

Clinical Practice Guidelines for Bipolar Affective Disorder (BPAD) in Children and Adolescents

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INTRODUCTION

According to the census of India, 40% of individuals are children below 16 years of age. There is a paucity of prevalence studies of mental disorders in children and adolescents. There are some community studies who have reported prevalence rates of 9.4% in children aged 8–12 years, 12.5% in children aged 0–16 years, and 1.81% in adolescents aged 12–16 years. Bipolar affective disorder (BPAD) has been recognized in children since 1990; however, there is active controversy whether it could occur before the age of 12 years. Some robust Indian studies have reported 3%–4% prevalence of mood disorders in children and adolescents. Lifetime prevalence rates of BPADs in this age group have been calculated 2.1% equal in males and females.

These disorders are often associated with comorbid disorders such as anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorders (CDs). Some authors feel that bipolar disorders often start in adolescents with an episode of major depression, chronic fluctuating abnormalities of mood overactivity, cognition, and conduct disturbances. In the early stage, presenting symptoms are nonspecific and not limited to mood spectrum.

ASSESSMENT AND EVALUATION

Usually, the diagnoses in children are difficult because of commonly associated comorbidities. Children present with

atypical or mixed features such as labile mood, irritability, behavioral problems, and rapid cycling course. Some may have school problems such as fighting substance abuse and sexual behavior with nonepisodic and chronic course. Adolescent presentation may be mood incongruent, bizarre, and/or paranoid, which may make the diagnosis difficult. Normal imaginative play, overactivity, boastfulness, and grandiosity should not be mistaken for child BPAD. The assessment of children for BPAD should be done as follows:

Screening

One should look for clear periods of low moods with emphasis in context in which the symptoms occur. Family history of mood disorders, substance use disorders along with presence of any other stressors must be explored.

Diagnostic criterion

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) or International Classification of Diseases, 10th Revision Criterion is often used. Symptoms of BPAD (irritability/grandiosity/persistent sadness or low mood/loss of interests and/or pleasure, low energy, sleep and appetite disturbances, poor concentration or indecisiveness low self-confidence, suicidal thoughts and acts guilt or self-blame, and agitation or psychomotor retardation) should be present on the most days, most of the time for at least 2 weeks.

Instruments for evaluation

In case of difficulty or clarity, some instruments which can be used are severity rating using the Child Depression Inventory or Childhood Depression Rating Scale–Revised, Kiddie Schedule for Affective Disorders and Schizophrenia,

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and Mini-International Neuropsychiatric Interview for Children and Adolescents for the assessment of depression.

Evaluation of comorbidity

Comorbid disorders such as anxiety disorders, ADHD, ODD, and CDs may influence treatment decisions and also help in understanding long-term course, and hence, they should be evaluated and appropriate diagnosis should be made.

FORMULATING A TREATMENT PLAN

If possible, the diagnoses should establish using structured instrument for assessment and one should monitor the symptom patterns prospectively by providing a diary to record symptoms to the parents or caregivers of the patients. Baseline symptoms of mania or depression can be recorded using appropriate scales to be more objective (Young Mania Rating Scale/Children's Depression Rating Scale and global impression of the clinician).

Baseline height, weight, waist circumference, pulse electrocardiography, blood pressure, and appropriate baseline blood tests such as complete blood count, blood sugar, lipid profile, urea electrolytes, creatinine, and liver function tests may be recorded in case of female adolescents' serum prolactin.

Treatment has to be planned according to the presentation of BPAD.

Treatment for mild depression does not usually require medication. It will depend on the availability of psychological therapies, behavior therapies, counseling services, and family therapy. In some settings, medication and psychosocial management is provided simultaneously.

For moderate depression, a combination of antidepressant and psychotherapy is recommended.

For severe depression, psychopharmacological management with cognitive behavior therapy (CBT) and family therapy is advisable.

For manic symptoms of BPAD, treatment can be initiated with low-dose antimanic agents and mood stabilizers.

Guiding principles for treatment plan include:

- Begin with less, go slow, and monitor efficacy and adverse reactions
- Monotherapy is ideal; however, multiple medications are often required in the severely ill
- Allow adequate trial of treatment in children who are generally more ill and will often require longer periods of treatment before responding. Adequate time for such trials could be 8 weeks in BPAD patients
- Outcome should be monitored in outpatient department as well inpatient department patients settings
- Family must be educated regarding proper compliance

of the treatment in case long term treatment is required.

CHOICE OF TREATMENT SETTINGS

Invariably, it is preferable to treat youngsters in their family environment; however, some acute cases may require hospitalization. Appropriate consent should be taken from parents/caregivers preferably; they must stay with the patient in the inpatient setting.

PHARMACOLOGICAL TREATMENT

General principles

As children and adolescents are more likely to develop metabolic side effects of medications used to treat bipolar disorder, specially with atypical antipsychotics, a judicious use is recommended and polypharmacy needs to be avoided as far as possible. Growing evidence of increased risk of cardiovascular risk in this population emphasizes that lifestyle management including dietary regulation, substance use, smoking, and physical activity must be implemented and encouraged along with pharmacological and psychological interventions.

A minimum period of 4–6-week trial of adequate dose for each medication (8 weeks in case of lithium) is recommended to ensure the effectiveness of medication.

