Treatment Guidelines for Children and Adolescents With Bipolar Disorder: Child Psychiatric Workgroup on Bipolar Disorder

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ABSTRACT

Clinicians who treat children and adolescents with bipolar disorder desperately need current treatment guidelines. These guidelines were developed by expert consensus and a review of the extant literature about the diagnosis and treatment of pediatric bipolar disorders. The four sections of these guidelines include diagnosis, comorbidity, acute treatment, and maintenance treatment. These guidelines are not intended to serve as an absolute standard of medical or psychological care but rather to serve as clinically useful guidelines for evaluation and treatment that can be used in the care of children and adolescents with bipolar disorder. These guidelines are subject to change as our evidence base increases and practice patterns evolve. *J. Am. Acad. Child Adolesc. Psychiatry,* 2005;44(3):213–235. **Key Words:** bipolar, treatment guidelines, consensus, mood stabilizer, atypical antipsychotic

These treatment guidelines arose out of a need first voiced by members of the Child and Adolescent Bipolar Foundation (CABF), who noted that clinicians who treat children and adolescents with bipolar disorders (BPDs) are in desperate need of guidelines regarding

how to best treat these patients. In July 2003, a group of 20 clinicians and CABF members met over a 2-day period to develop these guidelines. There were four work groups: diagnosis, led by Mary Fristad; comorbidity, led by Boris Birmaher; and treatment, in two groups led by Karen Wagner and Robert Findling, respectively. The groups met to develop a draft of their sections that was circulated first to the separate work groups and then to the other work group members. Each group presented an overview of its guidelines to the whole group and then submitted its section's guidelines for further comment and refinement to the members of their group and the other group members. This process went on for approximately 6 months. The resultant consensus guidelines are contained in this document.

These guidelines are not intended to serve as an absolute standard of medical or psychological care. Standards of care are determined based on all clinical data available for an individual child or adolescent and are subject to change as our evidence base increases and practice patterns evolve. Adherence to these guidelines will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of

care aimed at the same results. When considering the diagnostic and treatment options available, the individual clinician must make the final judgment regarding a particular treatment plan, using the clinical data presented by the patient and the family.

There continues to be much debate about the diagnosis and longitudinal course of BPDs in children and adolescents. No one can say for sure what these children will look like when they grow up. However, it is clear that they manifest a serious disorder and that early diagnosis and aggressive treatment are necessary for these patients to function successfully within their families, peer groups, and schools. There is also the hope that early recognition and treatment of pediatric BPDs will reduce or eliminate the many negative outcomes associated with these disorders.

SECTION I: ASSESSMENT

Limitations of DSM-IV Criteria

There is continued debate over the appropriateness of *DSM-IV* criteria for classifying BPD in children and young adolescents (Biederman et al., 2000a; Findling et al., 2001). For these guidelines, we have used *DSM-IV* criteria, acknowledging that the current *DSM-IV* criteria for mania were developed for adults and are frequently difficult to apply to children. Identifying episode onset and offset can be difficult because many children with BPD present with frequent daily mood swings that have been occurring for months to years. Children with BPDs often present with a mixed or dysphoric picture characterized by frequent short periods of intense mood lability and irritability rather than classic euphoric mania (Findling et al., 2001; Geller et al., 2000; Wozniak et al., 1995a).

Geller et al. (2004) recently reported the results of a 4-year prospective study of 86 prepubescent and early adolescent subjects. This was the first prospective, longitudinal study of a group of children with bipolar symptoms. These subjects were evaluated every 6 months during a 4-year period by a research nurse using the Washington University Schedule for Affective Disorders and Schizophrenia for School-Age Children (WASH-U K-SADS) (Geller et al., 2001). To clearly differentiate mania from attention-deficit/hyperactivity disorder (ADHD), the investigators required the presence of elated mood and/or grandiosity in their bipolar

subjects. They defined an episode of mania as the entire length of the illness with cycles of manic symptoms as short as 4 hours. In this sample, 10% had ultrarapid cycling, and 77% had ultradian (daily) mood cycling. None of these subjects met *DSM-IV* criteria for rapid cycling (four or more episodes per year) but were described as having 3.5 ± 2.0 cycles per day. The average of onset of mania/hypomania was 7.4 ± 3.5 years, with an average episode length of 3.5 ± 2.5 years. Although this study demonstrates that in this research sample the symptoms of mania and hypomania persist over a 4-year period, it does not resolve the questions of whether these children will develop classic *DSM-IV* bipolar I disorder (BPD-I).

Clinicians who evaluate such children may use the *DSM-IV* course modifier "rapid cycling," although this description does not fit children very well because they often do not have clear episodes of mania (Findling et al., 2001; Geller et al., 2000, 2001; Wozniak and Biederman, 1997). Rather, they are best conceptualized as having severe mood dysregulation with multiple, intense, prolonged mood swings each day. This "mixed" type of episode frequently includes short periods of euphoria and longer periods of irritability. Comorbid diagnoses (e.g., ADHD, oppositional defiant disorder, conduct disorder, and anxiety disorder) are also common and complicate the diagnosis of BPD.

Bipolar II disorder (BPD-II) often comes to clinical attention when the child or adolescent experiences a major depressive episode. A careful history is required to detect past episodes of hypomania. Cyclothymia is also difficult to diagnose because hypomanic and mild depressive symptoms are subtle. Prospective mood charting can be helpful to clarify symptom presentation (see Fristad and Arnold, 2004, pp 71–73, or visit http://www.bpkids.org/learning/6-02.pdf for sample mood charts).

BPD not otherwise specified (BPD-NOS) represents the largest group of patients with bipolar symptoms (Lewinsohn et al., 2000). Children without clearly defined episodes whose episodes do not meet *DSM-IV* duration criteria or who have too few manic symptoms are often diagnosed with BPD-NOS (Leibenluft et al., 2003). The diagnosis of BPD-NOS also can be given when a BPD is present but secondary to a general medical condition (e.g., fetal alcohol syndrome, an alcohol-related neurodevelopmental disorder) (Burd et al., 2003). Little is known about prepubertal BPD-NOS, including whether

it will evolve into BPD-I or BPD-II. It is important that clinicians who use this diagnosis specify why it is being given.

Numerous medications and other medical disorders may exacerbate or mimic bipolar symptoms (Table 1). It is important to assess these potential confounds before initiating treatment.

Symptom Thresholds

When ascertaining the presence or absence of manic symptoms, we recommend that clinicians use the FIND (frequency, intensity, number, and duration) strategy to make this determination. FIND guidelines for the diagnosis of BPD include
Frequency: symptoms occur most days in a week
Intensity: symptoms are severe enough to cause extreme disturbance in one domain or moderate disturbance in two or more domains
Number: symptoms occur three or four times a day
Duration: symptoms occur 4 or more hours a day, total, not necessarily contiguous

For example, a child who becomes silly and giggly to a noticeable and bothersome degree for 30 minutes twice per week has some unusual behavior, but the frequency (twice per week), intensity (mild interference in two domains), number (one episode per day), and duration (30 minutes) may not qualify for a BPD diagnosis. On the other hand, a child described as ''too cheerful'' during many school days and every

TABLE 1
Medical Conditions That May Mimic Mania or Increase Mood Cycling in Children and Adolescents

Mimic mania
  Temporal lobe epilepsy
  Hyperthyroidism
  Closed or open head injury
  Multiple sclerosis
  Systemic lupus erythematosus
  Alcohol-related neurodevelopmental disorder
  Wilson's disease
Increase mood cycling
  Tricyclic antidepressants
  Selective serotonin reuptake inhibitors
  Serotonin and norepinephrine reuptake inhibitors
  Aminophylline
  Corticosteroids
  Sympathomimetic amines (e.g., pseudoephedrine)
  Antibiotics (e.g., clarithromycin, erythromycin, amoxicillin)
    (Abouesh et al., 2002)

day after school to the point that relations with teachers, parents, siblings, and peers are disrupted or severely impaired, with these ''high'' times lasting several hours several times per day on a nearly daily basis, has crossed the FIND threshold. It is also important to consider the context when deciding whether a symptom is present or a child is having normal elation and expansiveness. For example, elation on Christmas morning would be normal and not impairing, whereas similar elated, silly behaviors during church on other days would be pathological. Playing schoolteacher after school is within normal context, but telling the actual principal to fire teachers whom the child does not like is out of context and impairing. Examples of manifestations of prepubertal mania behaviors appear in Geller et al. (2002). It is important to note that these FIND thresholds have yet to be validated and are presented as clinically useful thresholds that the panel developed based on its extensive clinical and research experience working with these patients.

Symptom Descriptions

The differential diagnosis of manic symptoms can be challenging. Children might present with seemingly manic symptoms for a variety of reasons. Below we describe each symptom of mania and discuss what, other than BPD, may cause it. For any of these symptoms to be counted as a manic symptom, they must exceed the FIND threshold described above. Additionally, they must occur in concert with other manic symptoms because no one symptom is diagnostic of mania.

Euphoric/Expansive Mood. Children can be extremely happy, silly, or giddy when they are very excited about a special event, when they are disinhibited (i.e., secondary to prescription drug use such as steroids or substance abuse), or when they are manic. It is crucial that the clinician obtain a detailed history, with many examples that include context (e.g., was this the only child giggling at the time? was there an environmental trigger?), to ascertain whether this symptom meets the FIND threshold.

