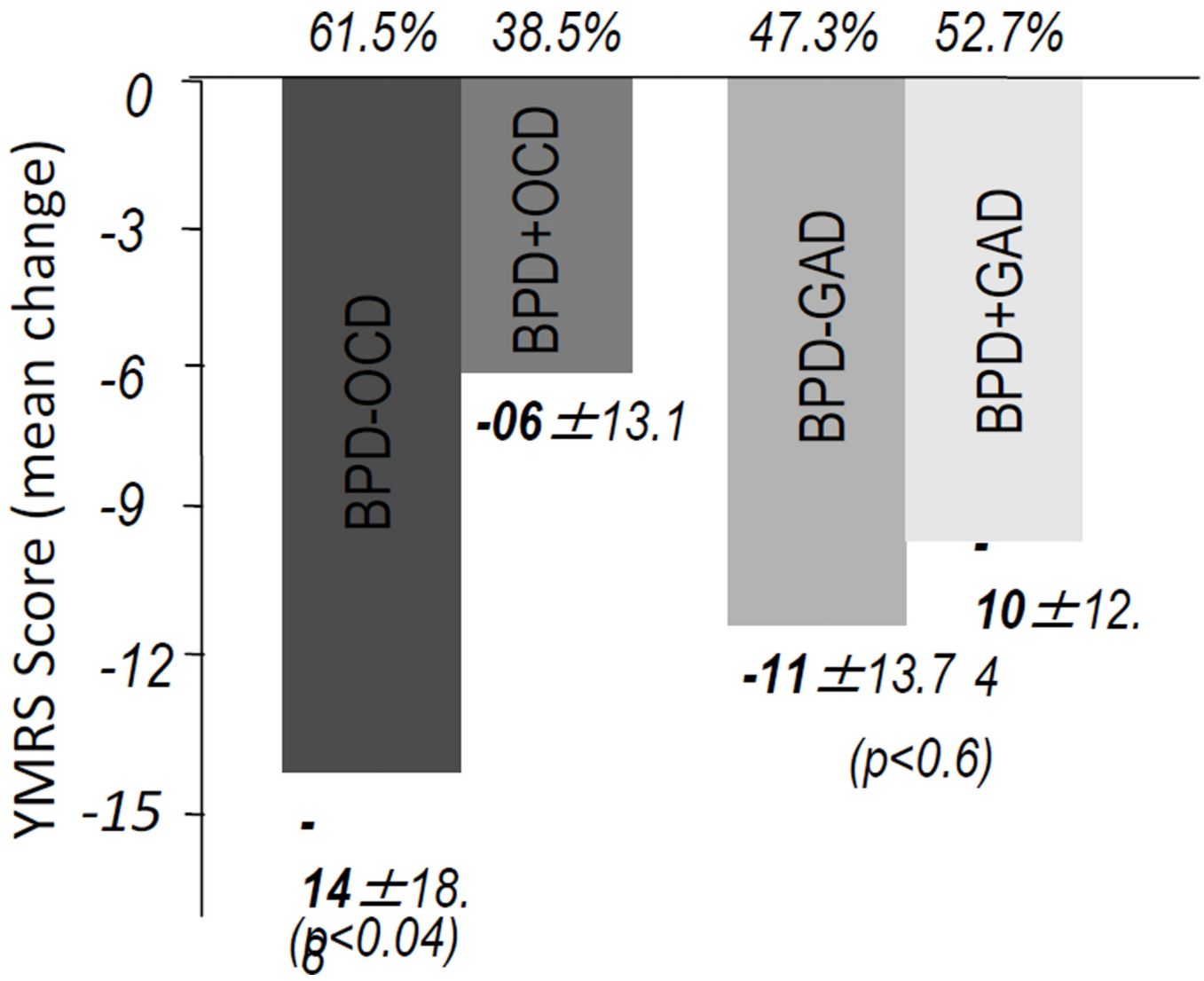

Figure-5.
Endpoint YMRS Score Mean Change BPD+OCD *Vs.* BPD+GAD