Key points of pharmacotherapy

- Patients and caregivers' preference must be taken into account wherever possible in guiding the treatment
- Psychological interventions should be preferred over pharmacological treatment unless the latter is necessary
- Olanzapine, quetiapine, and risperidone are the antipsychotics of choice for the treatment of mania
- Fluoxetine is most preferred antidepressant in treating bipolar depression and only in combination with the atypical antipsychotic olanzapine
- In case of long term treatment, lithium is the most preferred medication and should be used first line.
- In case of mania, tapering and discontinuation of antidepressant is advised.

OVERVIEW OF PHARMACOTHERAPY

Pharmacotherapy is the mainstay of treatment for children and adolescents with bipolar affective disorder. Following principles should be used to select drug of choice:

- Scientific evidence of effectiveness
- Phase of illness
- Subtype of disorder (psychosis, mixed episode, and rapid cycling)
- Adverse effect profile with respect to the particular patient
- Previous treatment response history
- Possibly, also a family member's history of medication response.

Table 1: Acute management of mania

Choice of treatment	Drug/Medication
First line	Lithium, risperidone, asenapine, quetiapine, aripiprazole
Second line	Olanzapine, ziprasidone
Third line	Divalproex

Table 2: Acute management of bipolar depression

Choice of treatment	Drug/Medication
First line	Lurasidone
Second line	Lithium, lamotrigine
Third line	Olanzapine-fluoxetine combination Quetiapine Escitalopram, sertraline

It is recommended that the antidepressant should be used cautiously in BD-I and BD-II. Always prefer combining antidepressants with mood stabilizing medication. BD – Bipolar disorder

Table 3: Maintenance treatment

Choice of treatment	Drug/Medication
First line	Aripiprazole, lithium, divalproex Combination of lithium/divalproex plus risperidone Combination of lithium plus divalproex/carbamazepine Lamotrigine (adjunctive) in those ≥ 13 years
Other	Quetiapine, asenapine, risperidone, ziprasidone

Table 4: Pharmacological options for behavior disorder in children and adolescents

Mood stabilizer	Lithium	For short term (not more than 2 weeks)
Antipsychotics	Quetiapine, risperidone, ziprasidone, aripiprazole, asenapine, lurasidone, clozapine, olanzapine	
Anticonvulsants	Divalproex/valproate, carbamazepine, lamotrigine, gabapentin	
Antidepressants	SSRIs, bupropion, mirtazapine	
Adjunctive medication	Benzodiazepines, hypnotic-sedative (to restore sleep or counter irritability/agitation not caused by psychosis)	

SSRIs – Selective serotonin reuptake inhibitor

CHOICE OF MEDICATION

Types of medication

Pharmacological management of BPD in children and adolescent can broadly be categorized into four main classes of medications, namely mood stabilizers including anticonvulsant, atypical antipsychotics, anticonvulsant drugs, and anti-depressants. Different types of medications and combinations are used depending on the phases of illness (mania/hypomania/depression/mixed) and response to medicine.

Certain amount of risk of adverse effect is associated with all classes of medications used in this age group. Family

members and patients should be given detailed overviews about such risk factors, and risk versus benefit in this regard should also be discussed. Informed consent must be obtained before starting medication.

Rapid cycling (4 or more acute episodes in a year)

- Look for other conditions which may cause rapid cycling such as substance abuse, hypothyroidism and treat accordingly.
- Gradually stop antidepressant
- Treatment should be targeted according to manic or depressive episodes.
- Many patients may require the combination of mood stabilizers and antipsychotics.

MAINTENANCE TREATMENT

It is recommended that the treatment that improves the patents in the acute phase of treatment also helps in maintenance and hence should be continued. Lithium, divalproex, olanzapine, and quetiapine are the most commonly used medications in maintenance therapy in children and adolescents. However, it is better to prefer mood stabilizers over SGA for maintenance treatment due to their high potential to produce notable side effects [Tables 1-15] and [Figures 1-3].

In case of BPD with psychotic symptoms, it is better to avoid long-term use of antipsychotics due to their side effect profile and it is recommended to withdraw SGA gradually after 12 weeks of symptom remission.

Medication discontinuation should be considered by gradual tapering only after a patient has achieved remission for minimum 12 months or more.

Special consideration should be given if patient has suicidal behavior, Increased aggression and psychosis. Sometimes, treatment may have to be continued even longer or lifelong.

Side effects and their management

Most of the side effects of antipsychotics medication and their management has largely been documented in chapter of Childhood onset Schizophrenia which may be referred for further reading. However, following precautions are advised to avoid such undesirable effects.

Children and adolescents have less tolerance for antipsychotics in comparison to adults. While treating this group of population, we should look for presence of Extrapyramidal symptoms(EPS),increase in prolactin and increase in weight. It is advised that:

- Provide adequate information to patients and family in deciding treatment choice

Table 5: Commonly used medications for behavior disorder in children and adolescents

