

# Clinical Practice Guidelines for Bipolar Disorder in Children and Adolescents

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## Introduction

According to census of India 40% individuals are children below 16 years of age. There is 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 to 12 years, 12.5% in children aged 0 to 16 years and 1.81% in adolescents aged 12 to 16 years. BPAD have been recognised in children since 1990 however there is active controversy whether it could occur prior to age of 12 years. Some robust Indian studies have reported 3 to 4% prevalence of mood disorders in children and adolescents. Life time prevalence rates of Bipolar affective disorders in this age group has been calculated 2.1% equal in male and female.

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

## Assessment and evaluation

Usually the diagnosis in children is difficult because of commonly associated co-morbidities. Children present with atypical or mixed features like labile mood, irritability, behavioural problems and rapid cycling course. Some may have school problems like fighting substance abuse and sexual behaviour with non-episodic 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. Assessment of children for BPAD should be done as follows.

1. **SCREENING**- one should look for clear periods of low moods with emphasis on contacts in which the symptoms occur. Look for family history of mood disorders, substance use disorders and if there is presence of any stressor.
2. **DIAGNOSTIC CRITERION**- DSM-V or ICD-10 Criterion are 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 inebecisiveness low self confidence, suicidal thoughts and acts guilt or self blame and agitation or psychomotor retardation) should be present on most days most of the time for at least 2 weeks.
3. **INSTRUMENTS FOR EVALUATION**- In case of difficulty or clarity some instruments which can be used are: Severity rating using child depression inventory (CDI) or childhood depression rating scale revised (CDRS-R), Kiddie-schedule for affective disorders and Schizophrenia (K-SADS) and Mini international neuropsychiatry interview for children and adolescents MINI-KID for assessment of Depression.
4. **EVALUATION OF COMORBIDITY**- Comorbid disorders like anxiety disorders, attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder and conduct disorders may influence treatment decisions and also help in understanding longterm course hence they should be evaluated and appropriate diagnosis should be made.

## Formulating a treatment plan

If possible the diagnoses should be established by using structured instrument for assessment and one should monitor the symptom patterns prospectively by providing a diary to record symptoms to the parents or care givers of the patients. Baseline symptoms of mania or depression can be recorded by 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 ECG, blood Pressure and appropriate baseline blood tests like CBC, Blood sugar, Lipid profile, urea electrolytes, creatinine, and LFT 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 availability of psychological therapies, behaviour therapies, counselling 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 CBT and family therapy is advisable.

For **manic symptoms** of BPAD treatment can be initiated with low dose antimanic agents and mood stabilisers.

Guiding principles for treatment plan include:

- a. Begin with less, go slow and monitor efficacy and adverse reactions.
- b. Mono therapy is ideal however multiple medications are often required in severely ill.
- c. Allow adequate trial of treatment children are generally more ill and will often require longer periods of treatment before responding. Adequate time for such trials could be eight weeks in BPAD patients.
- d. Outcome should be monitored in OPD as well IPD patients settings.
- e. Medication education should be provided to the family in case need for medication is for long period.

## Choice of treatment settings

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

## Pharmacological treatment

### General principles

Since children and adolescents are more prone to develop metabolic side effects of medications used to treat bipolar disorder, in particular atypical antipsychotics, a judicious use is recommended and poly pharmacy needs to be avoided as far as possible. Growing evidences of increased risk of cardiovascular risk in this population emphasizes, life style 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 to 6 weeks trial of adequate dose for each medication (8 weeks in case of Lithium) is recommended to ensure effectiveness of medication.

### Key Points of pharmacotherapy

- Patients and care givers preference must be taken in to 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.
- For long term treatment of bipolar disorder, lithium is the most preferred medication and should be used first line.
- In case of mania, antidepressant should be tapered and discontinued.

### Overview of Pharmacotherapy

Pharmacotherapy is the mainstay of treatment for children and adolescents with bipolar disorder. Choice of drug should be based on:

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

### Choice of Medication:

#### Acute Management of Mania

<b>First line</b>	Lithium,risperidone, Asenapine,quetiapine,ariprerrazole
<b>Second line</b>	Olanzapine,Ziprasidone
<b>Third line</b>	Divalproex

#### Acute Management of Bipolar depression

<b>First line</b>	Lurasidone
<b>Second line</b>	Lithium,lamotrygine
<b>Third line</b>	Olanzapine –fluoxetine Combination Quetiapin Escitalopram,Seertraline

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

### Maintenance Treatment

<b>First line</b>	Aripiperazole,lithium,Divalproex  Combination of Lithium/Divalproex plus Risperidone Combination of LithiumplusDivalproe/Carbamezapine Lamotrygine(adjunctive) in those $\geq$ 13 year
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<b>Other</b>	Quetiapine, Asenapine, Risperidone, Ziprasidone
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### Types of Medication:

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

Certain amount of risk of adverse effect are associated with all class 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.

