REVIEWS

Pediatric-Onset Bipolar Disorder: A Neglected Clinical and Public Health Problem

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Bipolar disorder (BPD), probably the most prevalent psychotic disorder in adults, has been relatively neglected or controversial in children and adolescents over the past century. We reviewed the literature on early-onset BPD.* Estimates of prevalence, particularly before puberty, are limited by historical biases against pediatric mood disorders and by formidable diagnostic complexity and comorbidity. Although clinical features of pediatric and adult BPD have similarities, pediatric cases probably cannot be defined solely by features characteristic of adult cases. Onset was before age 20 years in at least 25% of reported BPD cases, with some increase in this incidence over the past century. Pediatric BPD is familial more often than is adult-onset BPD, may be associated with a premorbid cyclothymic or hyperthymic temperament, and can be precipitated by antidepressant treatment. Pediatric BPD episodes frequently include irritability, dysphoria, or psychotic symptoms; they are commonly chronic and carry high risks of substance abuse and suicide. BPD is often recognized in adolescents, but the syndrome or its antecedents are almost certainly underrecognized and undertreated in children. Controlled studies of short- and long-term treatment, course, and outcome in this disorder remain strikingly limited, and the syndrome urgently requires increased clinical and scientific interest. (HARVARD REV PSYCHIATRY 1995;3:171–95.)

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See also "Developmental Subtypes of Juvenile Bipolar Disorder," by Joseph Biederman, later in this issue.

*Medline, Index Medicus, and Current List of Medical Literature were used to search the literature published between 1895 and June 1995; search terms were adolescents, bipolar disorder, carbamazepine, children, diagnosis, manic-depressive illness, lithium, mood disorders, onset, pediatric psychiatry, psychosis, suicide, and valproate.

"... in those periods of life with which much heat and blood are associated, persons are most given to mania, namely, those about puberty, young men, and such as possess general vigour."

— Aretaeus of Cappadocia, ca. 150 A.D.[1]

Bipolar manic-depressive disorder (bipolar disorder [BPD]) was included with a broader group of manic-depressive illnesses (MDIs) by Kraepelin[2] nearly a century ago. Such illnesses were later separated by polarity[3] and eventually divided into the current subgroups:[4] major depression without mania (unipolar depression), with mania (type I bipolar disorder), or with hypomania (type II bipolar disorder). BPD in adolescents (age 13–18 years) and even in children (age 12 years or less) was recognized and well described in antiquity by Aretaeus,[1] in the early 1800s by Esquirol,[5] and later by Kraepelin[2] and his contemporaries. Despite this long history of recognition, systematic studies of BPD in pediatric populations have been infrequent, perhaps reflecting an impression that BPD is an adult illness. Several reviews[6–21] consider pediatric BPD. The present overview considers the epidemiology, phenomenology, course, treatment response, and outcome of pediatric-onset BPD. The timeliness of such a review is evident in view of the recent recognition of BPD as the most prevalent psychotic disorder in the United States[21–24] and in North American psychiatric centers;[25] a reported shift toward an earlier age at onset of major mood disorders in this century, with high rates of morbidity, dysfunction, and suicidal behavior;[17,26–30] and emerging interest in the timely diagnosis and treatment of patients with major mood disorders at all ages so as to decrease morbidity and mortality.[12,13,21,31]

HISTORICAL BACKGROUND

Early clinical observations between the mid-19th and early 20th centuries accepted the presence of mania and clinical depression in children and adolescents, but from the 1930s to the recent past, BPD was widely considered to be rare before puberty. In 1838 Esquirol[5] described three cases of prepubertal mania and melancholia. In the 1880s Moreau de Tours[32] described excited psychotic states in children, Ritti[33] reported a pediatric case of circular psychosis (now BPD) starting at age 12 years, and Emminghaus[34] and his contemporaries[35] noted many symptomatic similarities between adult and pediatric mania and melancholia. Between 1900 and 1910, Soukhanoff and Gannouchkine[36] found an onset before age 15 years in 18% of 84 BPD patients, and Friedmann[37] distinguished three types of pediatric BPD: periodic psychosis with brief alternating episodes of depression and manic excitement and short euthymic intervals; isolated episodes of depression or excitement, sometimes related to stress; and brief episodes of mild depression or excitement

progressing to more-typical cyclic BPD in adulthood. Other authors,[38–41] anticipating recent studies of secondary mania,[21,42] observed isolated episodes of mania in medical conditions such as fever or neurological disorders (epilepsy, chorea, mental retardation). In his seminal early textbooks, Ziehen[40,41] classified BPD in children as involving single or recurring episodes of mania, or circular (bipolar) insanity, more commonly the latter. In the 1920s Rumke[39] described mania as the most frequent psychosis in children, Lange[43] observed that brief episodes and catatonic features were common, and Homburger[44] noted the frequent occurrence of anxiety and of mixed mood states in children with BPD. Since midcentury, several series of early-onset BPD cases have been reported. In 18 cases of major mood disorder before age 16 years, Campbell[45] found that a third represented BPD, that mild depression or mania were often misdiagnosed as other illnesses, and that many children severely ill with BPD had been diagnosed as schizophrenic. In children under age 11 with BPD, Spiel[46] reported rapid mood shifts, irritability, anxiety or apathy, and disturbed sleep to be common, and Stutte[47] found episodes to be shorter than in adults.

In the 1930s through the 1960s, clinical theorists[48–51] hypothesized that melancholia and mania were unlikely in children; they associated major mood disorders with dysfunction of the postpubertal or late adolescent superego and tended to include psychotic disorders of children with schizophrenia. The influential academic child psychiatrist Kanner[49] did not discuss major mood disorders of children in his textbook from 1935 to 1957. Bradley (who, by introducing the amphetamines, inaugurated the modern era of pediatric psychopharmacology[52]) stated in 1945[53] that BPD is very rare before puberty, and Lurie and Lurie[54] concluded in 1950 that it simply does not occur in childhood. These views, by limiting consideration of the possibility of BPD in pediatric populations, probably contributed to overlooking cases and using alternative diagnoses. Objective support for the postulated rarity of mania or melancholia in children was actually provided by case surveys, although these results may reflect a lack of recognition of the possibility of mood disorders in children and a corresponding lack of diagnostic criteria for them. In a 1952 retrospective case review of 2200 child and adolescent psychiatric patients aged 5–16 years evaluated clinically over many years, Barton Hall[55] found major affective disorders in only six patients and BPD in only two (a total of 0.091%), all over age 13 years, although she recognized cyclothymia and hypomania in children. In an important study Anthony and Scott[6] proposed operational diagnostic criteria for pediatric BPD in 1960, based primarily on contemporary conceptualizations of the adult syndrome. They could identify only three prepubertal cases of childhood-onset BPD in the literature and concluded, "occurrence of manic-depression in early

childhood as a clinical phenomenon has yet to be demonstrated." They did not assess BPD in adolescence, and their review as well Barton Hall's may well have reflected the diagnostic expectations of that era without necessarily authenticating them. As late as 1972, Rutter[56] again supported the hypothesis advanced[6,48-55] and sustained by others[57-59] that a postpubertal level of maturity is necessary to express and sustain mania and severe depression. Carlson[60] investigated the role of puberty in the phenomenology of affective symptoms in pediatric BPD to test this hypothesis in 1980, concluding that cognitive maturation influences mainly the content of manic or depressive preoccupations.

This background of both theoretical and clinical bases for doubting a common occurrence of adultlike melancholic or manic conditions in pediatric populations limited interest in pediatric BPD in some centers well into the 1970s,[11,57] despite clinical observations of mania and melancholia in the young since antiquity.[1,61] Interest in BPD was greatly stimulated by the discovery and clinical application of the antimanic effects of neuroleptic drugs, and of the antimanic and mood-stabilizing effects of lithium salts and certain anticonvulsants.[17,21,62-67] In a 1976 review on childhood mania, Weinberg and Brumback[7] further piqued interest in the disorder by recommending new diagnostic criteria based on those proposed for adult mania by Feighner and colleagues.[68] Similar criteria for a childhood variant of BPD syndrome were then proposed by DeLong[64] and Davis.[69] Recent American Psychiatric Association (APA) diagnostic criteria[4] have also extended application of adult criteria for mania to adolescents and children. In one of the few population-based pediatric epidemiological studies to include BPD as a possible diagnostic category, Lewinsohn and co-workers[17] recently found a lifetime prevalence of BPD of 0.90–1.41% in samples totaling over 1700 adolescents, and of milder BPD-like symptoms in as many as 9.0%. Most of the BPD cases involved bipolar II disorder or cyclothymia; only two cases of type I disorder were identified (apparent morbid risk < 0.2%). Although the reported risk for adolescent bipolar I disorder is low, this level of risk of conditions diagnosed as BPD is strikingly similar to recent estimates of 1-year or lifetime morbid risks for BPD of 1.2–1.5% in general adult populations, compared to rates of only 1.0% or less for schizophrenia combined with other idiopathic psychotic disorders.[22-24] Lewinsohn and colleagues[17] noted that previous similar epidemiological studies in pediatric psychiatry had not even considered BPD as a possibility!