Medication	Doses	Adverse effects
Lithium carbonate (12 years and above)	Dose adjustment by monitoring serum level and patient response; 10-30 mg/kg/day twice-daily schedule	GI distress, lethargy or sedation, tremor, enuresis, weight gain, cognitive dulling hypothyroidism, diabetes insipidus, toxicity in dehydration, polyuria, polydipsia, renal disease
Divalproex sodium/valproic acid (12 years and above)	Dose adjustment by monitoring serum levels 15-30 mg/kg/day twice- or thrice-daily schedule	Sedation, platelet dysfunction, liver disease, alopecia, weight gain Elevated liver enzymes or liver disease bone marrow suppression
Aripiprazole (12 years and above)	2 mg once daily can be increased up to 10 mg Once daily schedule	Nausea, Vomiting, dizziness, insomnia, headache, akathisia, constipation
Carbamazepine	10-20 mg/kg/day dose adjustment by monitoring serum blood levels Twice-daily schedule	Dizziness, drowsiness, rashes, liver toxicity (rare) Bone marrow suppression
Asenapine (10 years and above)	2.5 mg-10 mg SL	Somnolence, oral paraesthesia children more sensitive to develop dystonia
Risperidone (10 years and above)	0.25 mg bid or 0.5 mg at bedtime initially; target dose 2-4 mg/d	Weight gain, sedation, galactorrhea, EPSEs
Quetiapine (10 years and above)	50 mg bid initially, may go as high as 400-600 mg/d	Sedation, weight gain hyperglycemia
Olanzapine (12 years and above)	2.5-5 mg at bedtime initially; target dose 10-20 mg/d	Weight gain, dyslipidemia, sedation, or orthostasis Metabolic syndrome, EPSEs (rare)
Clonazepam	0.01-0.04 mg/kg/day at bedtime or divided bid	Sedation, ataxia, abnormal coordination, abuse potential
Fluoxetine (8 years and above)	10 mg-20 mg/day	Headache, nausea, insomnia, anorexia, anxiety, diarrhea, manic switch
Sertraline (12 years and above)	50-200 mg/day	Dry mouth, constipation, nausea, weight loss, anorexia, myalgia, insomnia, dizziness, headache, agitation, anxiety, tremor, abdominal pain, tinnitus, sweating, rash, hypertension, rare seizures
Escitalopram (12 years and above)	10-20 mg/day	Nausea, Dry mouth, dizziness, Orthostatic hypotension, akathisia, skin rashes, EPS
Bupropion	20 mg at bedtime may be given up to 60 mg usually in 2 divided doses	Akathisia, Nausea, Weight Gain, Sedation, tachycardia
Ziprasidone	20-80 mg/day	Hyperprolactinemia, may increase risk of diabetes and dyslipidemia

EPSEs – Extrapyramidal symptoms

Table 6: Monitoring of lithium and valproate/divalproex treatment

Stages	Tests
Before starting lithium	Renal function tests; urea and electrolytes (U&Es) - Thyroid function tests (TFTs) Weight or BMI or waist circumference
During maintenance treatment	Serum lithium level every 3 months At 6 month interval Renal function tests; urea and electrolytes, Thyroid function tests Weight or BMI or waist circumference

- Family preference should be considered while choosing Antipsychotics
- Aim of antipsychotic treatment is to target symptoms.
- Start with low dose and monitor the dose depending on response
- Prefer Mono therapy
- Poly pharmacy should be used in case of nonresponse with monotherapy.
- Indicated adequate trial period with one drug should be given before changing the medication.
- Review the dose of drug and side effect profile regularly.

TREATMENT OF COMORBID PSYCHIATRIC DISORDERS

Pediatric-onset bipolar disorder (BPD) rarely occurs in the absence of comorbid conditions. The occurrence of comorbid disorders complicates both the accurate diagnosis of BPD and its treatment.

Youths with BPD are among the most impaired population, and the presence of comorbidity intensifies disability, complicates treatment, and probably worsens the prognosis in this population.¹

ATTENTION-DEFICIT HYPERACTIVITY DISORDER

The response to lithium has been reported to be less robust in the presence of ADHD comorbidity in youth with BPD, suggesting that this subgroup of BPD may constitute a unique genetic subform with a differential treatment response.

In youngsters with BPD, comorbid ADHD could be addressed selectively with the anti-ADHD armamentarium but only after mood stabilization.

The stimulants have been reported to be efficacious in treating comorbid ADHD without precipitating (hypo) mania in mood-stabilized BPD youth in two controlled trials.

Table 7: Therapeutic blood monitoring

Medication	Steady state (days)	When to take blood sample	Therapeutic level
Lithium	4-5	12 h after the last dose	0.6-1.0 mmol/L
Valproate	2-3	12 h after the last dose	50-125 mg/L
Carbamazepine	14	12 h after the last dose	6-12 mg/L

Table 8: Goal

To prevent relapse
 To ensure mood stability
 To minimize suicidal risk
 To overcome associated psychosocial issues

Table 9: Risk factors for relapse

Duration of illness
 Higher number of episodes before stabilization
 Co-administration of other agencies that may that may destabilize patient's mood
 Emotional/environmental factors: sleep deprivation, stress, negative cognition