### Pharmacological Options for BD in Children and adolescents

<b>Mood Stabilizer</b>	Lithium	<b>For short term (not more than 2 week)</b>
<b>Antipsychotics</b>	quetiapine, Risperidone, Ziprasidone, Aripiperazole, Asenapine, Lurasidone, Clozapine, Olanzapine	
<b>Anticonvulsants</b>	Divalproex/valproate, carbamazepine, Lamotrigine, gabapentine	
<b>Antidepressants</b>	SSRIs, Bupropion, Mirtazepine	
<b>Adjunctive Medication</b>	Benzodiazepines, hypnotic-sedative (to restore sleep or counter irritability /agitation not caused by psychosis)	

### Commonly used Medications for BD 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; drug-drug interactions and sodium intake may alter therapeutic serum levels
Divalproex Sodium /Valproic acid (12 years and above)	15-30 mg/kg/day dose adjustment by monitoring serum levels twice- or thrice-daily schedule	Sedation, platelet dysfunction, liver disease, alopecia, weight gain Elevated liver enzymes or liver disease, drug-drug interactions, bone marrow suppression

Aripiprazole (12 years and above)	2 mg once daily can be increased up to 10 mg Once daily schedule	Prolactinemia , tardive dyskinesia, dystonia, parkinsonism, hyperglycemia; use with caution in epilepsy and cardiac problem
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 to 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; titrate as tolerated to target dosage of 2-4 mg/d; not to exceed 6 mg/d	Weight gain, sedation, Galactorrhea, extrapyramidal symptoms
Quetiapine (10years 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; titrate as tolerated to target dosage of 10-20 mg/d	Weight gain, dyslipidemia, sedation, or orthostasis Metabolic syndrome, extrapyramidal symptoms(rare)
Clonazepam	0.01-0.04 mg/kg/d at bedtime or divided bid	Sedation, ataxia ,abnormal coordination, abuse potential
Fluoxetine (8 year and above)	10 mg to 20 mg/day	Headache, nausea, insomnia, anorexia, anxiety, , diarrhea, may exacerbate manic symptoms when not coadministered with an antimanic or mood-stabilizing agent  Dry mouth, constipation, nausea, weight loss, anorexia, myalgia, insomnia, dizziness, headache, agitation, anxiety, tremor, abdominal pain, tinnitus, sweating, rash, hypertension, rare seizures.
Sertraline (12 years and above)	50-200mg/day	
Escitalopram(12 year and above)	10 to 20 mg/day	
Bupropion	3 to 6 mg/kg/day	
Ziprasidone	20 mg at bedtime; can increase to 40 mg (not to exceed 60 mg), usually in 2 divided doses for children	Akathisia, nausea Risk of sudden cardiac death due to prolonged QT prolongation, avoid if there is family history of cardiac sudden death due to conduction abnormalities

Lurasidone (12 years and older)	20-80 mg/day	Nausea, Somnolence <sup>c</sup> , Weight gain, Vomiting, Dizziness, Insomnia, Decreased appetite, Abdominal pain, upperFatigue, Diarrhea, Extrapyramidal symptoms <sup>d</sup> Abnormal dreams, Oropharyngealpain,influenza
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### Monitoring of Lithium and Valproate/Divalproex Treatment

<b>Before starting Lithium</b>	-Renal function tests; urea and electrolytes (U&Es) including creatinine (or e-GFR or creatinine clearance)  - Thyroid function tests (TFTs)  -Weight or BMI or waist circumference
<b>During maintenance treatment</b>	-Serum lithium level every 3 months  - U&Es and TFTs every 6 months  - Weight or BMI or waist circumference during the last year
<b>Valproate/Divalproex</b>	
<b>Base line</b>	Weight and BMI CBC,LFT
<b>During maintenance treatment</b>	Weight and BMI CBC,LFT every 3-6 month