A fundamental psychopathological and syndromic similarity of pediatric and adult BPD is assumed by current diagnostic schemes. Whether or not such an assumption is valid, it must affect the findings and conclusions of this review. Its validity is least secure with respect to prepubertal presentations of conditions later recognized as typical major affective illness in adolescents or adults. BPD may actually be rare before puberty, or more likely, it may occur in early subsyndromal or precursor forms that are not typical of adult BPD.[10,11,17,20,21]

CONTEMPORARY DIAGNOSTIC CHALLENGES

The diagnosis of BPD in children and adolescents presents many challenges to avoid under- or overdiagnosis, to consider differential diagnosis and comorbidity, and to minimize substance abuse, suicidal acts, and other risky behaviors.* Rarely have diagnostic standards specifically applicable to pediatric populations been developed and field-tested. Some BPD-like behaviors (such as adolescent emotional turmoil and moodiness, willfulness, egocentrism, bravado, and risk-taking) are relatively common in youth and diagnostically nonspecific. Diagnostic assessment is further complicated by comorbidity. BPD is to be differentiated from attention-deficit hyperactivity disorder (ADHD) and disorders of development, conduct, or personality, early schizophrenia and other psychoses, neuropsychiatric disorders, anxiety, and substance use disorders. Finally, concern about stigmatization can discourage diagnosis of conditions in children that may require prolonged medical treatment, supervision, or hospitalization, with an uncertain or potentially gloomy long-term prognosis.

Such diagnostic difficulties are not new: as early as 1931, Kasanin[76,77] found that a quarter of pediatric-onset BPD cases were misdiagnosed. Current diagnostic formulations such as the APA's *Diagnostic and Statistical Manual*[4] (DSM) or the Research Diagnostic Criteria are somewhat effective in diagnosing pediatric BPD but may miss early prodromes by assuming that adult psychopathology is a sufficient model. Despite the probable limitations of extending adult criteria to pediatric psychopathology, BPD can be reliably differentiated, at least from schizophrenia and ADHD, in pediatric populations.[19,45,78,79] Diagnostic reliability may be greater in adolescents than in prepubertal children, especially given information on family history and long-term follow-up; even diagnoses of major mood disorders made cross-sectionally can probably be reasonably reliable in adolescents if current diagnostic criteria are used.[80-82]

For many years, an especially serious source of confusion was the broad and uncritical application of the diagnosis of schizophrenia or childhood psychosis in the differential assessment of idiopathic psychotic, pervasive developmental, and severe behavioral syndromes in pediatric psychiatry.[10,11,16,45,80-86] This source of variance, by itself, can account for perhaps half to three-quarters of misdiagnoses, based on application of recent DSM criteria aided by pro-

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*References 17, 20, 33, 37, 45, 50, 65, 68, 70–75.

longed follow-up.[85,86] The failure to differentiate pediatric BPD from schizophrenia or schizoaffective disorders has been particularly common in the manic phase of BPD.[85-87]

Prominent hyperactivity and impaired concentration make consideration of ADHD an important differential diagnosis in early BPD, and the two are strongly related. Since these syndromes share features, misdiagnosis may occur, probably more often in children than in adolescents.[20,79,82,88] Many children later considered to have BPD present with behaviors supporting a simultaneous diagnosis of ADHD,[17,20,79] although BPD is not common in the larger ADHD group.[13,19,20,89-91] A recent study by Wozniak and her colleagues[20] helps to clarify this relationship: 91% of children evaluated with current or previous mania also met criteria for ADHD, while only 19% with a diagnosis of ADHD also met DSM-III-R criteria for current or previous mania. Similar diagnostic distributions persisted even after elimination of obviously similar symptoms found in both syndromes, such as hyperactivity, talkativeness, and distractibility. The overlap of ADHD and BPD may diminish with maturation, since a recent large population study[17] found ADHD in only 8.7% of adolescents with relatively mild BPD, although conduct and oppositional-defiant disorders added another 14.8% comorbidity. The nature of ADHD as a prodrome, phenocopy, comorbid condition, or misdiagnosis with respect to pediatric BPD may become clearer with long-term follow-up of pediatric ADHD patients.

A common problem is prediction of future bipolarity in pediatric patients who present with depression. Suggested predictive features include psychomotor retardation, hypersomnia, hyperphagia, psychotic features, multiple relatives with affective illness, and new agitation or hypomania during antidepressant treatment.[79,92] There is insufficient information to estimate with confidence the proportion of pediatric patients with depression or dysthymia who later manifest typical BPD, but it is high. More than half of cases eventually diagnosed as BPD probably start as depression,[9,11,16,17,93-99] and the risk of developing BPD has averaged 21.0 ± 9.7%* within several years after onset of major depression or dysthymia.[94-97]

Less information is available on differentiation of pediatric BPD from alternative or comorbid conditions, such as anxiety, conduct, developmental, personality, or substance use disorders. Several studies[17,20,100,101] report that 30–50% of youngsters with BPD also have anxiety disorders. Famularo and colleagues[102] found BPD or cyclothymia in 70% of preadolescents abusing alcohol; conversely, substance abuse was reported in about a third of young BPD patients.[17,85,103]

A DSM personality disorder was also found during euthymic periods in about a third of adolescents with BPD.[104] Secondary pediatric BPD has been associated with neuropsychiatric or developmental disorders, including Tourette's syndrome[105] and mental retardation.[106-108]

PRESENTATION VERSUS AGE OF ONSET

In children hyperactivity is perhaps the most typical behavioral manifestation of mania, although psychosis has often been reported as well.[83,109] Prepubertal children, particularly those below age 8 years, commonly present with irritable or labile mood in mania;[20] grandiosity has also been observed.[110] In many children with BPD, mood changes typically are relatively brief (hours or days) and labile, sometimes with tantrumlike "affective storms"; the course of the mania is often less clearly episodic than in adolescents or adults, and sustained irritability, dysphoria, or lability, as well as functional impairment, are common.[7,33,79] In older children and adolescents mania is likely to present as a syndrome similar to that in adults, with a more clearly episodic course, euphoric-irritable mood, grandiosity, racing thoughts, and flight of ideas.[79]

Assessments of symptoms of mania in children, adolescents, and adults† yield some data permitting quantitative comparisons (see Table 1). These pooled observations indicate that psychomotor hyperactivity was common in mania at all ages. Symptoms of manic excitement (pressured speech, flight of ideas, euphoric elation, and grandiosity) often considered typical in adults tended to rise with maturation or to be more prevalent in adults. The general similarity of symptoms in pediatric and adult mania may reflect some circularity in case identification and need not exclude the possibility that BPD may present with a dissimilar symptom pattern in some children. Dysphoric irritability marked a majority of juvenile BPD cases at all ages, suggesting that mixed mood states may not be unusual in pediatric populations. Delusions and hallucinations tended to be somewhat more common in children or to decrease in frequency with age. Psychotic features may be overrepresented in cases recognized as early mania, while nonpsychotic manic children are probably underrecognized or considered to have other disorders such as ADHD or a conduct disorder. The distribution of symptom frequencies by age supports clinical impressions that manic symptoms are similar in adolescents and adults but may differ in children. The tentative pattern in children with probable mania is a predominance (> 50% of cases) of hyperactivity, insomnia, irritability, and perhaps psychotic features; pressured

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*Numerical data throughout this paper are expressed as means ± SD unless otherwise noted.

†References 20, 69, 78, 85, 87, 89, 96, 99, 110–127.

TABLE 1. Frequency (%) of Symptoms in Pediatric and Adult Mania*

Symptoms	Children (n = 16)	Adolescents (n = 117)	Adults (n = 32)	χ^2	p
Hyperactivity	100.0	73.5	96.9	9.9	< 0.01
Delusions	75.0	68.4	53.1	3.2	NS
Distractibility	68.8	47.9	43.8	2.8	NS
Irritability	68.8	55.6	81.2	7.4	< 0.05
Hallucinations	56.2	31.6	37.5	3.8	NS
Pressured speech	50.0	75.2	100.0	11.6	< 0.01
Euphoria/elation	43.8	73.5	84.4	8.9	< 0.02
Flight of ideas	43.8	67.5	71.9	4.2	NS
Grandiosity	25.0	63.2	81.2	14.5	< 0.001

*Data are pooled and reanalyzed from previous reports.[19,69,85,92,112,113,116,117,120–122] Note that items are ranked by their frequency in children. χ^2 tests are based on overall analyses of 3 × 2 contingency tables for an effect of age; NS = p > 0.05. By rank correlation across symptom frequencies, adolescents resembled adults (r_s = 0.61, p = 0.055) more closely than they did children (r_s = 0.24, p = 0.44) or than children resembled adults (r_s = 0.21, p = 0.51). Insomnia was also observed in a majority of children and adolescents, whereas hypersexuality was recognized in only a minority of children. The relatively high risk of psychotic features may, to some extent, reflect biased consideration of bipolar disorder in severely ill children and adolescents in the past.

speech, flight of ideas, euphoria, and grandiosity are less common than in adults (see Table 1).