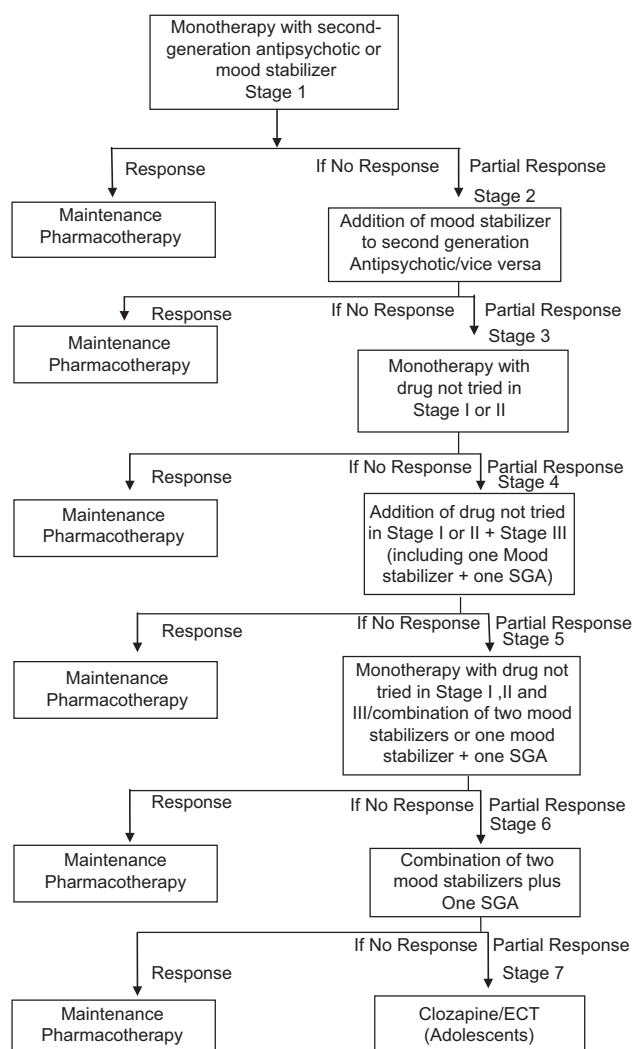
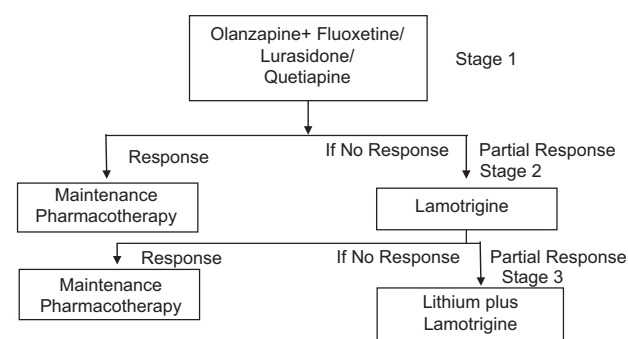
Table 10: Monitoring medication in child & adolescent BPAD

Patient and family should be directly involved in decision-making regarding the choice of medication
 Choice of antipsychotic should be based on patients preference, previous response (if any), response in family member (if any), available data on efficacy, and side effect profile
 Aim of using antipsychotic should be symptoms not the diagnosis
 Starting dose should be low with gradual increase according to response
 One antipsychotic should at one time except when switching over from one to another antipsychotic
 Ensure adequate trial period with one medication in therapeutic dose before changing (8-12 weeks is a reasonable time for adequate benefits of treatment to be witnessed in children and adolescents)
 Only one medication should be changed at a time
 Effect, tolerability, and dose should be regularly reviewed

A controlled trial of stimulants as an adjunctive therapy for ADHD in BPD youth with manic symptoms stabilized on divalproex found mixed amphetamine salts to be safe and efficacious for the treatment of ADHD in the context of BPD.

Another evidence reported that in youth stabilized with a stable dose of at least one mood stabilizer, concomitant treatment with methylphenidate improved ADHD in a dose-dependent manner without destabilization of mood.

Furthermore, an open trial of the nonstimulant anti-ADHD agent bupropion in adults with predominately mood stabilized bipolar II disorder and ADHD reported a significant improvement in ADHD without activation of mania.

**Figure 1: Treatment Algorithm for Acute mania/mixed mania****Figure 2: Treatment Algorithm for Acute depressive episode (if not on lithium/valproate)**

These aggregate data suggest that the treatment for BPD needs to precede ADHD treatment and that, in general, stimulants and nonstimulants may be cautiously introduced.

Table 11: Side effects of medications and their management

Side Effects	Management
Lithium	Reduce the dose or once daily dose medication
Weight gain polyuria, polydipsia	Advise entire dose at night time.
Neurological	Use different preparation (CR)
Memory impairment, tremors, ataxia, dysarthria, delirium	For GI disturbances take medicine with food, use antacids
Renal	For tremors avoid caffeine, use beta-blockers
Interstitial fibrosis, diabetes insipidus	For polyuria and polydipsia, add diuretics cautiously while reducing lithium by 50%
GI	For hypothyroidism, add levothyroxine
Nausea, diarrhea, abdominal discomfort	Switch to another medication if side effects still persist
Endocrine	Consult appropriate specialty for further management of side effects if they do not improve
Hypothyroidism	
Cardiovascular	
Bradycardia, hypotension, sick sinus syndrome, arrhythmia	
Dermatological	
Acne, rash, alopecia	
Hematological	
Leukocytosis	
Valproate	Reduce the dose or once daily dose medication.
Weight gain	Advise to take a maximum dose at night time to avoid sedation
Neurological	For GI disturbances, use antacids
Headache, ataxia, tremors, dizziness, sedation	For tremors avoid caffeine, use beta-blockers
GI	Multivitamin with zinc and selenium for alopecia
Abdominal pain, nausea, diarrhea, vomiting, constipation, dyspepsia, decreased appetite	Switch to another medication if side effects still persist
Hepatotoxicity, pancreatitis	Consult appropriate specialty for the further management of side effects if they do not improve
Dermatological	
Alopecia	
Metabolic/endocrinal	
Hyperinsulinemia, lipid dysregulation, hyperandrogenism	
Decreased bone density	
Polycystic ovaries	
Carbamazepine	Reduce the dose
Neurological	Advise to take a maximum dose at night time to avoid sedation
Unsteadiness, headache, dizziness, confusion, sedation	For GI disturbances take medicine with food, use antacids
GI	CNS side effects can be significantly lowered with controlled release preparation
Nausea, vomiting, diarrhea	For hypothyroidism, add levothyroxine
Hematological	Switch to another medication if side effects still persist
Leukopenia, aplastic anemia, agranulocytosis	Consult appropriate specialty for further management of side effects if they do not improve
Dermatological	
Rashes, Stevens-Johnson syndrome	
Metabolic/endocrinal	
SIADH with hyponatremia, hypothyroidism	
Ophthalmological	
Blurred vision	
Lamotrigine	Reduce the dose
Neurological	Advise to take a maximum dose at night to reduce daytime sedation
Headache, dizziness, tremor, ataxia, poor coordination, insomnia, aseptic meningitis	Antihistaminic/topical steroids for rashes and pruritus
GI	For GI disturbances take medicine with food, use antacids
Nausea, vomiting, pain abdomen, dyspepsia, constipation	Switch to another medication if side effects still persist
Hematological	Consult appropriate specialty for further management of side effects if they do not improve
Leucopenia, aplastic anemia, agranulocytosis	
Dermatological	
Rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis	
Hematological	
Blood dyscrasias	
Ophthalmological	
Blurred vision, double vision	