Irritable Mood. Irritability is nearly ubiquitous in childhood psychopathology. Children with major depressive disorder, dysthymic disorder, or oppositional defiant disorder routinely experience irritable moods. Irritability is also common in children with pervasive developmental disorder (PDD), anxiety disorders,

schizophrenia, and ADHD. Children with these latter diagnoses can turn hostile quickly when requests/demands are not met. Children on stimulant medications often have a "whiny" period in the evening as their dose of medication wears off, and serotonin reuptake inhibitors (SSRIs) can cause irritability. Moreover, hot, hungry, stressed, and/or tired children without psychopathology may become irritable. Manic irritability sometimes can be differentiated from other causes of irritability by its episodic (often with a pulsating, volatile quality) and extreme nature. Children with BPD who experience irritability frequently have extreme rages or meltdowns over trivial matters (e.g., a 1- to 2-hour tantrum after being asked to tie their shoes). Aggressive and/or self-injurious behavior often accompanies this irritability.

Grandiosity. Because some children possess special talents and abilities, it is important to verify the veracity of children's claims. Additionally, children who lack adequate access to healthy peer play may continue with fantasy play longer than usual. Thus, it is important to ascertain whether the child can distinguish pretend-play from reality. For example, a 10-year-old who lives in a dangerous neighborhood may choose to stay indoors and print out "checks" on the computer and volunteer to do his or her mother's taxes but realizes this is pretend-play. By contrast, pathological grandiosity typically exceeds a child's normal fantasy or imagination for his or her age. Further, stating "I am the best baseball player, dancer, etc." or "I am Superman" may be developmentally acceptable, depending on the child's age, the context in which these words are spoken, the persistence with which they are stated, and the effects of these words on the child's behavior. By contrast, a child of 8 who jumps out the window and sustains serious injuries because he believes he *is* Superman is pathologically grandiose. It is useful to ask the child how he or she knows that he or she is the best or how he knows that he is Superman to ascertain the child's reality testing. If the child answers, "Because I just know," this demonstrates impaired reality testing and is not normal. If a child acts on his or her belief (e.g., repeatedly calling his or her coach to tell him how to run the team), it is impairing. Children who play "teacher" after school and reprimand the "students" are engaging in normal, contextually appropriate behavior. Children who daily tell other students what they should learn while refusing to do schoolwork because they already know everything have impairing, pathological grandiosity.

Decreased Need for Sleep. It is important to distinguish decreased need for sleep from more common forms of insomnia that result in fatigue the next day. To meet this manic criterion, a child's sleep should be decreased by 2 or more hours per night for his or her age without evidence of daytime fatigue. Whereas children with other forms of insomnia (due to poor nighttime routines, excessive environmental stimuli, anxiety, depression, or ADHD) may lie in bed trying to sleep, manic children are full of energy. They often get up and wander the house in the middle of the night, looking for things to do. These children may sleep 4 to 5 hours per night yet appear fresh and energetic the next day. When depressed and anxious, children often lie in bed and brood, whereas children in a manic state are on the computer, talking on the family cell phone, rearranging the furniture in their room or in other rooms in the house, watching television (often with sexual content), and so forth.

Pressured Speech. Children who are excited, nervous, or angry often speak rapidly. This is a transitory phenomenon and not a sign of mania. Some children always talk a lot, particularly those diagnosed with ADHD. For such children, a change from baseline functioning is critical to count pressured speech as a symptom of mania. Additionally, when manic, children may be loud, intrusive, and difficult to interrupt.

Racing Thoughts. Whereas jumping from topic to topic as in flight of ideas can be observed by others, ascertainment of racing thoughts requires asking the child whether his or her thoughts seem to be going too fast. Children may describe racing thoughts with developmentally appropriate concrete phrases such as "my brain is going 100 miles per hour" or "there is an Energizer Bunny up there." Racing thoughts are impairing when they occur so frequently that the child cannot keep his or her daily activities on track. To ascertain flight of ideas, ask whether topics of discussion change rapidly, in a manner quite confusing to anyone listening. For an interviewer unfamiliar with a child and his or her background, it is necessary to determine whether a parent or other knowledgeable adult can easily follow the stream of words. Younger and less verbally facile children who are talkative can be confusing to follow due to their limited ability to organize language, but this is not flight of ideas.

Distractibility. For distractibility to be considered a manic symptom, it needs to reflect a change from baseline functioning, needs to occur in conjunction with a "manic" mood shift, and cannot be accounted for exclusively by another disorder, particularly ADHD. First, ask the parent and child to identify a time when the child was as close to euthymic as possible ("even mood," "not up or down," "having the fewest problems"). Then, ascertain the presence or absence of ADHD by asking about ADHD symptoms during this relatively uneventful time. Next, after establishing the time interval of a possible manic episode, ask whether distractibility during this time was worse than usual (i.e., was distractibility worse than during euthymia). A child who becomes distractible during a manic or depressive episode may change from a B or C student to a child unable to focus on any school lessons. He or she may suddenly become flighty at home, not remembering from one minute to the next what he was doing or playing. Conversely, children with ADHD who are successfully treated with stimulant medications are usually distractible before medication is taken in the morning and as medication wears off in the evening. Depressed children frequently experience impaired concentration. Anxious children may be preoccupied and appear distracted. Children with learning disabilities can appear distracted at school or while they are doing their homework.

Increase in Goal-Directed Activity/Psychomotor Agitation. Whereas increased goal-directed activity is relatively specific to mania, psychomotor agitation is a common and nonspecific symptom in childhood psychopathology. Therefore, increased goal-directed activity is more informative than psychomotor agitation in diagnosing mania. Children, when manic, may draw copiously, build extremely elaborate and extensive block towns, or write novels in a short period of time. (This needs to be differentiated from the generally high productivity of a very bright, very self-directed child.) With regard to psychomotor agitation, it should represent a distinct change from baseline. For example, children with ADHD are frequently full of energy and activity. For this symptom to count toward a diagnosis of mania, the level of activity or agitation has to be more than is typically seen in the child with ADHD. Children who are depressed, anxious, or traumatized can be agitated or display "nervous habits," such as chewing their shirt collars or picking apart the soles of their tennis shoes.

The agitation witnessed in children with BPD often has a pressured quality to it, as if the child might pop out of his skin if the feeling does not go away or the craving is not satisfied. Children or adolescents who are hypomanic may be fairly productive, but if their mania progresses, they may become increasingly disorganized and nonproductive.

Excessive Involvement in Pleasurable or Risky Activities. Children with BPD are often hypersexual. It is important to rule out sexual abuse or exposure to sexually explicit materials or behaviors as a possible cause of hypersexual behavior in any child, including one with BPD. However, sexually provocative behavior in the absence of any indication that the child has been inappropriately touched by another person is commonly seen in children with BPD. This hypersexual behavior frequently has an erotic, pleasure-seeking quality to it, whereas the hypersexual behavior of children who have been sexually abused is often anxious and compulsive in nature. The hypersexual behavior of a child with BPD frequently has a flirtatious aspect that would be appropriate if done in private between consenting adults (e.g., a child trying to open-mouth kiss his mother or trying to touch others' private parts, dancing in an erotic manner in front of a mirror). Adolescents may seek out sexual activity multiple times in a day. These behaviors are thought to be the child counterparts of adult promiscuity and multiple marriages (Geller et al., 2002).

Psychosis. In addition to core symptoms of mania, psychotic symptoms, including hallucinations and delusions, are frequently present in children with BPD (Geller et al., 2002; Kafantaris et al., 2001b). It is useful to distinguish benign perceptual distortions that are not impairing and are not considered signs of psychosis (e.g., hearing one's name being called or hypnagogic [before sleep] and hypnopompic [upon awakening] perceptual phenomena) from those that are impairing and that can be life threatening (e.g., hearing voices that command the child to stab her mother with a butcher knife). It is also important to assess whether the psychotic symptoms are mood congruent or incongruent, secondary to another psychiatric disorder (e.g., schizoaffective disorder or secondary to age-appropriate cognitive distortions).

Suicidality. Although not a core symptom of mania, children with BPD are at extremely high risk of suicidal ideation, intent, plans, and attempts during a depressed or mixed episode or when psychotic (Geller et al., 2002; Lewinsohn et al., 1995).

Components of a Comprehensive Evaluation

It is important to interview, at minimum, the child and one parent. Ideally, both parents will attend the evaluation. Children may report euphoric symptoms of which their parents are unaware, whereas parents may focus more on irritability because this affects family functioning the most. Children may also report suicidal ideation, hallucinations, or anxiety symptoms that they are reluctant to reveal to their parents. Discrepancies between informants are common (Hawley and Weisz, 2003; Jensen et al., 1999). If one parent and the child, for example, deny a symptom that the other parent reports, it can be useful to use a "tie breaker" approach, meaning that input from another informant should be elicited (e.g., a teacher) for the symptom to be counted. Significant discrepancies between parents suggest the need for family intervention, described below.

Obtaining school input is very useful, particularly as treatment progresses. Other informants might include a child's coach or child care provider. Obtaining medical records from the family and other physicians who have treated or evaluated the child (and, in turn, sending records of the current evaluation) is important, especially if others will participate in medication monitoring.