### Monitoring of

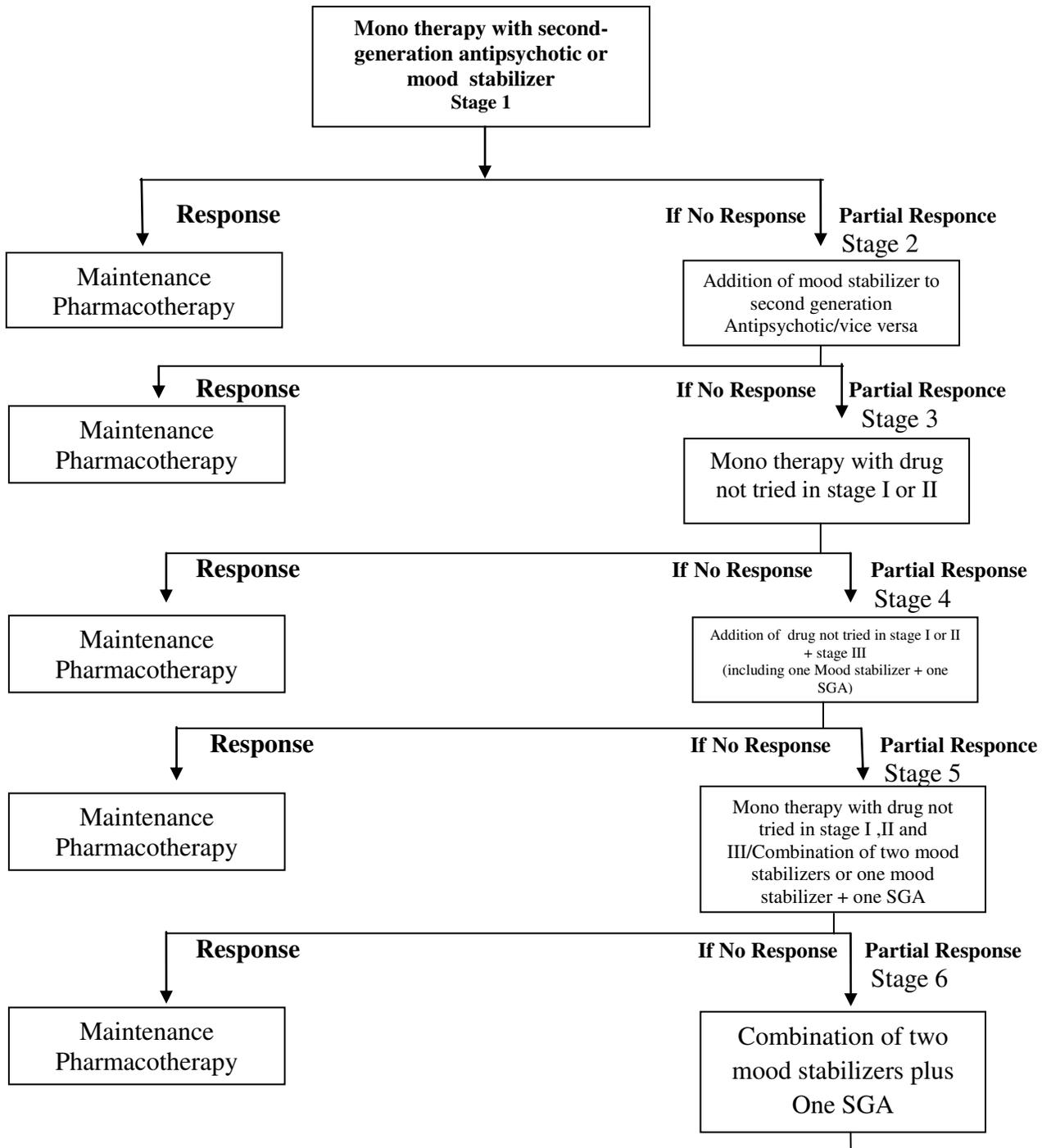
<b>Base line</b>	Weight and BMI CBC,LFT
<b>During maintenance treatment</b>	Weight and BMI CBC,LFT every 3-6 month