OPPOSITIONAL DEFIANT DISORDER

Treatment of ODD is primarily behavioral in nature, when comorbid with other medication-responsive psychiatric

conditions (BPD and ADHD), pharmacological treatment of the comorbid disorder often reduces overall symptoms of the ODD.

Table 12: Measures to improve medication compliance

Consider patients and caregiver preference while prescribing medication
 Prescribe least possible number of medication
 Preferably give once daily dose
 Explain when and how to take medication
 Explain explicitly about the latent period before the therapeutic effects become evident
 Explain the need for continued medication even after the symptoms have improved
 Explain about the possible side effects of treatment and advise to inform
 Explain the need of regular follow-up

Table 13: Common coexisting psychiatric disorder with BAD

ADHD	Anxiety disorder
ODD	Substance abuse
Conduct disorder	

ADHD – Attention-deficit hyperactivity disorder; ODD – Oppositional defiant disorder

Table 14: General principle of management of comorbid psychiatric disorders

Stabilize the symptoms of BPD first
 Review the need of treatment for comorbid disorder
 If comorbid disorder adversely affects child's academic or psychosocial functioning, treatment is warranted
 Psychosocial therapies should be tried first before initiating pharmacological treatment
 Each comorbid disorder must be treated sequentially
 BPD – Bipolar disorder

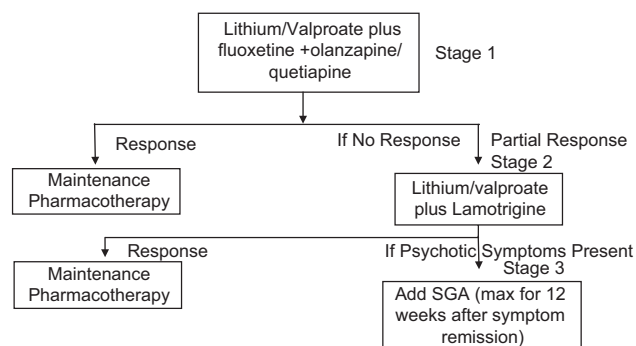
Table 15: Differentiating symptoms of BPAD and attention-deficit hyperactivity disorder

Symptoms	BPAD	ADHD
Irritability	Yes	Yes
Grandiosity	Yes	No
Elevated mood	Yes	No
Overactivity	Yes (goal directed)	Yes (unproductive)
Sexually inappropriate behavior	Maybe present	Absent
Sleep problems	Yes (early/and late insomnia)	Yes (persistent/generalized)
Distractibility	Yes	Yes
Impulsivity	Yes	Yes
Over talkative	Yes	Yes
Episodic	Yes	No

ADHD – Attention-deficit hyperactivity disorder; BPAD – Bipolar Affective Disorder

To date, risperidone is the most extensively studied atypical antipsychotic for disruptive behavior disorder (DBD). Several trials indicate that risperidone can be useful for DBD, especially the aggressive features, in both short-term and long-term use.

Quetiapine is the other most studied atypical antipsychotic for DBD in youth. In youth with DBD and ADHD who fail to respond to methylphenidate monotherapy (at 54 mg/day dose), the addition of

**Figure 3: Treatment Algorithm Acute depressive episode (if taking lithium/valproate)**

quetiapine (at a mean dose 329 mg/day) has been shown to be effective in controlling symptoms of ODD and aggression.

Open-label and placebo-controlled studies suggest that divalproex is efficacious for the treatment of mood lability and explosive temper in children and adolescents with DBD.

ANXIETY DISORDERS

Considering that treatments for BPD with traditional mood stabilizers do not generally treat anxiety disorders and that treatment of anxiety disorders with selective serotonin reuptake inhibitors (SSRIs) can aggravate the BPD, the pharmacological approach to bipolar children with comorbid anxiety disorders needs to be defined. As BPD and anxiety disorders respond to different treatments, identification of the comorbid state is essential for proper treatment and for achieving optimal functioning.