AGE OF ONSET

Onset of typical, primary BPD in late adolescence and early adulthood is common,* but several potential confounding factors need to be considered in evaluating the age at onset of juvenile BPD: (1) Some studies probably include BP-II cases, cyclothymia, or recurrent depression as manic-depressive disorders. (2) Depressive, hypomanic, or mixed BPD episodes, continuing as such or only later presenting with mania, can lead to underdiagnosis of BPD. (3) Combining adolescent and early adulthood–onset cases precludes separate assessment of adolescent risk. (4) Overdiagnosis of conduct disorder, ADHD, or schizophrenia or other psychotic disorders tends to exclude pediatric BPD. (5) Arbitrary exclusion of cases starting before age 18 years has sometimes precluded consideration of earlier BPD. (6) The assumption that BPD is an illness of adulthood limits its consideration in pediatric populations. Furthermore, most of the studies reviewed that estimated juvenile risk of BPD failed to use well-defined diagnostic criteria, rigorous epidemiological methods, and prospective assessments or did not provide follow-up information. With these caveats, reported rates of early onset of nearly 20,000 cases of BPD (almost all with mania)† are summarized (see Table 2). Since the majority of studies found reported on illness observed before age 20,

early-onset BPD is defined, accordingly, as starting before then.

The rate of early-onset BPD averaged 25 ± 15% but ranged from 6%[111,132] to 58%.[141,144] Similar to recent researchers, Kraepelin[2] and his contemporaries Lange[43] and Wertham[130] recognized that BPD rather frequently begins before adulthood (in 34.8%, 20.0%, and 18.0% of cases, respectively), and that at least 18% of those with early depression eventually manifested mania.[130] Rates of early-onset BPD have tended to rise since the 1920s, with a significant rank correlation of rate versus year (r_s = +0.47, p = 0.01; see Table 2). This increase may reflect actual changes in the nature of major affective disorders through this century, with rising risk and earlier onset in succeeding generations;[26–30] alternatively, it may reflect increased interest in BPD with the application of lithium and other effective modern treatments, and an associated increase of awareness of major mood disturbances in pediatric populations.[12,21,25,145] Additional evidence of the common onset of BPD in adolescence or perhaps childhood is that the mean age of onset in BPD in the recent national Epidemiological Catchment Area study of nearly 19,000 persons in the general population[22] was found to be 21.2 years, suggesting that a large proportion of contemporary cases were recognized to have started before age 20 years.

GENDER DIFFERENCES

In adults the reported risk ratio of female to male cases of BPD is close to unity.[12,144] Data on 2168 patients with pediatric-onset BPD were obtained from a total of 34

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*References 41–43, 70–72, 111, 112, 128–130.
†References 2, 86, 87, 89, 92, 111–113, 115–117, 123, 127, 130–144.

TABLE 2. Proportion of Bipolar Disorder Cases with Onset before Age 20 Years

Study	Year	Criteria	Proportion*	%	Comments (ages in years)
Kraepelin[2]	1921	Clinical	654/1704	38.4	Mania before age 20
Kasanin & Kaufman[111]	1929	Clinical	4/65	6.2	Hospitalized, psychotic before age 16
Wertham[130]	1929	Clinical	360/2000	18.0	First admission for mania, onset before age 20
Paskind[112]	1930	Clinical	91/615	14.8	MDI with mania, onset before age 20
Pollock[131]	1931	Clinical	417/4737	8.8	First psychotic admission before age 20 (1918–1922)
Olsen[132]	1961	Clinical	28/450	6.2	Hospitalized before age 19
Winokur et al.[113]	1969	RDC	34/100	34.0	Bipolar, onset before age 20
Taylor & Abrams[133]	1973	RDC	15/50	30.0	Onset before age 20
Hudgens[115]	1974	RDC	13/110	11.8	Random inpatients aged 14–19
Carlson[116]	1977	RDC	28/100	28.0	Manic onset before age 20
Petterson[117]	1977	Clinical	24/123	19.5	First episode before age 20 (5% manic)
Loranger & Levine[134]	1978	Feighner	40/200	20.0	Onset before age 20
Welner et al.[135]	1979	Feighner	12/77	15.6	Hospitalized adolescents
Coryell & Norten[136]	1980	DSM-III	20/41	48.8	First admission in adolescence
Strober & Carlson[92]	1982	Feighner	12/60	20.0	Depressed, aged 13–16, 3- to 4-yr outcome
Baron et al.[137]	1983	Feighner	18/142	12.7	First symptoms before age 20
Gammon et al.[138]	1983	RDC	4/17	23.5	Inpatients, aged 13–18
Rosen et al.[139]	1983	RDC	13/71	18.3	Based in lithium clinic
Smeraldi et al.[140]	1983	DSM-III	28/120	23.3	Onset age 12–20
Joyce[87]	1984	DSM-III	60/200	30.0	23% treated, 26% hospitalized before age 20
Akiskal et al.[89]	1985	Feighner	16/68	23.5	Relatives of BPD patients, referred for clinical evaluation
Egeland et al.[141]	1987	RDC	22/38	57.9	First episode before age 20
Carlson & Kashani[123]	1988	DSM-III	20/150	13.3	Hypomanic, aged 1–16
McGlashan[86]	1988	DSM-III	35/66	53.0	Onset before age 20
Zis[142]	1990	NA	21/105	20.0	First symptoms before age 20
Faedda et al.[143]	1993	DSM-III-R	13/38	34.2	On lithium, onset before age 20
McMahon et al.[144]	1994	RDC	124/214	57.9	Onset ages for BP-I = BP-II
Tondon[127]	1995	DSM-III-R	55/247	22.3	Bipolar I and II, onset before age 20
Total/mean ± SD	(28 reports)		2,181/11,908	25.4 ± 14.6	

DSM, APA *Diagnostic and Statistical Manual of Mental Disorders*;[4] *Feighner*, Washington University–St. Louis criteria (see references 115, 116); *NA*, not available; *RDC*, Research Diagnostic Criteria.

*The numerators are early-onset cases, and the denominators represent all cases of BPD; weighted mean rate of early onset = 18.3%, median = 20.0% (range = 6.2–57.9%); the proportion of cases with reported early onset rose over the years (rank r_s = 0.430, p = 0.028).

studies.* (Case reports or series with fewer than four subjects were excluded.) The resulting overall risk ratio showed only a slight excess of females (1134:1033), similar to gender-based incidence ratios in adult BPD.[11,21] However, if only cases with prepubertal onset are considered, BPD was diagnosed 3.85 times as often in males as in females (50 male and 13 female subjects in 63 cases).[20,63,68,81,124] It is not clear whether this suggestive evidence of early recognition of BPD in boys is due to a true gender difference in age of onset or to differences in presenting symptoms. For example, disruptive or aggressive behaviors in boys with mania may lead to early recognition and intervention; also, comorbid ADHD[20] may call attention to boys with BPD. Since other work[144] suggests that age of onset of BPD may be younger in girls, this matter requires further study.

FAMILY HISTORY

The importance of hereditary factors in the etiology of mood disorders was recognized early,[39] and the topic has been reviewed extensively.[151,152] Assessment of familial risk of BPD or major depression has usually relied on determining morbid risk among first-degree relatives of index cases, including the offspring of affected parents, who are presumably at high risk. Many studies pertaining to familial risk of pediatric-onset BPD are limited by inconsistent methods of diagnosis and case ascertainment, reliance on reported family history rather than direct examination, or lack of comparison or control groups to support diagnostic specificity. A particular problem for family studies of BPD, especially in older and international studies in which BPD often was not considered as a distinct diagnostic group within the MDI spectrum, is the tendency to mix these disorders with recurrent unipolar major depression.

Ziehen[41] proposed in 1917 that a family history of mood disorder is the single most important risk factor for the development of "circular insanity" (BPD) and found such a family history in 60% of a large case series. Other observers also found affective illness, including cases of pediatric onset,† to be common in family members of patients with BPD.[2,45] The overall familial risk of major affective disorders in relatives of BPD index cases averages 51%. In a limited subset of studies with comparative data, familial risk of mood disorders among relatives was much greater than risk for substance use (21%) or anxiety disorders (12%), suggesting some specificity of the association (see Table 3).

As in adult BPD, familial risk in pediatric BPD includes recurrent depression, with an uncertain proportion of cases representing a BPD spectrum or group of related disorders — bipolar II disorder, recurrent mania, cyclothymia, and perhaps some forms of schizoaffective or episodic psychosis.[144,152] In previous reviews of 21 family studies of BPD

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*References 17, 20, 45, 62, 63, 68, 74, 78, 81, 85-87, 100, 102, 108, 111, 112, 115-117, 119, 123-125, 130-132, 136, 137, 146-150.
†References 60, 78, 85, 92, 110, 119, 124, 133, 136, 153-158.

probands with any age of onset,[152,157] the weighted mean morbid risk in first-degree relatives was somewhat greater for nonbipolar depression (11.6%) than for BPD (7.3%). Familial risk for mood disorders, and perhaps for BPD in particular, may be especially strongly associated with BPD of pediatric onset. In some of the 16 studies of BPD with relatively early onset summarized in Table 3, familial risks of unipolar depression (28.5%) and BPD (29.8%) were similarly high, and several studies found familial mood disorders of all types to be especially common with juvenile BPD probands; overall, BPD itself was 4.1 times as prevalent in the relatives of young BPD patients as in the relatives of BPD patients of any age.[110,151,152,157] Familial risk may even differ within the juvenile BPD population: Strober and colleagues[155] found that patients with childhood-onset BPD more often had BPD in first-degree relatives and a poorer response to lithium than did those whose BPD started during adolescence. Familial risk may include milder forms of cyclic mood changes: Carlson[60] found a family history of BPD or cyclothymia in up to 95% of patients whose BPD began before age 12 years.