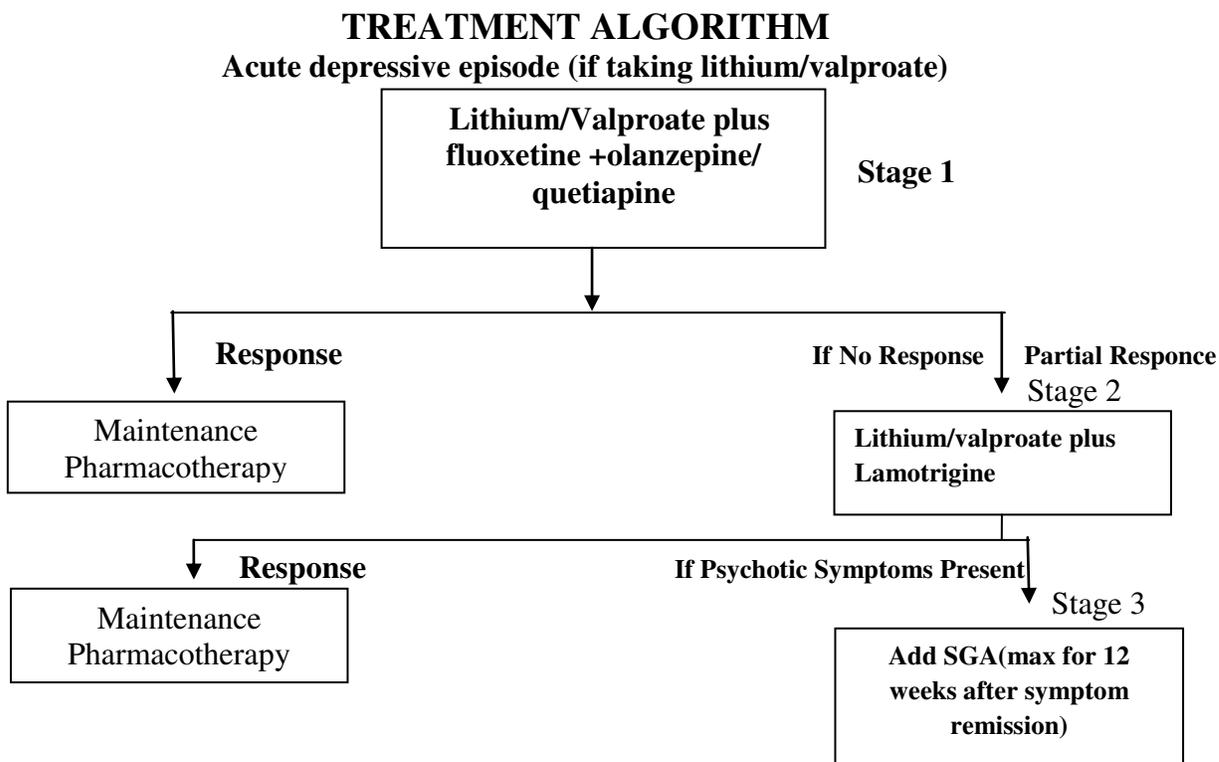
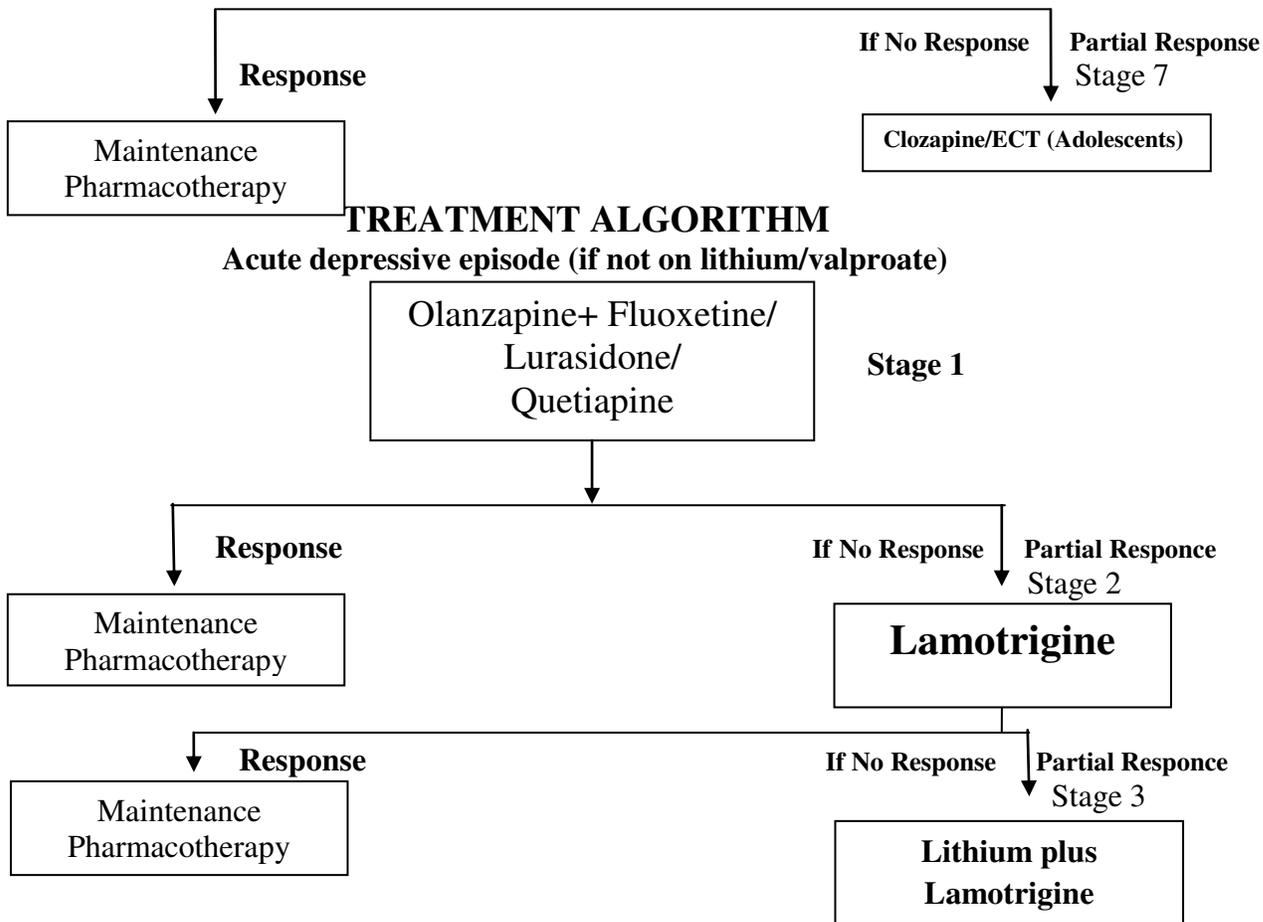
### Therapeutic blood monitoring