SSRIs may be indicated in the presence of comorbid anxiety because they have a more favorable risk/benefit ratio in this disorder.

Trials of pediatric anxiety disorders exclude children with BPD by protocol design, and similarly, children with a BPD diagnosis are typically excluded from the trials of treatment for both depression and anxiety.

In general, mood stabilization is the priority before specific anxiety treatments are considered.

SUBSTANCE USE DISORDERS

While treating comorbid disorders such as bipolar disorder and SUD, clinicians should consider a simultaneous approach. Both psychosocial and medication strategies should be considered simultaneously in these comorbid adolescents. There is evidence that pharmacological interventions are effective for youth with SUD and BPD.

Two studies have reported that mood stabilizers, specifically lithium and valproic acid, significantly reduced substance use in bipolar youth.

A controlled, 6-week study of treatment with lithium in youth with affective dysregulation and substance dependence reported a clinically significant decrease in the number of positive urines as well as a significant increase in overall global functioning.

In a 5-week open trial of valproic acid in adolescent outpatients with marijuana abuse/dependence and “explosive mood disorder” (mood symptoms were not classified using the DSM IV), significant improvement in marijuana use and affective symptoms was reported.

Nonpharmacological treatment

Nonpharmacological management includes:

Physical methods of treatment

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is an effective treatment for the treatment of depression not responding to antidepressant treatments. It has to be judiciously used in child and adolescent population. Patient’s caregivers have to be explained if ECT is required for a given patient. With the provisions of prevalent law (MHCA, 17), the caregivers have to give in writing to the treating psychiatrist, and after approval by regulatory body, it can be administered as per clinical decision. A number of treatments usually required are 5–7. However, it can be decided by the treating psychiatrist.

Repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation, and vagus nerve stimulation are the therapeutic modalities reported in various disorders recommended in severe cases of illness when other treatment modalities do not work. In child population, rTMS has been tried in some studies in small samples with inconclusive results. Most patients included were suffering from major depression and few patients with bipolar depression. rTMS has proven a modality of some efficacy.

Psychosocial and behavior therapy

Bipolar disorder in children and adolescents affects 1%–2% of the population. Psychosocial treatment is integral and necessary adjunctive treatment to pharmacological interventions for bipolar disorder in children and adolescents. Pediatric bipolar disorder (PBD) is characterized by chronic and episodic mood disturbances and long-term serious consequences including frequent hospitalizations, poor academic performance, poor quality of life, poor interpersonal relationships with family and friends, gross impairment in social, occupational, and personal functioning, and suicidal attempts. With limited efficacy and side effects of pharmacological treatment, the role of

psychosocial treatment has been getting more useful day by day. Effective interventions share common elements such as adjunctive approach, individual and family psychoeducation approach to explain nature, symptoms, etiology, course and outcome, and prognosis of bipolar disorders. The psychosocial approach also focuses on developing coping skills to control their mood fluctuations and for the betterment of interpersonal functioning. A comprehensive multimodal treatment approach combining pharmacology with psychosocial therapies is almost always useful. There are few psychosocial treatment approaches to PBD which will be discussed briefly.

1. Multifamily psychoeducation group psychoeducational psychotherapy (PEP) – Fristad *et al.*
2. Individual family psychoeducation (PEP) – Fristad *et al.*
3. Family-focused treatment for adolescents (FFT-A/FFT-HR)
4. Interpersonal and Social Rhythm Therapy for adolescents (IPS-RT-A)
5. Dialectical therapy for adolescents
6. Child and family-focused (CFF) CBT (rainbow program)
7. CBT for bipolar disorders in adolescents
8. Interpersonal psychotherapy
9. Mindfulness-based intervention
10. Cognitive remediation
11. Intensive psychosocial intervention.

FAMILY-FOCUSED TREATMENT

FFT has been adopted for adolescents with mood disorders in adolescents. FFT-A is designed for the age group of 12–17 years with mood disorder and involves 21 sessions of varying frequency delivered to patients, siblings, and caregiver/guardian/parents over a 9-month period (12 weekly sessions, 6 biweekly sessions, and 3 monthly sessions) and it will counter the criticism, expressed emotion and conflicts, and to improve cost and to cope up with the illness and also improves functioning of the family. This therapy involves psychoeducation which focuses on improving understanding of the symptoms of the illness, self-management, better compliance for medicines, triggers of mood episodes and relapse prevention, communication enhancement training, and problem-solving skill training. The standard family intervention for BD targets the whole family and not only the patient and includes elements of psychoeducation, communication enhancement, and problem-solving skills training. It also includes support and self-care training for caregivers. The primary goal of FFT-A is to reduce symptoms by increased awareness of coping strategy to deal with the illness, decreased levels of familial expressed emotions, and improved family problem solving and communication skills.