Studies of children of affectively ill parents also indicate high risks of mood disorders including BPD in their children. Klein and coworkers[159] found mood disorders to occur 7.6 times as often in children with at least one affectively ill parent (38%) as in those without (5.0%), and Gershon and colleagues[160] reported the risk of mood disorders in offspring if none, one, or both parents were affected to be 8%, 27%, and 74%, respectively. Family studies involving parents with BPD indicate a very high familial association with pediatric mood disorders. In a prospective investigation of 68 offspring and younger siblings of patients with BPD, Akiskal and colleagues[89] found that 57% were diagnosed with a BPD during 4 years of follow-up (bipolar I, 28%; bipolar II, 17%; cyclothymia, 9%; rapid cycling, 3%). These and other findings[28,122,126] suggest that BPD types I and II may both occur in the same pedigrees rather than existing as separate clinical entities. O'Connell and coworkers[118] found various psychiatric disorders in 45% of 22 children (ages 7–17) who had at least one parent with BPD. High risks (25–38%) of mood disorders in children or adolescents of parents with BPD have been reported by several[120,121,161–165] but not all[166] groups. Assessments of relatives of children with ADHD also support a familial relationship between that syndrome and BPD.[167]

This compelling body of evidence for a strong familial risk of BPD, particularly in relatives of early-onset BPD probands, strongly encourages early recognition of pediatric mood disorders as well as vigorous searches for genetic markers of BPD to help differentiate it from unipolar depression, schizophrenia, schizoaffective disorders, periodic psychoses, ADHD, and other disorders. Initiation of genetic studies based on pedigrees identified by early-onset cases may be a particularly powerful strategy due to the high association of pediatric onset with abundant familial expression.[168] In addition to the genetic implications of the high familial risk for major mood disorders, there is also

TABLE 3. Family History in Probands with Pediatric-Onset Bipolar Disorder*

Study	Year	n	Criteria	Familial risk of disorders (%)			Comments
				Affective†	Substance‡	Anxiety‡	
Landolt[153]	1957	60	Clinical	75	NA	NA	Probands hospitalized before age 22
Taylor & Abrams[133]	1973	50	RDC	44	46	NA	144 relatives; proband onset before age 30
Brumback & Weinberg[63]	1977	6	Weinberg	83	NA	NA	Proband onset before age 14
Horowitz[78]	1977	8	RDC	25	25	NA	Probands hospitalized before age 18
Carlson[60]	1980	28	Feighner	54	Rare	Rare	Proband onset before age 20
Coryell & Norten[136]	1980	20	DSM-III	70	NA	NA	Probands hospitalized before age 20
Hassanyeh & Davison[119]	1980	10	Weinberg	60	NA	NA	Proband onset before age 16
Strober & Carlson[92]	1982	12	RDC	92	NA	NA	Probands: BPD in 3- to 4-yr follow-up
Sylvester et al.[110]	1984	2	Clinical	100	50	NA	Probands prepubertal
Hsu & Starzynski[85]	1986	14	DSM-III	79	21	NA	Probands aged 14–19
Dwyer & DeLong[154]	1987	20	DSM-III	41	20	21	249 relatives of 20 children
Strober et al.[155]	1988	50	RDC	45	6	3.5	523 relatives of probands aged 13–17
Varanka et al.[124]	1988	10	DSM-III	70	60	NA	Probands aged 6–12
Kutcher & Marton[156]	1991	23	DSM-III	33	NA	NA	Probands aged 13–19
Pauls et al.[157]	1992	22	RDC	30	NA	NA	Probands under age 20, risk age-corrected
Wozniak et al.[158]	1995	16	DSM-III-R	37	NA	NA	Prepubertal BPD + ADHD probands
Totals/mean ± SD§	(16 studies)	351		51.3 ± 20.4	20.6 ± 12.3	12.2	

DSM, APA *Diagnostic and Statistical Manual of Mental Disorders;*[4] *Feighner*, Washington University–St. Louis criteria (see references 115, 116); *n*, number of pediatric BPD probands; *NA*, data not available; *RDC*, Research Diagnostic Criteria; *Weinberg*, Weinberg & Brumback.[7]

*Familial risk of BPD reported in 11 studies (indicated in *italics*) involving 195 probands averaged 29.8 ± 23.6%; risk of unipolar depression in 7 studies (indicated in **boldface**) involving 149 probands averaged 28.5 ± 23.1%.

†Median familial risk for major affective disorders = 65.0% (range = 25–100%).

‡Data concerning the familial risk of substance use and anxiety disorders are very limited and therefore provide only highly tentative impressions.

§All means are weighted by n/study.

a developmental impact of being raised in a family whose members have mood disorders.[169]

PREMORBID CHARACTERISTICS AND PRECIPITANTS

In his early clinical observations, Kraepelin[2] reported that, prior to acute episodes of mania, young patients often had an assertive or gregarious personality type that could be considered extroverted. This observation was later supported by Campbell,[45] and Barton Hall[55] proposed that

pronounced cyclothymic traits or affective lability in childhood may predispose a person to adult BPD. Dysthymic as well as cyclothymic and hyperthymic features have often been found in children of patients with BPD, further suggesting the presence of inherited traits or prodromal dysregulation of mood prior to the onset of overt BPD.[99,156,170] Such early affective features have by no means been found consistently. In a study of six pediatric BPD patients previously diagnosed as schizophrenic,[147] only two were considered to have been extroverted, while four were described as

having been more reserved and less socially competent than their peers. Moreover, Hassanyeh and Davison[119] found extroverted-cheerful and quiet-withdrawn premorbid personality traits to have been equally common in ten patients with onset of mania before age 16 years, while Hsu and Starzynski[85] found no historical evidence of psychiatric disturbances in 14 adolescent BPD patients prior to the onset of affective disorder.

Although premorbid extroversion, cyclothymia, emotional lability, or dysthymia have not been found consistently in the backgrounds of pediatric BPD patients, other forms of psychopathology have been reported. These include evidence of disorders of personality, conduct, attention, anxiety, and substance abuse.[20,100,101,171–174] Among 30 adolescents with BPD, evidence of prodromal or comorbid psychopathology included anxiety disorders (53%), self-destructive behavior (20%), substance abuse (10%), anorexia nervosa (3%), hyperactivity (3%), and conduct disorder (3%).[100] A high risk of early anxiety was also found in 63% of 43 prepubertal children with BPD.[20] In another 20 then-euthymic adolescents diagnosed with BPD by DSM-III-R criteria, 35% also met criteria for a personality disorder and were less responsive to lithium and more likely to be given a neuroleptic than those lacking such comorbidity.[104] Early BPD is commonly associated with comorbid conduct disorders, including oppositional-defiant behavioral syndromes.[17,175,176]

When such traits or symptoms as described above arise prior to the diagnosis of BPD, they may be predisposing factors or comorbid conditions; alternatively, they have often been assumed to represent attenuated early prodromal forms of BPD. Conclusions would require more-adequate follow-up of subjects at risk. Recognition of antecedents of adult BPD and refinement of syndromal descriptions of early BPD require further testing by long-term follow-up of children with suspected BPD or of the children of adults with the disorder.

An association of environmental factors and stressful life events with the onset of BPD in children and adolescents also remains unclear. Kraepelin[2] and Ziehen[41] were among the first to propose that stressful emotional, environmental, and medical factors may play a special role in MDI. Neuromedical illnesses have been viewed as either stressful precipitants or possible causal factors in secondary juvenile BPD. Some recent studies[100,177] support an association between emotional distress or medical illnesses with early BPD episodes, although others[45,178–180] found only minor, infrequent, or inconsistent associations or no consistently different frequency of such factors prior to manic or depressive episodes in children and adults. Stressful life events or somatic illnesses may contribute to the timing of onset of acute episodes in some predisposed persons. Early-onset BPD can also arise independent of obvious precipitating factors as an apparently endogenous disorder. Given the

disagreement in the studies cited, there may well be a spectrum of sensitivity to environmental or psychogenic stressors in predisposed or genetically vulnerable persons.

TYPE OF ONSET

Typically, the first clinically noteworthy major affective episode (manic, depressive, or mixed) is considered to represent the onset of illness. Early presentations, particularly of mild symptoms, are probably commonly misidentified or overlooked in children. Manic onsets are likely to be more readily identified and less well tolerated by families and schools. Recall bias also may lead to underreporting of past hypomanic or depressive episodes or of even-less-obvious prodromal symptoms or aberrant behaviors. Pediatric BPD may start in a majority of cases with mild mood or behavioral disturbances, particularly dysphoric irritability or depression, with manic episodes arising later either spontaneously or in response to antidepressant treatment.

Recent estimates place the risk of depression in children at about 2–5%, and perhaps 20% of depressed children later manifest bipolarity before adulthood, suggesting a prevalence of BPD in children of about 0.4–1.0%.[11,181,182] Prospective follow-up studies of children with major depression have found that 32% of children with major depression[95] and 16% of those with dysthymia[97] later developed BPD. These findings indicate that depression is a common mode of onset or a risk factor for BPD. In 68 children or younger siblings of adult BPD patients, Akiskal and colleagues[89] reported that approximately half were later diagnosed with BPD. Among those who eventually proved to have BPD, the initial manifestation was depressive in 35% and manic or mixed in only about 12%, while nearly half presented with a "subaffective syndrome" of insidious or subacute onset or with polysubstance abuse.[89,99] In their study of prepubertal children with mania, Wozniak and coworkers[20] found a depressive onset in 44%, a manic onset in 19%, and a mixed onset in 37%. In 115 cases of BPD-like disorders diagnosed in adolescence, Lewinsohn and colleagues[17] found that onset occurred at an average age of 11.8 years and was depressive in 61%.