Medication	Steady state(in days)	When to take blood sample	Therapeutic level
<b>Lithium</b>	4-5	12 hour after the last Dose	0.6 -1.0mmol per litre
<b>valproate</b>	2-3	12 hour after the last Dose	50-125 mg per litre
<b>Carbamezapine</b>	14	12 hour after the last Dose	6-12 mg/ per litre

# TREATMENT ALGORITHM

## Acute mania/mixed mania





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

- Look for co morbid conditions such as hypothyroidism or substance misuse that may contribute to cycling and treat them.
- Gradually stop antidepressant..
- Treatment should be as for manic and depressive episodes
- Many patients may require combination of mood stabilizers and antipsychotics.

## **Maintenance Treatment**

### **Goal**

Prevention of Relapse and recurrence

Reduction of affective cycling and mood instability

Reduction of sub threshold symptoms

Reduction of suicidal risk

Reduction of social and vocational deficits

It is recommended that the treatment that improves the patients in acute phase of treatment also helps in maintenance.,hence should be continued. Lithium, Divalporex, Olanzapin 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 propensity to cause metabolic side effects.

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 patient has achieved remission for minimum 12 to 24 consecutive months

Potential risk of relapse should be weighed against risk of continued medication. Special caution should be paid to those patients who have severe aggression, history of suicidal behavior and psychosis.Sometimes treatment may have to be continued even longer or lifelong.

## **Risk factors for Relapse**

Duration of illness  
Higher number of episodes before stabilization  
Co administration of other agent that may that may destabilize patient's mood  
Emotional/Environmental factors: Sleep deprivation ,stress, negative cognition

## **Side effects and their management**

Although the side effect profile of antipsychotics and their management has largely been discussed in chapter of Childhood onset Schizophrenia which may be referred for further reading. Nevertheless, following precautions are advised to avoid such undesirable effects.

## **Precautions while prescribing Antipsychotics**

Antipsychotics are less well tolerated in children and adolescents than in adults. This age group has larger risk of developing adverse effect including extrapyramidal symptoms (EPSEs), prolactin elevation, sedation, weight gain and metabolic side-effects. It is recommended that :

- Patient and family should be directly involved in decision making regarding 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.

## **Side Effects of Medications and their management**

**Lithium**

<p>Weight gain Polyuria,polydipsia</p> <p><b>Neurological:</b> memory impairment,tremors, ataxia,dysarthria,delirium</p> <p><b>Renal</b> Interstitial fibrosis,diabetesinsipidus</p> <p><b>GI</b> Nausea ,diarrhea,abdominal discomfort</p> <p><b>Endocrine</b> Hypothyroidism</p> <p><b>Cardiovascular</b> Bradycardia,hypotension, sick sinus syndrome,arrhythmia</p> <p><b>Dermatological</b> Acne, rash, alopecia</p> <p><b>Hematological</b> Leucocytosis</p>	<ul style="list-style-type: none"> <li>• Reduce the dose or once daily dose medication.</li> <li>• Advise entire dose at night time.</li> <li>• Use different preparation(CR).</li> <li>• For GI disturbances take medicine with food, use antacids.</li> <li>• For tremors avoid caffeine, use beta blockers.</li> <li>• For polyuria and polydipsia ,add diuretics cautiously while reducing lithium by 50 percent.</li> <li>• For hypothyroidism add levothyroxine.</li> <li>• Switch to another medication if side effects still persists.</li> <li>• Consult appropriate specialty for further management of side effects if they do not improve.</li> </ul>
<b>Valproate</b>	
<p>Weight gain</p> <p><b>Neurological</b> Headache, ataxia,tremors,dizziness, sedation</p> <p><b>GI</b> Abdominalpain,nausea,diarrhea,vomiting, constipation,dyspepsia,decreased appetite hepatotoxicity,pancreatitis</p> <p><b>Dermatological</b> Alopecia</p> <p><b>Metabolic/Endocrinal</b> Hyperinsulinimia, lipid dysregulation,hyperendrogenism</p> <p><b>decreased bone density</b></p> <p><b>polycystic Ovaries</b></p>	<ul style="list-style-type: none"> <li>• Reduce the dose or once daily dose medication.</li> <li>• Advise to take max. dose at night time to avoid sedation.</li> <li>• For GI disturbances, use antacids.</li> <li>• For tremors avoid caffeine, use beta blockers.</li> <li>• Multi vitamin with zinc and selenium for alopecia.</li> <li>• Switch to another medication if side effects still persists..</li> <li>• Consult appropriate specialty for further management of side effects if they do not improve.</li> </ul>
<b>Carbamezapine</b>	
<p><b>Neurological</b> Unsteadiness,headache,dizziness,confusion, sedation</p> <p><b>GI</b> Nausea,vomiting,diarrhea</p> <p><b>Hematological</b> Leucopenia, aplastic anemia,agranulocytosis</p> <p><b>Dermatological</b> Rashes, SJ syndrome</p> <p><b>Metabolic/Endocrinal</b> SIADH with Hyponatremia, hypothyroidism</p> <p><b>Ophthalmological</b> Blurred vision</p>	<ul style="list-style-type: none"> <li>• Reduce the dose</li> <li>• Advise to take max. dose at night time to avoid sedation.</li> <li>• For GI disturbances take medicine with food, use antacids.</li> <li>• CNS side effects can be significantly lowered with controlled release preparation.</li> <li>• For hypothyroidism add levothyroxine.</li> <li>• Switch to another medication if side effects still persists..</li> <li>• Consult appropriate specialty for further management of side effects if they do not improve.</li> </ul>