A careful interview conducted by a clinician knowledgeable about children, adolescents, and mood disorders is essential. This will usually take several hours to complete. This can be done in sequential sessions or by dividing assessment tasks between clinicians in a multidisciplinary clinic. It is helpful for families to keep daily logs for at least a 2-week period before their first visit. Ideally, families would track mood, energy, sleep, and unusual behavior.

Developing a timeline with the primary informant to establish onset, offset and duration of symptoms provides an efficient way to understand the unfolding of the bipolar phenomena, as well as the comorbid conditions, over time. This should include all the "BAMO" symptoms of *b*ehavior, *a*nxiety, *m*ood, and *o*ther (Cerel and Fristad, 2001). It is useful to document on the timeline pregnancy/birth features, child care arrangements, school history, stressful life events, and treatment history so an integrated understanding of all these components can be facilitated. Methods for eliciting time frames in children include asking about relation to birthdays, holidays, school semester starts and ends, vacation times, and previous grades (e.g., asking a fourth grader whether symptoms were present in third grade or second grade). Children as young as age 7 who are of average intelligence usually can give onsets and offsets with these anchor probes.

The child's medical history should be reviewed, noting a history of allergies, asthma, chronic illnesses, staring spells, injuries (especially head trauma), and their treatment. Previous laboratory findings and brain imaging should be reviewed. Although no laboratory test or brain imaging is diagnostic of BPD, such data can contribute important information about the child. Some prescription medications, psychotropic and other, as well as illicit substances can induce manic-like symptoms (Table 1). If there is any suspicion that illegal drugs have been ingested, a drug screen is essential. Activation and disinhibition on psychotropic drugs, unfortunately, are not uncommon (Wilens et al., 1999). If symptoms appear to have been triggered by a prescription drug (e.g., stimulant, antidepressant, steroid), a 7- to 10-day washout period is recommended (2–3 weeks for steroids or fluoxetine). If symptoms continue after that point, a diagnosis of BPD should be considered.

In addition to longitudinal symptom information obtained in the timeline, cross-sectional documentation of current symptoms is essential. It can be useful to document worst, best, and current functioning, as reported by the parent. Obtaining information from children only on current functioning is sufficient because their ability to provide historical information on symptom severity is limited. A three-generation genogram can be generated to ascertain both a family history of psychiatric disorders as well as each parent's experience in his or her family of origin. The prompt "Can you tell me briefly what growing up was like for you (for your spouse)?" with follow-up prompts, as needed, to determine family, school, and peer functioning of the two parents provides an excellent lead in to review for a history of mood, anxiety, substance, behavior, learning, and psychotic disorders. Although the clinician's goal is to diagnose the child, not the family history, it is important to realize that children whose parents have BPD have two to three times the risk of developing a mood disorder (Chang et al., 2000; DelBello and Geller, 2001).

Before ascertaining symptom presence and absence, children and parents should be asked about children's functioning at home, at school, and with peers (see,

for example, the standardized questions in the Children's Interview for Psychiatric Syndromes (Weller et al., 2000), K-SADS (Kaufman et al., 1997), or WASH-U K-SADS (Geller et al., 1998b). This helps to provide a contextual base for probing symptoms, as described earlier.

Psychoeducational testing once the child's mood is stable can be very important in developing a comprehensive care plan. Children with BPD are at increased risk of learning disabilities (Wozniak et al., 1995b), and there is an indication that cognitive functioning deficits, such as verbal memory, executive functioning, and deficits in mathematics, may occur in children with BPD (Shear et al., 2002).

Family Considerations

There are several immediate considerations for families when diagnosing a child with BPD. First, information supplied by the family is essential to make the diagnosis, for reasons outlined previously. Second, in the process of diagnosing the child, clinicians frequently discover untreated (and sometimes, undiagnosed) mood disorders or other conditions, in immediate family members. Referring these individuals for treatment can greatly reduce stress in the household, thereby providing more resources for managing the child's BPD. Third, families need to become educated about BPD and its effects on the family. Currently, there are several resources that clinicians can recommend to families and that are listed at www.jaacap.com via the Article Plus feature.

It is important for clinicians to be sensitive to and help parents through the process of grieving the loss of their healthy child. This is particularly true for families in which the child experiences an acute onset of BPD. Families need to mourn the loss of the idealized well child before they can readily adapt to a child with a chronic illness, especially if that same illness has devastated the lives of other family members (e.g., a grandfather who completed suicide, an aunt who spent her life in a state hospital).

SECTION II: ACUTE PHASE MEDICATION TREATMENT FOR BPD

These medication treatment algorithms were developed for the acute phase treatment of children and ado-

lescents ages 6 to 17 years who meet *DSM-IV* criteria for BPD-I, manic or mixed episode. In the development of this algorithm, the consensus panel established four levels of evidence (A–D) that provided the guiding principle for the stages and branching within the treatment algorithm. These levels were as follows: level A data consisted of randomized, controlled clinical trials in children; level B data consisted of randomized, clinical trials in adults; level C data were based on open trials and retrospective analyses; and level D data were based on case reports and panel consensus as to recommended current clinical practices.

With this formulation, level A took precedence over level B, level B took precedence over level C, and level C took precedence over level D in determining treatment recommendations. This model is similar to that used with the Texas Children's Medication Algorithm Project for the treatment of major depression in childhood (Hughes et al., 1999), with the exception that with Texas Children's Medication Algorithm Project, level A data consisted of both child and adult clinical trials. It was determined by the consensus panel that, given the recent findings demonstrating lack of efficacy of some antidepressants for children (U.S. Food and Drug Administration, 2003) that were found to be positive in adults, level A evidence needed to be based on studies in children and adolescents. A summary of these levels of evidence is contained in Table 2.

The consensus panel recommended a minimum of 4 to 6 weeks at therapeutic blood levels and/or adequate dose for each medication trial. In some cases (e.g., treatment with lithium), 8 weeks of treatment may be required to assess the effectiveness of the particular psychotropic agent.

Treatment Algorithms

Two treatment-specific algorithms were developed for acute phase treatment of BPD-I in children and adolescents, manic or mixed, depending on whether the child presented with or without features of psychosis. There was no evidence in children and adolescents about the treatment of BPD-II, so no algorithms were developed for this. Both treatment algorithms consist of six potential stages of treatment. For all the treatment stages described below, when a child does not respond to treatment, it is important to consider factors frequently associated with nonresponse such as

TABLE 2
Summary of Levels of Evidence

	Bipolar I Disorder, Manic or Mixed, *Without Psychosis*	Bipolar I Disorder, Manic or Mixed *With Psychosis*	Bipolar Depressive Episode
Lithium	A & B	A & B	B & C
Divalproex	B & C	B & C	C
Carbamazepine	B	B	ND
Oxcarbazepine	D	D	ND
Topiramate	C	C	ND
Clozapine	C	C	ND
Risperidone	B & C	B & C	ND
Olanzapine	B & C	B & C	B
Quetiapine	B & C	B & C	B
Ziprasidone	B & C	B & C	ND
Aripiprazole	B & C	B	ND
Selective serotonin reuptake inhibitors	NA	NA	C[a]
Bupropion	NA	NA	D
Lamotrigine	C	C	B & D

Note: Level A data consist of child/adolescent placebo-controlled, randomized clinical trials. Level B data consist of adult randomized clinical trial. Level C data consist of open child/adolescent trials and retropective analysis. Level D data consist of child/adolescent case reports or the panel consensus as to recommend current clinical practices. ND = no data; NA = not applicable.

[a] May be mood destabilizing.

misdiagnoses, poor adherence to treatment, presence of comorbid disorders (e.g., ADHD, substance abuse, anxiety disorders), and exposure to environmental and biological stressors.

ALGORITHM I: BPD-I, MANIC OR MIXED, ACUTE, WITHOUT PSYCHOSIS (FIG. 1)

Stage 1: Monotherapy

Monotherapy with the traditional mood stabilizers lithium, divalproex, and carbamazepine and the atypical antipsychotics olanzapine, quetiapine, and risperidone was determined to be first-line treatment. Although lithium has had the most controlled study in children and adolescents with BPD (Brumback and Weinberg, 1977; DeLong, 1990; Geller et al., 1998a; Gram and Rafaelsen, 1972; Lena et al., 1978; McKnew et al., 1981), some limitations include small sample size and methodological problems. Evidence of these agents as monotherapy in stage 1 is found in open trials of lithium (Kafantaris et al., 2003), divalproex (Kowatch et al., 2000; Papatheodorou and Kutcher, 1993; Papatheodorou et al., 1995; Wagner et al., 2002; West et al., 1994, 1995), carbamazepine (Kowatch et al., 2000), olanzapine (Frazier et al., 2001), and risperidone

(Biederman, 2003) (level C), retrospective analysis of risperidone (Frazier et al., 1999) (level C), case reports of olanzapine (Kemner et al., 2002; Soutullo et al., 1999) (level D), controlled trials of quetiapine (DelBello et al., 2002a) (level A), and clinical experience (level D). Because the comparative efficacy of these agents has not been well investigated, the panel was unable to make a definitive recommendation as to initial selection among them. However, the majority of the panel recommended lithium or divalproex as the first medication choice for nonpsychotic mania. Both the clinical experience of the clinician in the use of these agents and the side effects profile of the medication for a given child must guide initial monotherapy selection.