Available data on the reported types of onset of BPD among children and adolescents* (see Table 4) indicate that many cases of pediatric BPD present as states other than acute mania, with depressive episodes being slightly more frequent (45%) than the sum of manic and mixed mood states (42%).

MIXED STATES

Some pediatric BPD patients present with very rapid alternations or admixtures of manic and depressive

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*References 20, 78, 85, 87, 89, 115, 116, 119, 124, 125, 127.

TABLE 4. Type of First-Diagnosed Episode in Pediatric Bipolar Disorder

Study	Year	n	Criteria	Ages (y)	Type of episode (%)*		
					Manic	Depressed	Psychotic
Hudgens[115]	1974	11	Feighner-like	14–19	54.5	45.5	40.5
Carlson et al.[116]	1977	28	Feighner	8–19	35.7	64.3	NA
Horowitz[78]	1977	8	Clinical	15–18	62.5	12.5	100.0
Hassanyeh & Davison[119]	1980	10	Weinberg	12–15	40.0	60.0	80.0
Joyce et al.[87]†	1984	60	DSM-III	1–19	48.3	50.0	≥ 70.0
Akiskal et al.[89]‡	1985	68	Feighner	6–24	11.8	35.3	11.8
Hsu & Starzynski[85]§	1986	14	DSM-III	14–19	50.0	42.9	85.7
Varanka et al.[124]	1988	10	DSM-III	6–12	70.0	30.0	100.0
Ghadirian & Roux[125]	1993	18	DSM-III	13–18	16.7	38.9	78.0
Tondo[127]	1995	50	DSM-III-R	1–20	46.0	50.0	12.0
Wozniak et al.[20]	1995	43	DSM-III-R	1–12	18.6	44.2	16.3
Total/mean ± SD‖	(11 studies)	320			34.4 ± 15.8	4.0 ± 14.9	40.9 ± 24.7

DSM, APA *Diagnostic and Statistical Manual of Mental Disorders; Feighner*, Washington University–St. Louis criteria (see references 115, 116); *n*, number of cases; *NA*, data not available; *Weinberg*, Weinberg & Brumback.[7]
   *Note that psychotic patients are also counted in other categories, and that some totals of the other categories do not add up to 100%, presumably due to unclassifiability in some cases. Mixed states evidently were not consistently considered: none were found in six studies,[85,87,115,116,119,124] and their incidence ranged from 4.0%[89,127] up to 25%[78] to 37%[20] in other reports, for an overall average of 7.8 ± 13.2%.
   †More than 70% were initially misdiagnosed as schizophrenic.
   ‡Includes 12 cases meeting criteria for dysthmyia, 11 for cyclothymia, and 11 for polysubstance abuse.
   §Includes one case of anorexia nervosa. Psychotic symptoms represent findings at any episode.
   ‖Means are weighted by n/study.

symptoms, further complicating their diagnostic assessment.[20,46,47,78,119,157,177] The occurrence during a manic episode of depressive or dysphoric symptoms with prominent irritability is commonly referred to as a bipolar mixed state (or dysphoric or "mixed" mania). The reported incidence of such complex states in pediatric samples averages 8% but varies from none to 37% (CV [SD/mean] = 168%; see Table 4). Such variability suggests underrecognition of the bipolar mixed state in pediatric populations or its confusion with depressive, psychotic, or other forms of severe psychiatric illness. This syndrome can be difficult to diagnose and to treat safely and effectively. It is often poorly responsive to lithium or other mood-stabilizing agents and may worsen during antidepressant treatment.[12,21,183] Wozniak and colleagues[20] found such mixed states in 37% of 43 children with BPD, irritability in 68%, euphoria in only 7%, and both elation and irritability in 16%; 80% of these children had previous episodes of major depression as well as mania, and almost all of the depressive states (94%) involved agitation or mixed moods. These findings support the possibility that mixed bipolar states, or at least admixtures of excited and depressive symptoms, may not be unusual in children—a proposal consistent with the impression that irritable, dysphoric, or psychotic features are common in pediatric BPD (see Tables 1 and 4). Although mixed states in adults suggest poor treatment response and poor long-term prognosis, their therapeutic and prognostic

implications for children and adolescents remain to be clarified.[12,21,183]

PSYCHOTIC FEATURES

As early as 1917, Ziehen[41] recognized that pediatric-onset mania often has psychotic features, including hallucinations, delusions, and formal thought disorder, and later observations* support that view. Common symptoms include auditory hallucinations, persecutory delusions, passive feelings of mind-control, and cognitive disorganization with loosening of associations and incoherence, as well as mood-congruent features more typical of adult BPD (for example, grandiosity, hypersexuality, and intrusive, inappropriate, disinhibited, or aggressive behavior).[115,116] Psychotic thinking was considered incongruent with the prevailing mood in about half of juvenile BPD cases with psychotic features.[85]

   Psychotic features and a chronic or unremitting course are common in pediatric BPD. No doubt, they contributed to the past confusion of BPD with schizophrenia or other psychotic conditions in children and adolescents,[139,185,186] to a continued tendency to describe pediatric mania as "atypical,"[89,109] and possibly to overuse of long-term neuroleptic treatment. The risk of psychotic presentations in pediatric

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*References 83, 86, 87, 100, 110, 115, 116, 119, 124, 139, 184.

BPD averages about 40% (range, 12–100%; see Tables 1 and 4). This wide variation suggests inconsistent methods of case identification or diagnosis, and perhaps reluctance to judge imaginative productions of young children as psychopathological. Variance may also arise from discounting irrational thoughts congruent with mania or depression (such as grandiose or nihilistic exaggerations) as psychotic and from considering "atypical" or mood-incongruent (such as passive, persecutory, or bizarre) delusions a basis for diagnosing a nonaffective psychosis.

The relationship of psychotic features in major mood disorders to phases of the life-cycle may be more complex than just an increased incidence of psychotic symptoms (particularly mood-incongruent features) with early-onset BPD. Psychosis may also be relatively common in late-onset BPD.[139,187] Rennie and Fowler[188] found delusions to occur more frequently with onset of BPD either before age 20 years (62.5%) or over age 60 years (72.0%) than in intermediate age groups (40.0%). In addition to this bimodal age-risk, there may be a gender effect: among hospitalized adolescent BPD patients, about twice as many psychotic features have been found in males as in females.[153] In early BPD implications of psychotic features for treatment response and later course of illness remain to be defined.

EPISODE LENGTH

Reported duration of pediatric manic episodes ranges from brief, tantrumlike affective storms lasting minutes or hours[20,64] to episodes persisting for days[36,43] or months.[33,41,67] These inconsistent estimates may reflect difficulties in diagnosing the disorder in young patients and limits imposed by duration criteria[4] derived from adult BPD. Many reports do not indicate whether reported duration refers to treated or untreated patients, or they include a mix of untreated patients and those given uncontrolled and usually unspecified treatments. Hsu and Starzynski[85] reported a mean duration for juvenile manic episodes of about 3 months; others suggested shorter durations (1–2 months),[116,119] particularly when lithium was used. In prepubertal BPD Wozniak and colleagues[20] found episodic manifestations of mania or depression in only 25% of cases; some symptoms persisted in 75% of cases, averaging a total of 4 years — nearly 40% of a child's life. Treatment can alter the short-term course of acute episodes in pediatric BPD, but chronic symptomatic illness or disability may be common. Further studies of the natural history of pediatric BPD are urgently needed, particularly to clarify relationships among episode length, rates of switching or rapid cycling of mood, and treatment response.