<b>Lamotrigine</b>	
<b>Neurological</b> Headache, dizziness, tremor, ataxia, poor coordination, insomnia, aseptic meningitis <b>GI</b> Nausea, vomiting, pain abdomen, dyspepsia, constipation <b>Hematological</b> Leucopenia, aplastic anemia, agranulocytosis <b>Dermatological</b> Rashes, SJ syndrome, Toxic Epidermal Necrolysis <b>Hematological</b> Blood dyscrasias <b>Ophthalmological</b> Blurred vision, double vision	<ul style="list-style-type: none"> <li>• Reduce the dose</li> <li>• Advise to take max. dose at night to reduce day time sedation.</li> <li>• Antihistaminic/topical steroids for rashes and pruritus</li> <li>• For GI disturbances take medicine with food, use antacids.</li> <li>• Switch to another medication if side effects still persists..</li> <li>• Consult appropriate specialty for further management of side effects if they do not improve.</li> </ul>

### Measures to improve medication Compliance

Consider patients and care giver 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
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### Treatment of Comorbid Psychiatric Disorders

#### Common co existing psychiatric disorder with BAD

ADHD	Anxiety Disorder
ODD	Substance Abuse
Conduct Disorder	

### General Principle of management of Comorbid Psychiatric Disorders

Stabilize the symptoms of BPD first  
 Review the need of treatment for co morbid 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

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.<sup>1</sup>

Youth with BPD are amongst the most impaired population and the presence of comorbidity intensifies disability, complicates treatment, and probably worsens the prognosis in this population.<sup>1</sup>

### **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.

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 non-stimulant antiADHD agent bupropion in adults with predominately mood stabilized bipolar II disorder and ADHD, reported a significant improvement in ADHD without activation of mania.

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

### **Differeciating symptoms of BPAD and ADHD**

Symptoms	BPAD	ADHD
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<b>Irritability</b>	<b>Yes</b>	<b>Yes</b>
<b>Grandiosity</b>	<b>Yes</b>	<b>No</b>
<b>Elevated mood</b>	<b>Yes</b>	<b>No</b>
<b>Over-Activity</b>	<b>Yes (Goal Directed)</b>	<b>Yes (Un productive)</b>
<b>Sexually inappropriate Behaviour</b>	<b>May be Present</b>	<b>Absent</b>
<b>Sleep problems</b>	<b>Yes (Early/ and late insomnia)</b>	<b>Yes (persistent/ generalized)</b>
<b>Distractibility</b>	<b>Yes</b>	<b>Yes</b>
<b>Impulsivity</b>	<b>Yes</b>	<b>Yes</b>
<b>Over talkative</b>	<b>Yes</b>	<b>Yes</b>
<b>Episodic</b>	<b>Yes</b>	<b>No</b>

## **Oppositional Defiant Disorder (ODD)p**

Treatment of ODD is primarily behavioral in nature, when comorbid with other medication-responsive psychiatric conditions (BPD, ADHD), pharmacological treatment of the comorbid disorder often reduces overall symptoms of the ODD.

To date, risperidone is the most extensively studied atypical antipsychotic for DBD (disruptive behaviour disorder). 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 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 **divalproexis** 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 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 Substance Use Disorder, 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.