Ziprasidone, aripiprazole, and oxcarbazepine were not included in the list of stage 1 monotherapy agents because of the lack of any data regarding their use in children and adolescents with BPD. However, as data become available, recommendations may change.

Stage 1A: Monotherapy Plus Augmentation

For children who have had a partial (moderate to minimal) improvement in initial monotherapy, it was recommended that an augmenting agent be used. There is some evidence to support augmentation strategies

Bipolar I Disorder, Manic or Mixed, without Psychosis
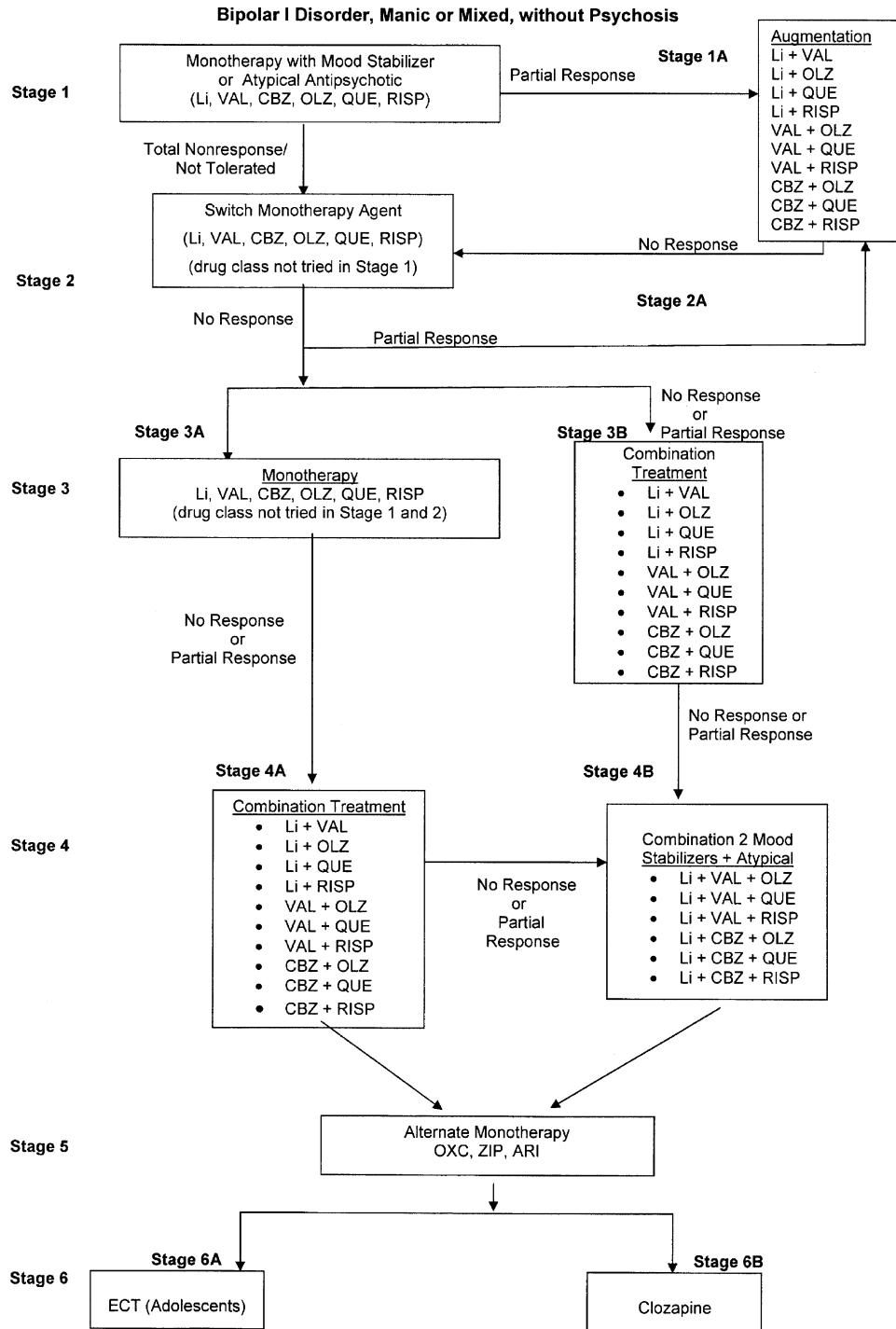
Fig. 1 Algorithm I: Bipolar I disorder, manic or mixed, acute, without psychosis. Algorithm II: Bipolar I disorder, manic or mixed, acute, with psychosis. Li = lithium; VAL = valproate; CBZ = carbamazepine; OLZ = olanzapine; RISP = risperidone; QUE = quetiapine; RISP = risperidone; OXC = oxcarbazepine; ARI = aripiprazole; ECT = electroconvulsive therapy.

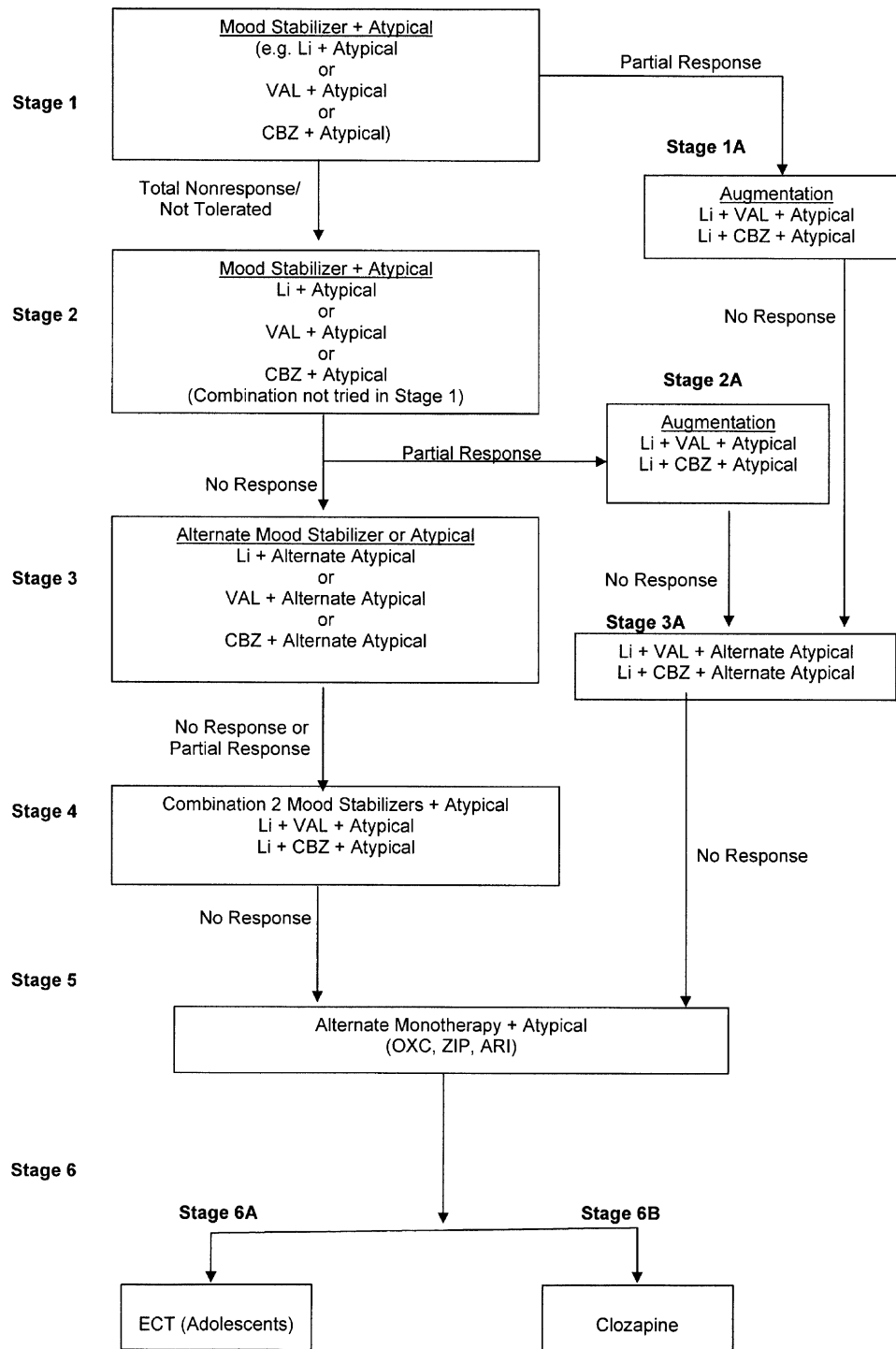**Bipolar I Disorder, Manic or Mixed, with Psychosis**

Stage 1

Mood Stabilizer + Atypical
(e.g. Li + Atypical
or
VAL + Atypical
or
CBZ + Atypical)

Partial Response

Stage 1A

Augmentation
Li + VAL + Atypical
Li + CBZ + Atypical

Total Nonresponse/
Not Tolerated

No Response

Stage 2

Mood Stabilizer + Atypical
Li + Atypical
or
VAL + Atypical
or
CBZ + Atypical
(Combination not tried in Stage 1)

Stage 2A

Augmentation
Li + VAL + Atypical
Li + CBZ + Atypical

Partial Response

No Response

No Response

Stage 3

Alternate Mood Stabilizer or Atypical
Li + Alternate Atypical
or
VAL + Alternate Atypical
or
CBZ + Alternate Atypical

Stage 3A

Li + VAL + Alternate Atypical
Li + CBZ + Alternate Atypical

No Response or
Partial Response

No Response

Stage 4

Combination 2 Mood Stabilizers + Atypical
Li + VAL + Atypical
Li + CBZ + Atypical

No Response

Stage 5

Alternate Monotherapy + Atypical
(OXC, ZIP, ARI)

Stage 6

Stage 6A

Stage 6B

ECT (Adolescents)

Clozapine

Fig. 1 Continued.