MANIC SWITCHING

Pediatric BPD does not always present with mania, and a first episode of mania or hypomania may emerge after depression or dysthymia or during treatment with an antidepressant. New mania during follow-up of depressed pediatric patients may become less common with advancing age.[94,95] Among seven studies involving the follow-up of over 250 depressed children and adolescents for 2–4 years,[89,92–95,98,189] the risk of mania or hypomania averaged 24.7 ± 7.9%, with about equal chances of mania and hypomania.[189] Since antidepressant treatment was often involved in these studies, the reported risk of mood switching may exceed the spontaneous rate in patients with untreated BPD.[95] Antidepressant treatment may well induce switching into mania, rapid cycling, or affective instability in the young,[84,189–191] as it almost certainly does in adults.[12,21] This possibility evidently brings special risks to the use of stimulants and antidepressants in treating ADHD patients who may have unrecognized comorbid BPD. Some researchers[192] have suggested that the risk may vary with specific types of mood-elevating agents, but this proposal remains tentative in adults and untested in pediatric BPD. In addition to exposure to antidepressants without the protection of a mood-stabilizing agent, several other factors may predict manic switching in pediatric BPD, including having multiple family members with mood disturbances; rapidly evolving hypersomnic, psychomotorically retarded depression; or agitated or psychotic dysphoria.[92,94,98,102] Comorbid substance abuse or minor neurological abnormalities are also suspected predictors.[102,103,191]

TREATMENT

Lithium

The efficacy of lithium has been evaluated in juvenile BPD — mainly in adolescents with adultlike mania.* This research is variable in quality and very limited in quantity. Among 23 available reports or case series concerning lithium therapy in pediatric mania,† only three[194,202,204] involve controlled designs, accounting for only 24 of 186 total subjects (13%; see Table 5). Results of additional controlled experimental therapeutic trials in pediatric BPD are anticipated.[198]

Despite the need for caution with these largely anecdotal findings, they suggest average response rates to lithium (82% of subjects; see Table 5) that are at least as favorable as those found in manic adults, which averaged 65.4 ± 16.2% in controlled trials.[12,21,208] However, this apparently favorable response may reflect overreporting of positive results in uncontrolled case series. Although manufacturers' statements do not specifically include FDA approval for use of lithium in children below age 12 years,[209] this agent is employed rather widely in pediatric psychiatry for BPD and other states of agitation. Such use sometimes includes

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*References 9, 16, 19, 62, 65, 67, 124, 164, 193–198.
†References 62, 63, 65, 67, 69, 78, 85, 89, 110, 119, 124, 147, 155, 194, 199–207.

TABLE 5. Short-term Response to Lithium Treatment in Patients with Pediatric-Onset Mania*†

Study	Year	n	Diagnostic criteria	Responders (%)	Comments
Blind, placebo-controlled trials‡					
Lena[202]	1979	11	NA	82	6 patients dropped out
McKnew et al.[194]	1981	2	DSM-III	100	Parents were lithium-responsive
DeLong & Nieman[204]	1983	11	NA	100	All relapsed following blind-discontinuation after 6 months
Open trials or case reports§					
Annell[62]	1969	2	Clinical	100	–
Dyson & Barcai[199]	1970	1	Clinical	100	13-year-old child of bipolar mother
Dugas et al.[200]	1975	9	Clinical	89	–
Feinstein & Wolpert[201]	1975	1	Clinical	100	–
Brumback & Weinberg[63]	1977	6	Clinical	100	Effective levels of lithium = 0.9–1.4 mEq/L
Horowitz[78]	1977	8	Feighner	100	–
Carlson & Strober[147]	1978	6	Feighner	50	Lithium also useful in later maintenance
Youngerman & Canino[65]	1978	18	NA	100	Reviewed other case reports
Davis[69]	1979	4	Clinical	100	Affective storms and tantrums
Hassanyeh & Davison[119]	1980	7	Weinberg	86	Discontinued in 1 for side effects
Rogeness et al.[203]	1982	1	Clinical	100	Had been diagnosed as schizophrenic for years
Sylvester et al.[110]	1984	2	DSM-III	100	–
Akiskal et al.[89]	1985	2	DSM-III	100	Adolescents switching on anti-depressants
Reiss[205]	1985	1	DSM-III	100	Mania followed initial depression, age 10 years
Hsu & Starzynski[85]	1986	8	DSM-III	50	2 poor responders had enlarged cerebral ventricles
Hsu[206]	1986	14	DSM-III	79	Failures (21%) responded to neuroleptic or carbamazepine
DeLong & Aldershof[67]	1987	11	DSM-III	73	63% doing well after 2.5-year maintenance
Strober et al.[155]	1988	50	RDC	68	6-week trial; only 40% responded if onset prepubertal
Varanka et al.[124]	1988	10	DSM-III	100	Response in 3–24 days at 0.6–1.4 mEq/L
Tomasson & Kuperman[207]	1990	1	NA	100	Repeated episodes from age 7 years; carbamazepine superior
Totals/mean ± SD‖	(23 reports)	186		82.3 ± 14.7%	

DSM, APA *Diagnostic and Statistical Manual of Mental Disorders;*[4] *Feighner*, Washington University–St. Louis criteria (see references 115, 116); *n*, number of subjects treated; *NA*, data not available; *RDC*, Research Diagnostic Criteria; *Weinberg*, Weinberg & Brumback.[7]
*The majority of cases involved adolescents.
†Only 3/23 reports (12.9% of cases) involved controlled designs; all used a crossover design.
‡Ages in the controlled studies ranged from 6 to 16 years.
§Positive results may have been reported selectively in uncontrolled studies and case reports.
‖Mean ± SD is weighted by n/study.

maintenance therapy, even though there are no controlled long-term studies of lithium in pediatric BPD comparable to those in adults.[12,21,208]

In adults abrupt discontinuation of lithium maintenance treatment or even a sharp reduction of plasma lithium concentration is associated with a relatively high risk of early recurrences of BPD, particularly of mania and perhaps suicidal behavior; this risk appears to be reduced by slow removal of the drug.[21,143,210] Similar effects probably also occur in pediatric BPD patients maintained on lithium[197] and may be a particularly common problem for them due to their typically unreliable compliance.[94,197,198] When lithium maintenance is interrupted, there may also be a loss of response to retreatment.[211]

Several studies suggest that lithium may be useful in pediatric conditions other than acute mania. These include psychotic disorders of uncertain types,[212] bipolar depression,[62] unipolar major depression,[21,208,213,214] episodes of aggressiveness,[14,175,176,215–222] or other cyclic behavioral disturbances (including the Kleine-Levin syndrome). Responsiveness seems particularly likely with a family history of lithium-responsive mood disturbances.[93,215,218] Lithium may also be beneficial in some cases of substance abuse comorbid with BPD,[198,223] but not in ADHD.[224] Although response to lithium in these varied disorders does not itself demonstrate misdiagnosis, it is consistent with the view that some cases of psychosis, aggression, substance abuse, and other episodic behavioral disorders of children and adolescents may represent early BPD or conditions comorbid with it.

Most clinical applications of lithium in pediatric patients have sought blood concentrations similar to those found to be effective and safe in adults, although dose-response relationships have been investigated only in adults.[21,195,196] Experience with antidepressants and other drugs indicates that their metabolic clearance in children is typically faster than in adults. Accordingly, doses per body weight required to attain blood concentrations considered to be therapeutic are usually higher than in adults.[225–227] Plasma elimination half-life of lithium is 18 hours or less in children, rising through adolescence to average adult rates of about 20–24 hours.[228] In children aged 6–12 years (18–24 kg body weight), an average daily dose of lithium carbonate of 28.2 ± 0.2 mg/kg (ca. 600 mg/day) was required to provide serum concentrations of lithium averaging 0.8 to 1.0 mEq/L.[66] This dose is nearly twice those typically required in young adults (ca. 900–1200 mg in persons weighing 60 to 70 kg, or about 12–20 mg/kg).[21] Because children eliminate lithium so rapidly, they usually require divided daily dosing or use of slow-release preparations of lithium carbonate to sustain blood levels and to avoid the potentially toxic peak concentrations associated with once-daily dosing.[208]

Several clinical factors may be associated with unfavorable responses to the treatment of early BPD. They include early

age of onset, heavy familial loading, the presence of prominent psychotic features, mixed-dysphoric mood states, cycling into depression before mania, rapidly cycling every few months or even a tendency toward chronic mood instability, and comorbidity with attention, personality, conduct, or substance use disorders; these features are often also associated with inconsistent adherence to treatment recommendations.* Many of these features also predict poor response in adult BPD patients.[12,21,183,205,208] In particular, the impact of psychotic features in pediatric BPD on responsiveness to lithium is uncertain; some researchers[124,198] have suggested that lithium responsiveness in pediatric mania is similar in the presence or absence of psychotic features, and that psychosis may respond to lithium without a neuroleptic.

The responsiveness to antidepressants in pediatric major depression is poor.[234–236] The relevant controlled trials have yielded a small overall difference between antidepressant and placebo response rates (33/92 [35.9%] vs. 40/117 [34.2%], respectively; Mantel-Haenszel $\chi^2 = 1.5$, $p = 0.22$),[237–242] although placebo rates are similar to those in adult major depression.[208] Uncontrolled trials suggest somewhat better overall outcomes (162/268 [60.4%] in 14 reports).[236] This curious phenomenon raises interesting questions: (1) Does this effect augur an inferior response to all mood-altering agents in pediatric mood disorders? (2) Does it protect against manic switching? (3) Does unrecognized BPD contribute to the effect? The first possibility requires study; the second is plausible. Unrecognized BPD might well contribute to poor performance by antidepressants since some depressed children are found to have BPD when they experience mania, rapidly fluctuating mood, agitation, or psychosis during treatment with an antidepressant.