## **Non pharmacological treatment**

### **Non pharmacological management includes:**

#### **Physical methods of treatment**

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

**rTMS, DBS, VNS** are the therapeutic modalities reported in various disorders recommended in severe cases of illness when other treatment modalities don't 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 are integral and necessary adjunctive treatment to pharmacological interventions for Bipolar Disorder in Children and adolescents. Pediatric Bipolar disorder 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 like adjunctive approach, individual and family psycho-education approach to explain nature, symptoms, etiology, course and outcome and prognosis of bipolar disorders. The psychosocial approach also focus on developing coping skills to control their mood fluctuations and for 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 pediatric bipolar disorder which will be discussed briefly.

1. Multifamily psycho-education group (MFPG/PEP) - Fristad et al
2. Individual family psycho-education (IFP/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 cognitive behavior therapy (Rainbow programme) (CFF-CBT)
7. CBT for Bipolar Disorders in Adolescents (CBT-A)
8. Interpersonal Psychotherapy (IPT)
9. Mindfulness Based Intervention
10. Cognitive Remediation
11. Intensive Psychosocial Intervention (IPI)

## **Family Focused Treatment (FFT-A)**

Family Focused Treatment (FFT) has been adopted for adolescents with mood disorders in adolescents. FFT for adolescents (FFT-A) is designed for 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) 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 psycho-education 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 not only the patient and includes elements of psycho-education, 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 Psycho-educational Psychotherapy**

The basic concept of psycho-education 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 non pharmacological treatment options and associated risks and no treatment at all, role of medication compliance, early detection of new episodes or co-morbid medical or psychiatric conditions and avoiding of substance abuse. Fristard et al have developed individual and group psycho-education based psychotherapy intervention (PEP) for school going children with Bipolar Disorder. PEP combines Psycho-education, Cognitive Behavior Therapy and family system to target affective symptoms and associated personal and social impairments via 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. Total 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, optimal academic and occupational performances including music, art, dance, literature, sports and athletics. Stress management is a very important part of psych-social interventions sine stress and trauma act as both contributing factors and as outcomes of any episodes of Pediatric Bipolar Disorder. Children are taught to develop a tool box of coping skills like they have to identify calming and enjoyable activities in each of 4 domains- ceative, 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 non verbal communcation skills and controlling of impulses.

### **Child and Family Focused Cognitive Behavior Treatment (The RAINBOW Programme**

Child and family focused CBT (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 psycho-education and CBT with mindfulness based intervention, positive psychology and interpersonal therapy. The CFF-CBT is a 12 session protocol treatment programme alternating between child, parent and family focused sessions, it has also been adapted to a 12 week group which consist of weekly 60 minute parallel parent and child group and effective is 15 minute parent/child component. In both format, therapy is structured around 7 core components that comprise the acronym “RAINBOW”

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 (DBT)**

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 total 36 sessions during the course of 1 year. It has 2 modalities: family skills training for the entire family which includes psycho-education 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, non suicidal self injury, emotional dysregulation and depressive symptoms after the therapy.

### **Interpersonal and Social Rhythm Therapy (IPSRT-A)**

On the basis of bio-psychosocial theory, Interpersonal and Social Rhythm Therapy (IPSRT-A) has been adapted for Paediatric Bipolar Disorder. 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 affects circadian systems. The IPSRT-A is 16-18 session individual based treatment which includes brief family psychotherapy which focus on stabilizing social and sleep routines and deals with psycho-social stressors through an interpersonal based approach and also give 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 (CBT)**

The CBT for adolescents modules focus on psycho-education, medication compliance, mood monitoring, modifying negative thinking, sleep regulation and family communication. The therapy consist 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 psycho-education seems 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.

<b>Intervention</b>	<b>Treatment Target</b>	<b>Format</b>	<b>Treatment Length</b>	<b>Core Elements</b>	<b>Empirical Support</b>
FFT-A, FFT-HR	Adolescent, Family, High Risk Group	Individual	21 Sessions, 12 Sessions (HR)	Psycho-education, communication, problem-solving	Two site RCT (FFT-A); Small RCT (FFT-HR)
MF-PEP, IF-PEP	Child, Parents, Family (MF-PEP)	Individual or Group	Group: 8 Sessions; Individual: 24 Sessions	Psycho-education with CBT-based skill building	Two RCTs (MF-PEP); Small RCT (IF-PEP)
CFF-CBT	Child, Parents, Family	Individual or Group	12 Sessions + 6 Booster Sessions	CBT with psycho-education, mindfulness, social skill development, family communication & problem solving	3 Open Trials; RCT with Preliminary findings
DBT-A	Adolescent, Family	Individual	36 Sessions	Mindfulness, Distress, tolerance, interpersonal effectiveness, problem solving	Small open trial
IPSRT-A	Adolescent, Brief Family Portion	Individual	16-18 Sessions	Social & Sleep Routines, Interpersonal Therapy	Small open trial; RCT underway
CBT	Adolescent, Brief/Parent Family Portion	Individual	12 Sessions	CBT with psycho-education, optional modules for specific problem areas	Small pilot trial with matched controls