(Chang and Ketter, 2000; DelBello et al., 2002a; Findling et al., 2003b; Kowatch et al., 2003) (level C) for children and adolescents with manic or mixed episodes. In this stage, if the initial monotherapy agent was lithium, then divalproex, carbamazepine, olanzapine, quetiapine, or risperidone could be added. Similarly, if divalproex were the initial monotherapy, then lithium, olanzapine, quetiapine, or risperidone could be augmenting agents. Some panel members recommended combining lithium and divalproex before combination treatment with an atypical antipsychotic for nonpsychotic mania. If the atypical antipsychotics resulted in a partial response, then lithium, divalproex, or carbamazepine could be added treatments. If there was no positive response to the augmenting agent, then stage 2 treatment with a monotherapy agent not used in stage 1 is clinically indicated.

Stage 2: Alternate Monotherapy

For those children who had no response to the initial monotherapy agent or who had intolerable side effects, monotherapy with one of the medications not tried in stage 1 is recommended.

Stage 2A: Alternate Monotherapy Plus Augmentation

If a child has a partial response to the monotherapy agent selected in stage 2, then augmentation with an agent that was not used in stage 1 is clinically indicated. For example, if lithium monotherapy had failed in stage 1 but divalproex monotherapy produced a partial response in stage 2, then an atypical antipsychotic such as olanzapine, quetiapine or risperidone could be added to the treatment regimen.

Stages 3A and 3B: Monotherapy or Combination of Two Mood Stabilizers

The consensus panel members were divided in their clinical opinions about the treatment strategy when a child with a mixed or manic episode has tried two monotherapy agents without success. Some panel members believed that to reduce the likelihood of side effects and to increase compliance, selection of monotherapy agents not tried in stages 1 and 2 would be a reasonable clinical choice (stage 3A). It was also clinical opinion (level D) that lack of response to two monotherapy agents did not predict failure of an agent of a different class. For example, failure to produce response to lith-

ium or risperidone did not predict failure to produce response to divalproex. However, it was the clinical opinion (level D) of other panel members that a child for whom two monotherapy trials had failed would be unlikely to respond to an alternative monotherapy agent. Stage 3B possible medication combinations are lithium plus divalproex, lithium plus an atypical antipsychotic (olanzapine, quetiapine, or risperidone), divalproex plus an atypical antipsychotic, or carbamazepine plus an atypical antipsychotic.

Stages 4A and 4B: Combination of Two Mood Stabilizers or Combination of Three Mood Stabilizers

For children who have had no response or a partial response to monotherapy in stage 3A, the recommendation in stage 4A is a combination of two mood stabilizers. Possible combinations include lithium plus divalproex, lithium plus carbamazepine, or lithium plus one of the atypical antipsychotics (olanzapine, quetiapine or risperidone); divalproex plus one of these atypical antipsychotics; or carbamazepine plus one of these atypical antipsychotics.

Stage 4B is for those children who had no response or a partial response to augmentation with a monotherapy agent (stage 2A) or who had no response or a partial response to a combination of two mood stabilizers (stage 3B). Possible combinations of three mood stabilizers include lithium plus divalproex plus olanzapine, lithium plus divalproex plus quetiapine, lithium plus divalproex plus risperidone, carbamazepine plus lithium plus olanzapine, carbamazepine plus lithium plus quetiapine, or carbamazepine plus lithium plus risperidone.

Stage 5: Alternate Monotherapy

Trials of alternate monotherapy with oxcarbazepine (Reimherr et al., 2002) (level D), ziprasidone (level D), or aripiprazole (level D) were considered as stage 5 treatment.

Although there is past clinical experience (level D) with typical antipsychotics, the atypical antipsychotics have the advantage of a more tolerable side effects profile. Double-blind, placebo-controlled trials in adults with acute mania have failed to demonstrate superiority of gabapentin compared with placebo (McElroy and Keck, 2000). Therefore, gabapentin is not recommended as monotherapy for the treatment of acute mania in children. Although lamotrigine has received U.S. Food and Drug Administration approval for long-term

maintenance treatment of BPD-I in adults (Bowden et al., 2003), there are no data available about its use for manic episodes in youths. Therefore, the panel did not recommend lamotrigine for treatment of acute manic episodes in children and adolescents.

Stage 6: Electroconvulsive Therapy (ECT) or Clozapine

For youths who did not show a positive response or who experienced intolerable side effects to all the treatments in stages 1 through 5, clozapine for children and adolescents is recommended, and treatment with ECT is recommended for adolescents only. Case reports of the effectiveness of ECT in the treatment of acute mania in adolescents (Rey and Walter, 1997) (level D) have been reported. In case series (Kovacs and Pollock, 1995; Masi et al., 2002) (level D), clozapine has been effective in the treatment of children and adolescents with BPD (Kowatch et al., 1995). There were insufficient data to recommend one treatment over the other.

ALGORITHM II: BPD-I, MANIC OR MIXED, ACUTE, WITH PSYCHOSIS (FIG. 1)

Stage 1: Mood Stabilizer Plus Atypical Antipsychotic

For children with BPD-I, manic or mixed with psychosis, it was recommended that initial treatment should be a combination of a traditional mood stabilizer (lithium, divalproex, or carbamazepine) and an atypical antipsychotic. As evidence, lithium plus an adjunctive antipsychotic in an open trial (Kafantaris et al., 2001a) (level C) was shown to demonstrate significant improvement for adolescents with acute mania and psychosis. Divalproex plus an atypical antipsychotic or carbamazepine plus an atypical antipsychotic, based on clinical experience (level D) were recommended as other treatment options.

Stage 1A: Augmentation

For children whose symptoms do not respond to a mood stabilizer plus an atypical antipsychotic, a combination treatment with three medications is recommended, based on clinical experience (level D). In this case, lithium plus divalproex plus an atypical antipsychotic or lithium plus carbamazepine plus an atypical antipsychotic would be the treatment regimen.

Stage 2: Mood Stabilizer Plus Atypical Antipsychotic

If a child's symptoms fail to respond or the child has intolerable side effects from the medication used in stage 1, then the combination of medications not tried in stage 1 is recommended. For example, if in stage 1 a child experienced insufficient response to lithium plus an atypical antipsychotic, then in stage 2 divalproex plus an atypical antipsychotic is recommended.

Stage 2A: Augmentation

If a child has a partial response to lithium plus an atypical antipsychotic, divalproex plus an atypical antipsychotic, or carbamazepine plus an atypical antipsychotic, augmentation is recommended, based on clinical experience (level D). For example, lithium plus divalproex plus an atypical antipsychotic would be the treatment combination.

Stage 3: Mood Stabilizer Plus Alternate Atypical Antipsychotic

For children who have not had a positive response to traditional mood stabilizers (lithium, divalproex, or carbamazepine) plus an atypical antipsychotic, then, based on clinical experience (level D), it is recommended that an alternate atypical antipsychotic be added to the mood stabilizer. For example, if the child had been treated with lithium and risperidone in stage 2, then lithium plus a different atypical antipsychotic would be a possible treatment combination.

Stage 3A: Lithium Plus Divalproex or Carbamazepine Plus Alternate Atypical Antipsychotic

If a child's symptoms fail to respond to stage 2A treatment with lithium plus divalproex plus an atypical antipsychotic or to lithium plus carbamazepine plus an atypical antipsychotic, substitution of an alternate atypical antipsychotic is recommended.

Stage 4: Combination of Two Mood Stabilizers Plus Atypical Antipsychotic

For children whose symptoms have not responded to treatment with lithium and two atypical antipsychotic trials, divalproex and two atypical antipsychotic trials, or carbamazepine and two atypical antipsychotic trials, combination treatment of two mood stabilizers plus an atypical antipsychotic is recommended, based on clinical experience (level D). In this case, lithium plus divalproex or carbamazepine plus an atypical antipsychotic would be the treatment regimen.

Stage 5: Alternate Monotherapy Plus Atypical Antipsychotic

If medications used in stages 1 through 4 all fail, then alternate monotherapy (oxcarbazepine) plus an atypical antipsychotic is recommended, based on clinical experience (level D).

Stage 6: ECT or Clozapine

For children and adolescents who have not responded to combinations of treatment with three medications, clozapine is recommended. ECT is recommended for adolescents only.