Induction of mania can complicate use of antidepressants without a mood-stabilizing agent in the treatment of apparently unipolar early depression or ADHD.† However, the difference between antidepressant-associated and spontaneous switching into mania or hypomania from depression or euthymia is not well quantified in adult or pediatric mood-disordered populations.[12,21,208] In over 2000 adults, most with apparently unipolar depression, treatment with an antidepressant was associated with a switch to mania or hypomania in as few as 6–9%,[245,246] whereas this risk was about twice as high (16.7%) in a recent follow-up study of 48 children initially selected as having nonpsychotic, apparently unipolar major depression treated with nortriptyline.[95] This provocative comparison is inconclusive due to a longer time at risk in this small pediatric sample. Using antidepressants without initial protection of a mood-stabilizing agent such as lithium is unwise in bipolar depression; they are potentially dangerous and contraindicated in the man-

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*References 16, 79, 129, 132, 153, 155, 163, 229–233.
†References 2, 189, 224, 232, 233, 241, 243, 244.

agement of mixed bipolar states, for which lithium, anticonvulsants, neuroleptics, and sedatives are more appropriate options.[21,208] It is also not clear whether stimulants induce mania, psychosis, or rapid cycling in children with ADHD and BPD, although the combination of lithium with methylphenidate has been well tolerated by such patients.[247]

Adverse effects and drug interactions of lithium in children resemble those that are common in adults, including early thirst and polyuria; tremor, confusion and ataxia at excessive doses; coma with a risk of irreversible brain damage after acute overdoses; and minor reduction of glucose tolerance as well as risk of diabetes insipidus at typical doses.[21,208] There is also an undefined risk of hypothyroidism or hyperparathyroidism, potentially complicated by subtle abnormalities of thyroid function sometimes found before treatment in youngsters with BPD.[248] Effects of lithium on cognition in children appear to be minor and transient.[247,249] In general, children and adolescents do not seem to present greater risks of side effects from lithium than do adults,* but they may be especially troubled by weight gain and skin eruptions. Further research is needed to evaluate the possible long-term physiological and developmental impact of minor effects on thyroid or parathyroid function and cognition in pediatric BPD patients. Adolescent pregnancy, another risk of BPD, can raise concerns about suspected teratogenic effects of lithium, particularly the moderately elevated chance of inducing Ebstein's tricuspid and septal defects of the heart in the first trimester, although this risk is probably lower than had been proposed earlier.[252]

Alternative mood-stabilizing treatments

Research on alternatives to lithium in the treatment of pediatric BPD is very limited. The most promising options are the antimanic and possibly mood-stabilizing anticonvulsants carbamazepine and valproate. These agents have been applied widely in adult BPD; their demonstrated efficacy and acceptable safety in children with epilepsy[253-255] encourage their consideration in pediatric BPD.[256-260] Additional options include neuroleptics, atypical antipsychotics, sedatives, and various antihypertensive agents; none has been systematically evaluated in pediatric BPD.[21,208,261-263]

Based on suggestive anecdotal experience, carbamazepine may be effective in pediatric BPD, particularly when combined with lithium.[198] It has also been used in other affective, behavioral, and neuropsychiatric disorders of children and adolescents, but controlled studies in pediatric BPD are lacking.[21,88,257,264,265] This tricyclic anticonvulsant (a dibenzazepine or iminostilbene) is not known to exert neuropharmacological actions like those of structurally analogous antidepressants;[208] nevertheless, it may be not only anti-

manic but also antidepressant in adult patients and may induce mania or excitement in some children.[265-270]

Information about the side effects of carbamazepine derives from extensive clinical application in pediatric epilepsy.[265,271,272] It appears to have limited risk of inducing untoward effects on cognitive and psychomotor performance in children.[255,272] Side-effects of carbamazepine in 220 epileptics under age 16 years were similar to those in adults.[271] They included excessive sedation (43%), vertigo or ataxia (26%), other evidence of mild cerebral intoxication (tremor, slurred speech, diplopia, or movement disorder, often with relatively high blood drug concentrations) or headache (16%), nausea and vomiting or other gastrointestinal complaints (9%), and rashes or other dermatological reactions (5%). Carbamazepine also has a substantial risk of inducing blood dyscrasias, most often leukopenia (ca. 2% risk), and less commonly anemia or platelet deficiencies; these reactions, although typically mild and not known to differ in frequency or severity between children and adults, call for regular blood-count monitoring.[273] When taken during pregnancy, carbamazepine may induce spina bifida or facial malformations in the fetus.[274] In addition, carbamazepine has a powerful inducing action on hepatic drug-metabolizing microsomal oxidases, leading to significant decreases in blood concentrations of itself and other agents and sometimes complicating treatment with multiple agents.[275]

Valproic acid appears to be an especially promising and generally well-tolerated alternative to lithium or carbamazepine.[21,208,259,276] This aliphatic (2-propylvaleric acid, or dipropylacetic acid or its sodium valproate salt) anticonvulsant has shown encouraging antimanic and possible mood-stabilizing actions in a few adolescent BPD patients.[277,278] Valproate remains to be studied in short-term pediatric trials; formal long-term studies are not yet available, but several are under way in adults. Valproate appears to have a particularly low risk of inducing mania and so is a plausible component of regimens for young BPD patients with comorbid ADHD who risk long-term exposure to stimulants and antidepressants. The anticonvulsants may be especially useful in BPD with mixed mood states, psychotic features, rapid cycling, or poor responsiveness to lithium alone.[258-260,264,265,276-278] Carbamazepine (typically at doses of 7.5–10 mg/kg)[279] or valproate (typically at 20 mg/kg) can be given in initial oral loading doses in adults and children to facilitate rapid control of agitation.[280]

Adverse effects of valproate include rare but potentially severe hepatic toxicity. The only cases of hepatic damage arising during valproate monotherapy have been in young children and infants, in whom an age-related risk may reflect the formation of hepatotoxic unsaturated (double-bond containing) metabolites formed through vigorous oxidation by youthful hepatic microsomes. At later ages en-

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*References 67, 124, 198, 217, 221, 250, 251.

TABLE 6. Outcome in Patients with Pediatric-Onset Mania

Study	Year	n	Follow-up (y)	Final status (%)*			Comments
				Good	Fair	Poor	
Early studies							
Strecker et al.[73]	1921	6	9–11	50	33	17	1 suicide, 1 lost to follow-up
Kasanin[77]	1952	10	10–15	0	50	50	Most hospitalized or disabled
Olsen[132]	1961	28	ca. 25	32	0	68	—
Subtotals/means	(3 studies)	44	9–25	27.2	15.9	57.0	—
Contemporary studies							
Carlson et al.[296]	1974	28	Several	64	18	18	1 suicide
Carlson & Strober[147]	1978	6	2.5–5	83	17	0	Best results with lithium + pyschotherapy
Hassanyeh & Davison[119]	1980	10	0.5–5	70	30	0	7 are outpatients, 1 still on lithium
Hsu[206]	1986	14	1–3	57	21	21	Average = 1 depressive, 2 manic episodes in follow-up
DeLong & Aldershof[67]	1987	45	2.5–3.5	87	0	13	28 maintained on lithium, all with good adjustment
Subtotals/means	(5 studies)	103	0.5–5	74.8	11.7	13.4	—
Totals/meant	(8 studies)	147	0.5–25	60.5	12.9	26.5	

*Status at end-point is based on clinical judgments expressed in each study.
†Means are weighed by n/study.

zyme induction may increase the formation of such products when other anticonvulsants, including carbamazepine, are combined with valproate.[281,282] There is also a suspected association of valproate with androgenizing effects in young females.[283] A potentially severe effect of valproate for pregnant adolescents is its association with the induction of spina bifida.[274,284,285] Valproate appears to lack a significant enzyme-inducing action but, in contrast to carbamazepine, may slightly increase blood concentrations of some other agents.[21,208]

Studies of long-term treatment of pediatric BPD with antipsychotic agents are surprisingly absent, although many cases are probably included among children misdiagnosed with schizophrenia or other psychotic disorders.[79,88] Neuroleptics are well established from decades of successful application for pediatric psychotic disorders but are unstudied for maintenance therapy in BPD at any age. Risk of tardive dyskinesias with their long-term or intermittent use is relatively low in children but probably elevated in adult mood disorders.[261] This risk is low with clozapine, an atypical antipsychotic with antimanic and perhaps mood-stabilizing activity in adults and children.[21,262,263]

Pediatric experience with other agents, such as verapamil or lecithin, or with electroconvulsive therapy (sometimes used in the treatment of adult BPD) is described only in rare anecdotes.[21,198,286–289] Finally, the cost-effectiveness of psychosocial and rehabilitative interventions in pediatric BPD remains to be evaluated systematically, although preliminary results in pediatric major depression are encouraging.[198,290–295] Of the various options discussed, lithium remains the standard agent for BPD; valproate is being employed increasingly commonly, encouraged by its favorable tolerability compared to lithium and its long history of use for pediatric epilepsy, and despite its lack of formal investigation in pediatric BPD.

OUTCOME

In addition to the preceding short-term evaluations of lithium or other treatments in mania, at least eight studies* have followed a total of 147 patients with pediatric-onset mania for an average of about 8.5 years (see Table 6). The majority of patients (60.5 ± 31.2%) showed a favorable outcome, overall, although treatment usually was not well defined and has varied widely since some of the studies date back to the 1920s. (Three studies were reported between 1921 and 1961, and five between 1974 and 1987.) Much more favorable outcome was found in investigations carried

*References 67, 73, 77, 119, 132, 147, 206, 296.

out since the 1970s, in which contemporary pharmacotherapies have been employed: the weighted average proportion with a favorable outcome in the earlier years was $27.2 \pm 25.2\%$, vs. $74.8 \pm 13.1\%$ ($p < 0.05$) in the more recent ones. Interpretation of this striking 2.8-fold difference is limited by uncertain diagnostic criteria and lack of controlled treatment, as well as by a confounding difference in time at risk (earlier studies involved much longer follow-up—15.8 ± 8.0 years in 44 early cases, vs. 3.0 ± 0.7 years in 103 later ones). These observations do not conclusively favor an effect of improved treatment on better outcome in recent decades.