## **Psychiatric/Medical Comorbidity in Pediatric Bipolar Disorder**

The presence of Psychiatric and Medical Co-morbidity 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 seems to be related to additional Psychiatric Co-morbidity with more severe episodes. Identification and management of these associated co-morbidities may help alleviate the severity of impairment and duration of each episodes in bipolar disorders. BPD responses to Lithium is less effective in the presence of co-morbid ADHD. Stimulants are more effective and safe for the treatment of associated ADHD after the manic episode is stabilized. Management of BPD with Valproic Acid and Lithium results in reduction of SUD. Response to psychopharmacology in PDD with mood dysregulation is less effective with higher chances for adverse effects. The ADHD co-morbidity 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 co-morbid conditions. The co-morbidity complicates both the diagnosis and management. Co-morbid disorders may have a significant impact on the various indices of BPD correlates. Early identification and appropriate treatment may lead to improved overall functioning, prevention of co-morbid conditions. If these co-morbidities 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 co-morbidity is the determination of the level of care needed.

### **Medical Comorbidity**

- A) Enuresis/Encopresis
- B) Epilepsy
- C) Headache/Migraine
- D) Menstrual Cycle Disorders
- E) Gastric Symptoms
- F) Polycystic Ovarian Syndrome

### **Psychiatric Comorbidity**

- A) Attention Deficit Hyperactivity Disorder (ADHD)
- B) Anxiety including Panic Disorder
- C) Substance Use Disorder
- D) Disruptive Behavior Disorder
- E) Pervasive Developmental Disorder (PDD)
- F) Obsessive Compulsive Disorder (OCD)
- G) Oppositional Defiant Disorder (ODD)
- H) Conduct Disorder (CD)
- I) Post Traumatic Stress Disorder (PTSD)
- J) Personality Disorders
- K) Mental Retardation/Intellectual Disability
- L) Movement Disorder/Tics

## **The management of psychiatric co-morbidity in PBD**

The presence of co-morbid disorders with PBD results in a more severe clinical condition. Earlier onset PBD seems to be related to additional co-morbidity and more severe episodes and cycle acceleration. PBD response to lithium is less robust in the presence ADHD. Stimulants are efficacious and safe for ADHD once mania is stabilized. Management of PBD with lithium and valproic acid results in attenuation of active SUD. In PBD with co-morbid OCD but not GAD is associated with poor antimanic response. Response to psychotropics in PDD with mood dysregulation is found to be less robust with more side effects.

## **Conduct Disorder (CD)**

Available data on Psychiatric co-morbidity in PBD suggests that pre-pubertal onset PBD is a non episodic, chronic, rapid cycling, mixed manic state that maybe associated with conduct disorder or ADHD. As both CD and PBD are highly impairing conditions, their co-occurrence shows severe clinical picture and need to be attention. The association between CD and Mania is consistent with the co-morbidity between CD and Major Depression and bipolar nature of juvenile depression. The irritable outburst often includes threatening or attacking behavior towards teachers, peer group, siblings and family members which overlaps with CD. Reports suggested that manic episode of PBD shows serious acting out behavior like burglary, stealing, vandalism and school suspensions. High rates of CD are reported in PBD patients and this co-morbidity has a more complicated course and outcome with high rates of admissions. Furthermore CD is reported to be severe in patients of PBD. As PBD may antisocial and aggressive behavior of CD. The promising role of atypical antipsychotic trials to assess the efficacy and response of CD. 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 treatment of CD with aggressive behavior has been increasing. In one trial suggesting that short and long term treatment with quetiapine was safe and well tolerated. In one study the treatment with olanzapine resulted in improvement of aggressive behavior but was also associated with weight gain.

## **Obsessive Compulsive Disorder (OCD)**

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

## **Post Traumatic Stress Disorder (PTSD)**

The reported rates of PTSD co-morbidity in patients with PBD have varied from 7% to 50%. Rate of SUD are much higher in youths who had a lifetime diagnosis of PTSD before age 18 years as compared to those who had never experienced a trauma. Though no empirical evidence is available for the management of co-morbid PBD and PTSD but valproate maybe effective in treating certain combat related PTSD symptoms. Several studies showed that carbamazepine maybe useful for treating PTSD symptoms like 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 (PDD)**

In the presence of co-morbid 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 a smaller increments. Available limited literature on the management of PBD with PDD suggest that typical antipsychotics (haloperidol, chlorpromazine, thioridazine) and traditional mood stabilizers (lithium, 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, and 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 an typical antipsychotic; and other mood stabilizers should be added as necessary. The use of other medications and/or psychosocial treatment target other PDD symptoms (eg 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 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 target both disorders, such as carbamazepine, divalproex and oxcarbamazepine 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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