Acute Phase Treatment for BPD-I, Depressed

Because there are no prospective studies in children and adolescents for the treatment of BPD-I, depressed, the panel agreed that there was insufficient evidence to develop a treatment algorithm. Based on data available on adults with bipolar depression treated with lithium (level B) (Zornberg and Pope, 1993), lithium was recommended as a treatment option for bipolar depression in children and adolescents. A retrospective review (Biederman et al., 2000b) (level C) showed that SSRIs improved depressive symptoms for children and adolescents with bipolar depression. However, the SSRIs had destabilizing effects in some of these youths, although they were not all being treated with mood stabilizers. Another antidepressant treatment option is bupropion, based on clinical experience (level D). It was recommended that SSRIs and bupropion be used as adjunctive treatments after mood is stabilized with a mood stabilizer. As with adults, it was recommended that antidepressant medication be continued for at least 8 weeks after there is depressive symptom remission. In randomized, controlled trials in adults, lamotrigine has been found efficacious for the acute phase and for prevention of depressive episodes (Bowden et al., 2003; Calabrese et al., 1999). In children, other treatment alternatives are lamotrigine, based on a retrospective analysis (Carandang et al., 2003) (level D) and clinical experience and divalproex, based on clinical experience (level D).

Studies in depressed youths have shown that cognitive-behavioral therapy (CBT) and interpersonal psychotherapy are efficacious for the acute treatment of depression (Birmaher et al., 2000; Mufson et al., 1999). However, studies on depressed bipolar children and adolescents are needed. In adults, CBT and family-focused therapy have been shown to reduce the number and extend the time to relapses/recurrences, particularly periods of depression (Miklowitz et al., 2000, 2003). In cases of severe depression associated with BPD, ECT is also a treatment consideration in adolescents with severe, treatment-resistant bipolar depression (Bloch et al., 2001; Rey and Walter, 1997).

Newer Agents

As mentioned above, gabapentin has not been found to be more effective than placebo in treating adults with acute mania (Frye et al., 2000; Pande et al., 2000). Therefore, it is not currently recommended that gabapentin be used as a primary mood stabilizer in children with BPD. However, gabapentin is usually very well tolerated and does not seem to preferentially cause mania (Erfurth et al., 1998; Schaffer and Schaffer, 1999), but manic reactions in adults (Leweke et al., 1999) and behavioral side effects, such as behavioral disinhibition, have been reported in children (Kafantaris et al., 1996). Additionally, several studies have suggested a role for gabapentin in treating anxiety disorders, such as social phobia (Pande et al., 1999) and panic disorder (Pande et al., 2000). Therefore, gabapentin may prove to be a useful agent for treating comorbid anxiety in youths with BPD because treatment with SSRIs may exacerbate mania.

Lamotrigine is effective in adult bipolar depression (Calabrese et al., 1999), rapid cycling BPD (Calabrese et al., 2000), and prophylaxis of mood episodes in adults with BPD (Bowden et al., 2003). Data in children with BPD are limited (Carandang et al., 2003). Lamotrigine carries a black box warning from the U.S. Food and Drug Administration that children younger than the age of 16 are at increased risk of Stevens-Johnson syndrome, based on early epilepsy data. However, more recent data suggest that the incidence of serious rash in children taking lamotrigine may be 1 in 10,000 (Messenheimer, 2002). Nevertheless, more data on lamotrigine use in children with BPD are needed before a consensus recommendation can be made. Initial data indicate that with proper combination pharmacotherapy with lithium and divalproex, residual depressive symptoms may be largely eradicated (Findling and Calabrese, 2003). However, the treatment of bipolar depression in children and adolescents also requires further study.

Oxcarbazepine is a promising agent for acute mania in adults (Hummel et al., 2001; Nassir Ghaemi et al., 2002). Again, no child data are available. It should be noted that this agent does not appear to be interchangeable with carbamazepine, regarding clinical effectiveness and tolerability, so further randomized controlled trials are recommended.

Aripiprazole is likewise promising for treating acute mania in adults (Keck et al., 2003), but there are no data on such use in children and adolescents. Initial experience with aripiprazole indicates that dosing strategies for youths may differ from those for adults (Findling et al., 2003a). Randomized, controlled trials with this agent in pediatric BPD may also be warranted.

Omega-3 fatty acids (OFAs) have been studied somewhat, but only in adults with BPD (Stoll et al., 1999). Although the efficacy and safety of relatively large doses of OFAs in children are unknown, the U.S. Food and Drug Administration has approved the use of as much as 3 g/day of OFAs in the general population. Methodologically rigorous studies of OFAs in pediatric BPD are needed to determine what role OFAs might have in the treatment of young people. As with any "natural" treatment, another potential danger of treating with OFAs may lie in ignoring more effective treatments as the illness worsens.

Topiramate has not been shown to have efficacy in adults with mania. However, it has been relatively unstudied in pediatric psychiatry. Retrospective chart reviews and open data suggest that it may be useful as adjunctive treatment for some adolescents with BPD (DelBello et al., 2002b). However, once again, well-controlled studies in children are not available and are needed.

Newer anticonvulsants, such as levetiracetam, zonisamide, and tiagabine, are completely unstudied in pediatric BPD. Furthermore, there are few data to support their use in adult mania. Therefore, treatment with these agents in children and adolescents with BPD is not currently recommended.

SECTION III: TREATMENT OF COMORBID PSYCHIATRIC DISORDERS

As described in the section on assessment, most children and adolescents with BPDs have other coexisting (comorbid) psychiatric disorders, particularly ADHD, oppositional defiant disorder, conduct disorder, anxiety disorder, and, during adolescence, substance abuse. In this section, the treatment of these comorbid disorders is described. However, it is important to emphasize that there are very few controlled studies for the treatment of comorbid disorders in youths with BPD and that almost all the literature is anecdotal.

General Principles

If it is confirmed that a child with BPD has one or more comorbid disorders, the treatment plan should be modified to include treatment of each disorder because comorbid conditions worsen the prognosis of BPD. This is a complex process that may require one or more periods of trial and error to achieve the correct combination of medications and psychotherapy.

All coexisting disorders should be carefully monitored at baseline and over time, and the benefits and side effects of each treatment must be continuously assessed. For this purpose, the instruments that are specific to each comorbid disorder should be used. The information collected through these instruments will help monitor the child's response to treatment of the BPD symptoms as well as the symptoms of comorbid psychiatric and medical conditions.

Before treating the comorbid disorder(s), it is important to first stabilize the symptoms of BPD. Once the bipolar symptoms are stabilized, the need for treatment of comorbid disorders should be reviewed. If the symptoms of the comorbid condition(s) are negatively affecting the child's psychosocial or academic functioning, then treatment is warranted. The panel recommended that it is best to use available medications and/or psychosocial treatments for each specific comorbid disorder, particularly if the efficacy and safety of these treatments have been evaluated by randomized, controlled trials. However, it is important to ascertain the availability of treatment (e.g., therapists with good training in CBT) and patient/family beliefs and motivation to follow through with any specific modality of treatment.

Whenever appropriate, using psychosocial therapies to treat coexisting disorders is recommended. For example, CBT has been found to be helpful for the treatment of depression, anxiety, and obsessive-compulsive disorders (Gaynor et al., 2003), and interpersonal psychotherapy is effective for the treatment of major depression in teens (Mufson et al., 1999). In contrast

to some medications, psychosocial therapies do not generally cause mood dysregulation and can therefore be used without the risk of aggravating bipolar symptoms.

Although it is important to treat most of the impairing comorbid symptoms as soon as possible, it is best to begin treatment for each comorbid disorder sequentially, one at a time after the BPD has been adequately treated. It is recommended to introduced medications one at a time, if possible, to discern the benefits and side effects of each agent.

Attention-Deficit/Hyperactivity Disorder

ADHD is one of the most common comorbid conditions, occurring in 70% to 90% of prepubertal children and 30% to 40% of adolescents with BPD (Geller and Luby, 1997; Kafantaris et al., 1998; Wozniak et al., 1995a). The panel recommended treating the bipolar symptoms first and then, if the ADHD symptoms are still present and impairing the child's functioning, treating the ADHD. The most efficacious treatment, particularly for moderate to severe ADHD symptomatology, is pharmacological management (Biederman et al., 2004). Psychosocial interventions, including parent behavior management training and school consultation and support, are also indicated (Jensen et al., 2001; Swanson et al., 2001).

Currently, the medications used to treat ADHD include the stimulants (methylphenidate and derivatives of amphetamine) and nonstimulants (atomoxetine, bupropion, the tricyclic antidepressants), and to a lesser extent the α_2-agonists (clonidine and guanfacine) (Biederman et al., 2004). Of all these medications, stimulants are the agents of choice for ADHD uncomplicated by BPD (Connor et al., 2002).

Because the symptoms of ADHD may worsen and complicate the treatment of BPD, until further research with larger samples becomes available, it was recommended to carefully use the stimulants if clinically indicated and only after the child's bipolar symptomatology has been controlled with a mood stabilizer. Of the nonstimulants, atomoxetine (Kratochvil et al., 2002), the tricyclic antidepressants, and, to a lesser extent, bupropion have been found in randomized, controlled trials to be efficacious for the treatment of ADHD (American Academy of Child and Adolescent Psychiatry, 2002; Pliszka, 2001). However, all these medications are antidepressants or have tricyclic-like

activity and can induce switches to mania/hypomania and mixed and rapid cycling episodes (Biederman et al., 1999). Although there are no controlled studies to guide treatment decisions, some experts have found the α_2-agonists helpful for the aggressive behavior in children with ADHD (Hunt, 1987).