INDIVIDUAL/MULTIFAMILY PSYCHOEDUCATIONAL PSYCHOTHERAPY

The basic concept of psychoeducation for pediatric mood disorders is to training of patients and parents regarding

the general awareness and information about the illness, causes and symptoms, different pharmacological and nonpharmacological treatment options and associated risks and no treatment at all, role of medication compliance, early detection of new episodes or comorbid medical or psychiatric conditions, and avoiding of substance abuse. Fristard *et al.* developed individual and group psychoeducation-based psychotherapy intervention (PEP) for school-going children with bipolar disorder. PEP combines psychoeducation, CBT, and family system to target affective symptoms and associated personal and social impairments through educating parents and children about the illness and their management, enhancing family support through interactions with other families and service providers building skills in symptom management which effects regulation, problem solving, and communication. A total of 24 sessions are conducted separately with parents and children in both group and individual formats of PEP with joint family portions. In addition, restoration of hope and reversal of demoralization for patient and their family and discussions with school teachers about the illness and optimal academic and occupational performances including music, art, dance, literature, sports, and athletics. Stress management is a very important part of psychosocial interventions since stress and trauma act as both contributing factors and as outcomes of any episodes of PBD. Children are taught to develop a toolbox of coping skills like they have to identify calming and enjoyable activities in each of four domains – creative, social, physical, and relaxation which can be used to counter negative emotional state. They are also taught skills for managing their emotions, improving verbal and nonverbal communication skills, and controlling of impulses.

CHILD AND FAMILY-FOCUSED COGNITIVE BEHAVIOR TREATMENT (THE RAINBOW PROGRAM)

CFF-CBT is a family-based adjunctive psychosocial intervention for the age group of 7–13 years with bipolar disorders and their families. CFF-CBT involves psychoeducation and CBT with mindfulness-based intervention, positive psychology, and interpersonal therapy. The CFF-CBT is a 12-session protocol treatment program alternating between child, parent, and family-focused sessions, and it has also been adapted to a 12-week group which consists of weekly 60-min parallel parent and child group and effective is 15-min parent/child component. In both format, therapy is structured around seven core components that comprise the acronym “RAINBOW” as follows:

- R – routine
- A – affect regulation
- I – I can do it
- N – no negative thoughts and live in the now
- B – be a good friend and balanced lifestyle for parents
- O – oh! how can we solve this problem

- W – ways to get support in the family, school, and community.

Topics covered include establishing a predictable routine, teaching behavioral management, increasing parent and child self-efficacy, decreasing negative and fatalistic cognitions, improving social functioning, engaging in collaborative problem solving, and increasing social support.

DIALECTICAL BEHAVIOR THERAPY

Goldstein *et al.* developed dialectical behavior therapy (DBT) for adolescents with suicidality. A primary focus of DBT is emotional dysregulation the intervention protocol based on the manual for adolescents with suicidality. The therapy involves a total of 36 sessions during the course of 1 year. It has two modalities: family skills training for the entire family which includes psychoeducation and development of mindfulness skills, distress tolerance, emotion regulation, interpersonal effectiveness, and individual psychotherapy for the patient. Individual therapy focused on problem behaviors with regular homework assignment and skills coaching available by telephone. Patients who received DBT showed decrease suicidality, nonsuicidal self-injury, emotional dysregulation, and depressive symptoms after the therapy.

INTERPERSONAL AND SOCIAL RHYTHM THERAPY FOR ADOLESCENTS

On the basis of biopsychosocial theory, IPSRT-A has been adapted for PBD. The IPSRT-A specifically targets a biological diathesis for the illness-instability in circadian rhythm and neurotransmitter systems involved in regulation and social routines that affect circadian systems. The IPSRT-A is 16–18-session individual-based treatment which includes brief family psychotherapy which focuses on stabilizing social and sleep routines and deals with psychosocial stressors through an interpersonal-based approach and also gives value of proper medication compliance and resolution of interpersonal problems. This may include interpersonal conflict, role transitions, and interpersonal functioning deficits. Overall, there are no convincing data on the usefulness of IPSRT during the maintenance phase of BD. There are, however, some data suggesting that if applied early and particularly already during the acute phase, it may prolong the time to relapse.

COGNITIVE BEHAVIOR THERAPY

The CBT for adolescents' modules focuses on psychoeducation, medication compliance, mood monitoring, modifying negative thinking, sleep regulation, and family communication. The therapy consists of 12 sessions primarily targeting individual work with the adolescent, with the entire family unit included in two sessions and one session devoted to parents. The review of

the available data gives limited support for the usefulness of CBT during the acute phase of bipolar depression as adjunctive treatment but not for the maintenance phase where booster sessions might be necessary. The literature suggests that interventions of 6-month group psychoeducation seem to exert a long-lasting prophylactic effect. However, this is rather restricted to manic episodes and to patients at the earlier stages of the disease who have achieved remission before the intervention has started.

PSYCHIATRIC/MEDICAL COMORBIDITY IN PEDIATRIC BIPOLAR DISORDER

The presence of Psychiatric and Medical Comorbidity with Bipolar Disorder in Children and Adolescents is also important and at times severe clinical condition which needs to be addressed properly. Early-onset mood disorders seem to be related to additional psychiatric comorbidity with more severe episodes. Identification and management of these associated comorbidities may help alleviate the severity of impairment and duration of each episode in bipolar disorders. BPD responses to lithium are less effective in the presence of comorbid ADHD. Stimulants are more effective and safe for the treatment of associated ADHD after the manic episode is stabilized. The management of BPD with valproic acid and lithium results in the reduction of SUD. Response to psychopharmacology in pervasive developmental disorder (PDD) with mood dysregulation is less effective with higher chances for adverse effects. The ADHD comorbidity is often associated with very early-onset BPD. A much higher prevalence of anxiety disorders is common in pediatric BPD. These patients experience more severity, poor response to treatment, and poorer functioning and course.