There is broad clinical agreement that psychosocial, educational, and rehabilitative interventions, as well as maintenance medication with an effective mood-stabilizer, are essential in the overall management of pediatric BPD to minimize long-term morbidity and disability, although research on the application of any of these approaches to the long-term optimization of outcome in pediatric BPD is almost nonexistent.[9,11,12,16,121,132,152] In addition, professional and public reluctance to employ maintenance medication in children can impede efforts to address the long-term benefits and risks of mood-stabilizing treatments for pediatric BPD.[11,87]

Defining the optimal assessment and long-term care of BPD in children remains a major task for contemporary pediatric psychiatry. Children present special and urgent challenges in light of the sometimes devastating and potentially lifelong impact of severe mood and psychotic illnesses of early onset[11] and due to a strong association of early-onset BPD or depression with substance abuse, and of both factors with high-risk behaviors, suicide, and other fatalities.[94,297,298] Rates of suicide attempts in children with depression or BPD may exceed 20% within the first several years of follow-up.[94,298] In addition to a lack of research to define the long-term effectiveness and potential risks of early intervention in definite or probable BPD in young patients, particularly prepubertal children, specific clinical factors in early BPD may limit treatment responsiveness. Early onset of BPD and a strong family history, for example, may anticipate an extensive course of life-long morbidity and impaired function, perhaps with limited responsiveness to treatment.[299] Moreover, repeated acute illness, particularly if not recognized and treated early, may itself lead to a more severe later course and poorer outcome, either through specific neurobiological mechanisms[300] or because of impaired personal, social, educational, and vocational development. Tendencies toward psychotic and mixed mood states, a chronic course of illness, a high frequency of comorbid psychiatric conditions or substance abuse, and sometimes poor compliance with prolonged use of medications and organized treatment programs in pediatric BPD all compli-

cate clinical management.[11,14,16] These factors also increase the likelihood of exposure of children and adolescents to complex and repeatedly interrupted or changing treatment regimens with undefined long-term adverse, interactive, or developmental consequences. In short, there are many uncertainties as to whether, how, and when to intervene with a comprehensive program of mood-stabilizing pharmacological treatment, psychological assistance, rehabilitation, and family support so as to obtain optimal long-term results in this age group.

COMMENT AND CONCLUSIONS

Several impressions emerge from this review. First and foremost, children and adolescents with BPD alone or comorbid with other conditions should no longer remain infrequently studied, underdiagnosed, and undertreated with mood-stabilizing agents—or overtreated with neuroleptics. Pediatric BPD only recently is emerging as a matter for substantial investigation and clinical interest and continues to be viewed skeptically by some experts in child and adolescent psychiatry and developmental psychopathology. It would be ironic if other childhood psychotic disorders have been overdiagnosed despite their association with severe social stigma and often less satisfactory response to treatment. A tendency to consider as schizophrenia or childhood psychosis virtually any early severe disorder with psychotic features has not entirely disappeared, although there has been considerable change in this tendency in pediatric as well as adult psychiatry since the introduction of DSM-III into American diagnostic practice in the early 1980s. Nevertheless, concordance on the view that BPD is a primary disorder that is not rare in children and not uncommon in adolescents remains less than universal.

Emphasis on psychotic rather than affective symptoms, common presentation as dysphoric-irritable mood and conduct disturbances, frequent comorbidity with ADHD and other conditions, and diagnostic dependence on characterizations of typical adult bipolar psychopathology probably all limit recognition of early BPD. In turn, not recognizing early BPD may encourage overtreatment with neuroleptic and perhaps mood-elevating agents and underutilization of mood-stabilizing drugs. Underrecognition of BPD in pediatric populations may reflect relative tolerance of emotional and behavioral turmoil in the young, the difficulty of differentiating attention and conduct disorders from early BPD, and possibly insufficient routine consideration of major affective disorders in clinical assessment. A particularly important clinical and research challenge is to clarify whether attention-deficit and conduct disorders are comorbid with BPD, represent precursor syndromes in some cases, or are nonspecific phenocopies arising from multiple etiologies.

Reports on age of onset of BPD rather consistently

suggest that onset of BPD and its prodrome is rather common before adulthood, with somewhat more frequent recognition in recent decades. Approximately 25% of BPD patients have been reported to experience onset before age 20 years, and many more cases may be undiagnosed or misdiagnosed. Accordingly, early identification, diagnosis, and treatment of juvenile cases is required to minimize recurrences, to reduce their morbid impact on development, education, and functioning, and to lower the risk of fatality due to suicide, drug abuse, accidents, or sexually transmitted infections.

Many similarities have been found between pediatric- and adult-onset BPD, particularly with regard to affective symptoms. However, pediatric diagnosis is strongly influenced by descriptions of manic and depressive psychopathology considered typical in adults. Certain features, particularly extreme mood lability and prominence of irritable, hostile, dysphoric mood, tantrums, or explosive behavioral dyscontrol, are characteristic in childhood BPD and may be initiated or worsened by use of mood-elevating agents. Their incidence in older BPD patients requires further study to test the hypothesis that some features diminish with maturation. It is also likely that recognition of labile, irritable, dysphoric, or mixed mood states and psychotic features has been insufficient in adult as well as pediatric BPD, perhaps because such features have been considered atypical. It follows that diagnosis based on traditional characterizations of "typical" psychopathology without a sufficiently comprehensive and prolonged longitudinal assessment of individual symptoms, family history, course, treatment response, and outcome may limit recognition and appropriate interventions in many cases of both pediatric and adult BPD.

Psychotic symptoms are reported with striking consistency to be more common in pediatric than in adult BPD. This phenomenon may reflect greater susceptibility to psychosis in childhood due to undefined developmental variables, or an expression of greater severity of early-onset BPD with familial loading. No doubt, the occurrence of mood-incongruent psychotic symptoms and formal thought disorder has encouraged considering early-onset BPD as atypical or schizoaffective. Since a separation of psychotic and nonpsychotic forms of early BPD may have important clinical implications, further studies of the course, treatment response, and outcome in these subtypes are needed to test their validity and utility.

Particular personality or temperamental traits (especially cyclothymia, hyperthymia, and extroversion) may be present in children prior to development of overt BPD. Such traits may thus represent antecedents or mild prodromal manifestations of BPD in some children, although in others they can be a transient phase of development or stable traits not leading to later major illness. A role of developmental or

environmental stressors or precipitants to the risk of manifesting acute symptoms of BPD in children is unproven; such precipitants might contribute to the initiation or timing of BPD episodes.

The relationship between BPD first diagnosed in childhood or adolescence and adult BPD remains incompletely defined. General similarity of bipolar affective syndromes across the age spectrum suggests that they represent the same disorder. An inescapable conclusion is that prepubertal cases of BPD are diagnosed less often than postpubertal cases, but the significance of this age-related diagnostic tendency remains unclear. Whether psychosexual immaturity limits risk of adultlike presentations of major mood disorders in children — or alternative forms of psychopathology occur in children who later manifest BPD in adulthood — remains to be resolved. The important question is not whether or how often typical (adultlike) forms of BPD occur in children, but rather, what are the precursors or early forms of psychopathology in children who later manifest classic manic-depressive syndromes in adolescence or adulthood. Recognition of hypothesized antecedents of adult BPD should be facilitated by long-term follow-up of children with suspected BPD or offspring of parents who have the disorder.

Several observations have associated the onset of BPD in childhood or adolescence with relatively high familial risk that may reflect developmental as well as genetic factors. Greater loading with affectively ill relatives seems to correspond to younger onset of BPD and, possibly, a worse prognosis.

Systematic studies of the responsiveness of early-onset BPD to lithium or other mood-altering agents, particularly with respect to efficacy and safety in long-term maintenance treatment, have been extraordinarily rare in children and infrequent in adolescents. Nevertheless, encouraging results have been reported with short-term use of lithium, carbamazepine, and valproate. These findings and the well-established efficacy and reasonable safety of anticonvulsants in the treatment of epileptic children encourage additional pediatric studies of agents found to be effective in adult BPD. There is a particular need to define optimal treatments for pediatric BPD patients who are in mixed states or bipolar depression, have comorbid ADHD, or have other conditions whose treatment with a mood-elevating agent without a mood-stabilizing agent might be destabilizing.

In conclusion, the material reviewed offers compelling evidence that BPD, even in its typical adult form, occurs frequently in adolescence and is not rare in childhood, when precursor states are commonly misdiagnosed. The disorder has not been studied sufficiently in pediatric populations, particularly with respect to possible early psychopathological precursors or prodromes of the adult form of BPD. Since

many BPD patients experience the onset of classic manic or depressive episodes before adulthood, or first become manic during treatment for depression, the identification of risk factors for developing BPD (for example, family history, premorbid temperament, and comorbid behavioral disorders, as well as specific environmental stressors or substance abuse) might facilitate identification and treatment of pediatric cases of these often severe, disabling, and life-threatening disorders. Improved early recognition of BPD or its precursors in pediatric populations should lead to appropriate early intervention, more-specific and more-effective treatment, and reduced long-term morbidity and developmental disability, functional impairment, and mortality.

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