Oppositional Defiant and Conduct Disorders

If a child has BPD and the behavior problems appear to be secondary to the mood disorder (mania, depression, or both), the panel recommended first optimizing the treatment of the BPD. If the behavior problems cannot be attributed to BPD or do not improve after the symptoms of mania/hypomania subside, treatment for both the bipolar and the behavior disorders is indicated.

Several modalities of parent behavior management have been shown to be effective for the treatment of behavior disorders (Goldberg-Arnold and Fristad, 2002) and can be used as adjunctive treatment for children with BPD and behavior disorders. Also, medications used for the treatment of BPD such as lithium (Campbell et al., 1984), divalproex (Steiner et al., 2003), the first generation of typical antipsychotics (Campbell et al., 1984), and the atypical antipsychotics have been found useful for the management of behavior disorders (Findling et al., 2000), particularly in the reduction of aggression. Because the typical antipsychotics have worse side effects profiles than the atypical antipsychotics, it is preferable to use the latter. Importantly, many children with behavior disorders have ADHD (Biederman et al., 2004); in these cases, the use of the stimulants may be warranted. Also, the possibility that the behavior problems are due to ongoing stressors, use of substances, or, in some cases, PDD should also be considered.

For many children, the combination of severe mood symptoms and dangerous behavior may require short-term psychiatric hospitalization. Malone et al. (1997) report that as many as 50% of children with severe aggression responded to hospitalization even before medication treatment began. However, Carlson and Youngstrom (2003) found that in children with pervasive mania (i.e., mania reported by both parent and teacher), this is much less likely. In those cases in which medication trials and hospitalization have not been successful, residential treatment may be necessary.

Anxiety Disorders

Comorbid anxiety disorders can be treated using psychotherapy and/or pharmacological interventions. Among the psychosocial treatments, CBT has been found efficacious for the treatment of separation, social, and general anxiety and for obsessive-compulsive and posttraumatic stress disorders (March, 1995; March et al., 1998). The SSRIs have also been found to be efficacious for the treatment of these disorders (Birmaher et al., 2003), but caution should be used because these agents may trigger manic, mixed, or rapid cycling episodes. Therefore, in most cases, particularly in patients with BPD-I, before attempting to use SSRIs to alleviate the anxiety disorder, it is advisable to first stabilize the BPD.

Currently, there are very few other pharmacological alternatives for the management of anxiety symptoms in patients with BPD. Clinical experience appears to indicate that buspirone is not an effective medication to treat anxiety disorders in children. The benzodiazepines have been shown to be efficacious for the treatment of adult anxiety disorders, but only a few studies with small samples have been conducted in children with anxiety (Bernstein and Shaw, 1997). Due to their potential for abuse and cognitive side effects, this group of medications is not recommended as first line treatment for children who have both anxiety and BPD. However, they can be used for the short-term treatment of agitation or anxiety problems until the other medication (e.g., the SSRIs) begins to work.

Substance Abuse

It is important to determine whether the mood symptoms were present before substance abuse began or if the mood changes are the result of substance abuse. If it is clear that the person has both substance abuse and BPD, both conditions need to be treated simultaneously without delay. A placebo-controlled trial in adolescents with comorbid BPD and substance dependence disorders showed that lithium was an efficacious treatment for both disorders (Geller et al., 1998a). The optimal treatment of adolescents with substance abuse and BPD involves an integration of treatment modalities rather than merely consecutive treatments with a specific focus on either substance abuse or BPD (Wilens et al., 1999). The treatment of BPD comorbid with substance abuse is usually managed on an outpatient basis, preferably by staff trained to deal with both disorders. However,

sometimes it will be necessary to admit patients to the hospital, day hospital, or a rehabilitation facility. In these settings, the youths will, it is hoped, not use illicit drugs or alcohol, allowing his or her true mood to be observed closely.

A number of family-related factors, such as parental alcoholism or other substance abuse, poor parent–child relationships, low parental support, inconsistent or ineffective discipline, and poor parent supervision and management of the teen's behavior, have been identified as risk factors for the development of substance abuse among teens. Thus, it is not surprising that several types of family therapy (e.g., functional family therapy, multisystemic therapy, multidimensional family therapy) have been found useful for the treatment of youths with substance abuse (Latimer et al., 2003; Liddle and Dakof, 1995).

Other Psychiatric and Medical Conditions

Youths with BPD who are experiencing significant tics should initially be offered treatment with the atypical antipsychotics to target their tics as well as their mood disorder. Patients with BPD and behavioral symptoms associated with PDD should also be initially treated with an atypical antipsychotic, and other mood stabilizers should be added as necessary. The use of other medications and/or psychosocial treatment to target other PDD symptoms (e.g., inattention, hyperactivity, obsessions) should be considered, taking into account that some medications may worsen the child's mood. If available, patients should be referred to an appropriate PDD program. Approaches to the treatment of youths with BPD and mental retardation are similar to those described for patients with BPD and PDD.

For youths with seizures or migraines in addition to BPD, medications that target both disorders, such as divalproex, carbamazepine, and oxcarbazepine should be tried first. Female patients with significant premenstrual dysphoria may be offered SSRIs after mood stabilization with lithium, divalproex, or other mood stabilizers.

Management of Suicidal Behaviors

Although it is beyond the scope of this article to review the assessment and management of suicide, it is important to be aware that suicidal behaviors are more frequent in BPD than in other psychiatric disorders

(Baldessarini and Jamison, 1999). Therefore, every child and adolescent with BPD needs to be evaluated for the presence of these symptoms. This evaluation should include the assessment of risk factors for suicide completion, including older age, male sex, previous attempts, depressive/manic symptoms (especially mixed or psychotic episodes), sexual or physical abuse, comorbid disruptive disorders, comorbid substance abuse, impulsivity, availability of method (e.g., guns at home), lack of support, presence of acute stressors, and family history of suicide (Brent, 1993; Gould et al., 2003). If a youth presents suicidal behaviors and several of the risk factors noted above, the first step is to evaluate whether the child is safe and whether the treatment needs to be carried out in an outpatient or inpatient setting. The data regarding long-term use of lithium are compelling: It is associated with an eightfold reduction in suicide and reported attempts in adults with BPD (Baldessarini et al., 1999). Management of suicidal behaviors requires successful treatment of the mood disorder and treatment of other risk factors such as substance abuse, behavior problems, and ongoing negative stressors (e.g., abuse, family conflicts), and removal of any available method. Involvement of the family is essential. Specific psychosocial therapies for the management of ongoing suicidality such as dialectic behavior therapy, if available, should also be considered (Rizvi and Linehan, 2001).

SECTION IV: MAINTENANCE/CONTINUATION TREATMENT

The basic goals of maintenance treatment include prevention of relapse and recurrence; reduction of subthreshold symptoms, suicide risks, affective cycling, and mood instability; reduction of vocational and social morbidity; and promotion of wellness. At present, it appears that the agents that help patients get well are the same ones that keep them well. Whereas lithium, divalproex sodium, and carbamazepine have been the agents most commonly used to treat children and adolescents with BPD (Weller et al., 2002), current research, mostly in adults, supports the efficacy of lithium, lamotrigine, and olanzapine as maintenance treatments (Keck Jr., 2003).

Unfortunately, there is a paucity of prospective randomized maintenance studies. The results of one trial suggest that in young patients with BPD who achieve syndromal remission with combination lithium and divalproex sodium therapy, maintenance monotherapy treatment with either lithium or divalproex sodium appears equally effective. Unfortunately, the use of either lithium or divalproex monotherapy treatment in this patient group was associated with a relatively rapid median time to relapse (Findling et al., 2003b). In a prospective case series, Strober et al. (1990) found that continuation of lithium decreased the 18-month relapse rate from 92.3% to 37.5% in 37 adolescents diagnosed with BPD.

Because pediatric BPD appears to be a chronic condition with a high risk of relapse, it was recommended that maintenance treatment studies be a high priority. Due to the possibility that drug monotherapy may not be associated with optimal long-term symptomatic control, future maintenance studies should compare combination pharmacotherapy with single-drug treatment.

There is also limited information regarding how long treatment for BPD should be maintained in young patients. For adults, the American Psychiatric Association's *Practice Guideline for the Treatment of Patients with Bipolar Disorder* recommends that treatment with a maintenance agent should continue for a minimum of 18 months after stabilization of a manic episode (Hirschfeld, 2002). However, there are no clear answers to definitively inform clinicians regarding how long treatment should be continued.

The panel recommended that medication tapering or discontinuation be considered if the patient has achieved remission for a minimum of 12 to 24 consecutive months. For less severely ill patients or in patients for whom a diagnosis is less clear, a briefer treatment period may be indicated. The risk associated with a potential relapse should be compared with the risk associated with continued pharmacotherapy. Patients for whom greatest caution should be taken are those with a history of suicidal behavior, severe aggression, and/or psychosis. It was acknowledged that for many patients, long-term or even lifelong pharmacotherapy might be indicated.