Childhood-onset bipolar disorder seldom occurs in the absence of comorbid conditions. The comorbidity complicates both the diagnosis and management. Comorbid disorders may have a significant impact on the various indices of BPD correlates. Early identification and appropriate treatment may lead to improved overall functioning and prevention of comorbid conditions. If these comorbidities are not appropriately addressed, then misattribution of impairing symptoms could lead to improper management, unnecessary exposure to pharmacotherapy, worsening of symptoms, delayed diagnosis, and misuse of maternal health resources.

The first consideration that the clinician should have in mind in the establishment of a specific treatment plan for child and adolescents with comorbidity is the determination of the level of care needed.

PSYCHIATRIC COMORBIDITY

- a. ADHD
- b. Anxiety including panic disorder
- c. SUD

- d. DBD
- e. PDD
- f. Obsessive–compulsive disorder
- g. ODD
- h. CD
- i. Posttraumatic stress disorder (PTSD)
- j. Personality disorders
- k. Mental retardation/intellectual disability
- l. Movement disorder/tics.

Conduct disorder

Available data on psychiatric comorbidity in PBD suggest that prepubertal-onset PBD is a nonepisodic, chronic, rapid cycling, mixed manic state that may be associated with CD or ADHD. As both CD and PBD are highly impairing conditions, their co-occurrence shows severe clinical picture and needs to be attention. The association between CD and mania is consistent with the comorbidity between CD and major depression and bipolar nature of juvenile depression. The irritable outburst often includes threatening or attacking behavior toward teachers, peer group, siblings, and family members which overlaps with CD. Reports suggested that manic episode of PBD shows serious acting out behaviors such as burglary, stealing, vandalism, and school suspensions. High rates of CD are reported in PBD patients, and this comorbidity has a more complicated course and outcome with high rates of admissions. Furthermore, CD is reported to be severe in patients of PBD. As BPAD may have comorbid antisocial and aggressive behavior of CD it is advised to try antipsychotics, the promising role of atypical antipsychotics and their efficacy has been reported. The antimanic agent lithium has been found to be effective anti-aggressive agent in these patients. The available literature also suggests that typical antipsychotic medication such as haloperidol is useful in decreasing aggression in these patients. Because of side effects of typical antipsychotics, the use of atypical antipsychotic agents in the treatment of CD with aggressive behavior has been increasing. One trial suggests that short term and long term treatment with quetiapine is safe and well tolerated. In one study, the treatment with olanzapine resulted in the improvement of aggressive behavior but was also associated with weight gain.

Obsessive–compulsive disorder

Few symptoms such as agitation, racing thoughts and feeling of distress in severe OCD can mimic a bipolar picture. Manic symptoms of goal directed activity or repetitive, unwanted hypersexual thoughts in BPAD can have negative effect on treatment outcome of the anxiety disorders and has been reported to show poor response to pharmacotherapy. Psychosocial treatment like CBT has been found to be useful and should be used with any of the pharmacological alternatives to SSRI.

Posttraumatic stress disorder

The reported rates of PTSD comorbidity in patients with PBD have varied from 7% to 50%. Rate of SUD is much higher in youths who had a lifetime diagnosis of PTSD before the age of 18 years as compared to those who had never experienced a trauma. Although no empirical evidence is available for the management of comorbid PBD and PTSD, valproate may be effective in treating certain combat-related PTSD symptoms. Several studies showed that carbamazepine may be useful for treating PTSD symptoms such as flashbacks, nightmares, and intrusive thoughts. In one trial, lamotrigine showed efficacy in the treatment of PTSD symptoms or re-experiencing, avoidance, and numbing in adults.

Pervasive development disorders

In the presence of comorbid PDD, the PBD patients experience an earlier age at onset and increased severity of PBD with a poorer level of functioning. Treatment response to pharmacology of these patients found to be less robust with higher rates of side effects to both medication and placebo. Thus, due to an atypical response and higher chances of side effects, it is advisable to initiate and titrate pharmacotherapy at a lower dose and titrate upward in smaller increments. Available limited literature on the management of PBD with PDD suggests that typical antipsychotics (haloperidol, chlorpromazine, and thioridazine) and traditional mood stabilizers (lithium and carbamazepine) are minimally effective in mania. In a recent secondary analysis of acute atypical antipsychotic monotherapy trials in PBD, the report suggests that acceptable tolerability and robust antimanic response to atypical antipsychotic use (risperidone, olanzapine, ziprasidone, quetiapine, or aripiprazole) in the presence of PDD are well tolerated and efficacious in treating irritability and aggression. Risperidone had a superior antimanic response in PBD with PDD and is found to be favorable safety, tolerability, and efficacy profile for irritability and aggression with possibility of side effects mainly weight gain.

CONCLUSION

Patients with PBD who are experiencing significant tics should initially be offered treatment with the atypical antipsychotics to target their tics as well as their bipolar disorder. Patients with PBD and behavioral symptoms associated with PDD should also be initially treated with a typical antipsychotic; other mood stabilizers should be added as necessary. The use of other medications and/or psychosocial treatment targets that other PDD symptoms (e.g., inattention, hyperactivity, and 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 patients with PBD and mental retardation are similar to those described for patients with PBD and PDD.

For patients with epilepsy or migraines in addition to PBD, pharmacotherapy that targets both disorders such as carbamazepine, divalproex, 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.

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Conflicts of interest

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