The consensus was that there appear to be several factors that might place a youth at higher risk of relapse during discontinuation of pharmacotherapy: coadministration of other agents that might destabilize the patient's mood, a greater length of illness, and a higher number of episodes before stabilization. If medications

are to be reduced in a patient with BPD, it was recommended that (1) medications be tapered and not abruptly discontinued, (2) the taper should occur at a time that would be associated with the lowest possible risk of dysfunction/poor outcomes, and (3) the environment be stable with adequate monitoring systems in place so that prodromal mood symptoms of relapse can be readily detected. In addition, emotional and environmental factors may trigger relapses/recurrences. These include sleep deprivation, stress, and negative cognitions. For these reasons, psychotherapeutic interventions that include the family may be helpful in solidifying treatment gains (Fristad and Goldberg-Arnold, 2002; Fristad et al., 2003; Goldberg-Arnold and Fristad, 2002; Miklowitz et al., 2003; Pavuluri et al., 2004).

Safety Issues

Unfortunately, there are very few long-term safety data available on many of the psychotropics used in the treatment of BPD. For this reason, diligent monitoring for side effects must be considered, particularly for youths in whom adverse events are occurring. For the individual patient, the risks of ongoing treatment must be balanced against the manifest therapeutic benefits that are associated with any given agent. Because combinations of medications are increasingly being prescribed for children with BPD and because long-term side effects are likely to occur more frequently with polypharmacy, it is particularly important that side effects associated with chronic treatment are tracked over time.

Weight Gain and Diabetes

Many agents used to treat young people with BPD are associated with weight gain. A series of general medical metabolic problems may occur as a result of increases in weight. These include type 2 (noninsulin dependent) diabetes mellitus, changes in lipid levels, and transaminase elevation (Clark and Burge, 2003; Lebovitz, 2003). Children who experience significant weight gain should be monitored especially closely for these possibilities and should be referred for exercise and nutritional counseling.

Recently, the American Diabetes Association in collaboration with the American Psychiatric Association published a monitoring protocol for all patients before initiating treatment with an atypical antipsychotic (American Diabetes Association and Association AP,

2004). This protocol includes a personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease; weight and height so that body mass index can be calculated; measurement of waist circumference (at the level of the umbilicus); blood pressure; fasting plasma glucose; and a fasting lipid profile. This group recommended that the patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing therapy with an atypical antipsychotic and quarterly thereafter at the time of routine visits. If a patient gains more than 5% of his or her initial weight at any time during therapy, the patient should be switched to an alternative agent. These guidelines should be taken into consideration in all children and adolescents treated with atypical antipsychotics. It should also be recognized that although these guidelines are extremely helpful, they were not written for a pediatric population and the 5% weight gain threshold may not be sensitive enough for children and adolescents.

Cognitive Side Effects

Although cognitive side effects associated with pharmacotherapy have not been well studied, anecdotal reports of word retrieval problems, working memory deficits, and cognitive dulling have been attributed to drugs from all classes of agents used in the treatment of BPD. These changes should be tracked over time. Given an increasing number of reports that many children with BPD have particular difficulties in the areas of executive function, planning, strategizing, organizing, relinquishing a task and changing set, and other related cognitive skills, neuropsychological testing may sometimes be helpful for those youths showing evidence of cognitive dysfunction either before the initiation of pharmacotherapy and/or during medication treatment.

Polycystic Ovarian Syndrome (PCOS)

A number of reports have described high rates of PCOS in women with epilepsy treated with divalproex (Isojarvi et al., 1993, 1998; Murialdo et al., 1997, 1998). These studies have prompted concern regarding the long-term use of divalproex in women with BPD, particularly when started at a young age (Soares, 2000). PCOS is characterized by polycystic ovaries, hyperandrogenism, and chronic anovulation. Clinical manifestations include hirsutism, alopecia, acne, and menstrual abnormalities. Laboratory abnormalities include chronically

elevated plasma testosterone, increased luteinizing hormone secretion due to enhanced pituitary sensitivity to gonadotropin-releasing hormone stimulation, and low or normal plasma follicle-stimulating hormone levels (Franks, 1995).

Relatively few studies of PCOS have been conducted specifically in women with BPD treated with divalproex (McIntyre et al., 2003; O'Donovan et al., 2002; Rasgon et al., 2000). Piontek and Wisner (2000) suggest advising patients receiving divalproex about its potential effects on weight gain and the need for good diet and exercise; monitoring body weight and body mass index during treatment, including lipid profile monitoring at baseline and yearly; and evaluating a woman's menstrual functioning by obtaining an initial menstrual history. Age at menarche, cycle length, duration of menses, and pattern over the preceding 3 months are suggested important components of the menstrual history. Subsequent charting of menstrual pattern with treatment was then encouraged. Of note, pelvic ultrasonography was not recommended as part of the routine monitoring of these patients. In addition, it should be noted that ovarian cysts may occur in healthy adolescent females without PCOS as a normal variant. For this reason, routine pelvic ultrasounds are not recommended for teenagers on divalproex unless there is a clinical indication to do so. In short, until more rigorous data are available, no definitive conclusions can be drawn about divalproex and PCOS in the treatment of BPD.

Other Side Effects

Individual agents are associated with other specific side effects for which clinicians should be watchful. For example, hypothyroidism may occur with lithium treatment, and abnormal involuntary movements may occur during antipsychotic therapy. Divalproex carries a black box warning about rare but potentially life-threatening pancreatitis that can occur in both new patients and those who have taken the medication for an extended period. Children treated with antipsychotic agents should be evaluated at each visit for movement disorders. Other side effects that may warrant concern during antipsychotic pharmacotherapy include prolactin elevation, the possibility of intracardiac conduction effects with ziprasidone, and hematological/neurological adverse events with clozapine, as well as neuroleptic malignant syndrome.

Role of Psychosocial Therapy

Once a child with BPD is stable on medication and is capable of learning new skills, it may be useful, if available, to pursue evidence-based therapy. It includes psychoeducation (i.e., teaching parents and children information about BPD, its symptoms and course, treatment, and systems of care) as well as skill building, especially communication and problem solving in regard to symptom management, emotion regulation, and impulse control (Fristad et al., 2003; Miklowitz, 2002; Pavuluri et al., 2004). Therapeutic techniques used are based in part on family systems interventions and cognitive-behavioral interventions.

A therapeutic alliance is essential when working with families of children with BPD. For a child to benefit from therapy, he or she must be comfortable talking with the therapist. Sometimes forcing a child to attend therapy has the potential to do more harm than good, turning a child off to the process of therapy, which may inhibit its use at a later stage in life. If the child does not wish to attend therapy, parents can still benefit greatly from sessions with a professional who can help them to recognize symptoms, learn problem solving skills to manage symptoms, and develop stress reduction strategies necessary for family preservation.

It is important for the therapist to have a good working knowledge of BPD and other child psychiatric disorders. Otherwise, it is very easy to fall into therapeutic traps (e.g., being disappointed when a finely constructed behavioral plan backfires when the child becomes manic [Mackinaw-Koons and Fristad, 2004]). Therapy do's and don'ts are outlined elsewhere (Fristad and Arnold, 2004; Fristad and Goldberg-Arnold, 2002). In addition to being ineffectual, therapy that "goes nowhere" uses up time, money, and hope. Conversely, when a therapeutic alliance is formed and the therapist is knowledgeable about childhood BPD, families can experience tremendous support. BPD tends to be a chronic illness like diabetes or epilepsy, and an alliance with a good therapist can help the family maintain course through the stormy seas of this illness.

WORKGROUP MEMBERS/CONTRIBUTORS

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Children's Violent Television Viewing: Are Parents Monitoring? Tina L. Cheng, MD, MPH, Ruth A. Brenner, MD, MPH, Joseph L. Wright, MD, MPH, Hari Cheryl Sachs, MD, Patricia Moyer, BS, Malla R. Rao, MEngg, DrPH

Objective: Violent media exposure has been associated with aggressive behavior, and it has been suggested that child health professionals counsel families on limiting exposure. Effective violence prevention counseling requires an understanding of norms regarding parental attitudes, practices, and influencing factors. Both theories of reasoned action and planned behavior emphasize that subjective norms and attitudes affect people's perceptions and intended behavior. Few data exist on violent television viewing and monitoring from a cross-section of families. By understanding the spectrum of parental attitudes, community-sensitive interventions for violence prevention can be developed. The objective of this study was to assess attitudes about and monitoring of violent television viewing from the perspective of parents. *Methods:* An anonymous self-report assisted survey was administered to a convenience sample of parents/guardians who visited child health providers at 3 sites: an urban children's hospital clinic, an urban managed care clinic, and a suburban private practice. The parent questionnaire included questions on child-rearing attitudes and practices and sociodemographic information. *Results:* A total of 1004 adults who accompanied children for health visits were recruited for the study; 922 surveys were completed (participation rate: 92%). A total of 830 (90%) respondents were parents and had complete child data. Of the 830 respondents, 677 had questions on television viewing included in the survey and were the focus of this analysis. Seventy-five percent of families reported that their youngest child watched television. Of these, 53% reported always limiting violent television viewing, although 73% believed that their children viewed television violence at least 1 time a week. Among television viewers, 81% reported usually or always limiting viewing of sexual content on television and 45% reported usually or always watching television with their youngest child. Among children who watched television, parents reported that they spent an average of 2.6 hours per day watching television. Limitation of television violence was associated with female parents and younger children. *Conclusions:* There was variability in attitudes and practices regarding television violence viewing and monitoring among parents. Attitudes and practices varied on the basis of the age of the child and the gender of the parent. **Pediatrics** 2004;114:94–99.