

# Clinical Practice Guidelines for The Treatment of Children and Adolescents with Affective Disorders

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Affective disorders or mood disorders are a group of clinical conditions where the essential features include mood disturbances, either depression or elation accompanied by related cognitive, psychomotor, psychophysiological and interpersonal difficulties. This causes significant impairment in the patient's and family's quality of life.

There is a vast body of literature on juvenile depression; whereas bipolar disorder literature in the child and adolescent population has been emerging since the 1990's.

Clinical practice guidelines are strategies for patient management, developed to assist clinicians in psychiatric decision making. This paper is intended to serve as guidelines only and is not intended to define standards of care. It describes generally accepted approaches based on literature from our country and the west. The ultimate judgment regarding the care of a particular patient must be made by the clinician in the light of all of the circumstances presented by the patient and his or her family, the diagnostic and treatment options available, and available resources. For detailed reviews on the treatment of affective disorders the reader is referred to the articles by Birmaher et al (1996a, b), Pavuluri et al (2005), National Institute of Health and Clinical Excellence (NICE) guidelines (2005), McClellan et al (2007) and Smarty et al (2007).

Henceforth, the words 'in the young', in 'youngsters', 'juvenile' denote children and adolescents.

## **DEPRESSION:**

Depression can refer to a symptom of low or sad mood, a syndrome encompassing a group of individual symptoms that consistently cluster together, or a disorder distinguished by a distinct course of illness, family history, treatment response, and outcome (Carlson and Cantwell 1980).

## **EPIDEMIOLOGY:**

Depressive disorders in the child and adolescent population is often under-recognized.

There has been a secular trend over the last few decades, with population-based studies showing rates of 0.4% to 2.5% in children and 0.4% to 8.3% in adolescents (Fleming and Offord, 1990) of depressive disorders?. A lifetime prevalence of 15% to 20% has been reported which is comparable with the lifetime prevalence of major depressive disorder (MDD) found in adults suggesting that depression in adults often begins in adolescence (Lewinsohn et al 1986; Kessler et al, 1994). Clinic based populations from India report a prevalence rate of 9.2% (Srinath and Bavle, 1987). The prevalence rates for dysthymia are 0.6%-1.7% in children and 1.6%-8% for adolescents. The sex ratio in children is equal, however in adolescents there is a female preponderance (F:M is 2:1) in the prevalence. There is a post pubertal rise in girls diagnosed with the depression (Harrington, 1994).

## **CLINICAL PRESENTATION:**

Depression does occur across all ages with the age of onset seeming to be getting younger over the years. The prominent symptoms are sadness of mood, loss of energy and inability to derive pleasure from routine activities

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as seen in adults. Developmental influences modify the presentation e.g. presence of irritability can be more common in this population than depressed mood. Somatic symptoms can be the presenting complaints and can be seen as a depressive equivalent especially in adolescents. In a study which consisted largely of adolescents with school refusal MDD was present in more than 60%. (Prabhuswamy et al, 2006). Symptoms of endogeneity and impairment of functioning increases with age (Birmaher, 1996a). A diagnosis of MDD and dysthymia can be made in youngsters with existing criteria.

Psychotic symptoms can occur in 30% of the youngsters with MDD. Presence of psychotic symptoms, psychomotor retardation and family history of bipolar disorder are risk factors for bipolar disorder in a youngster with MDD/ recurrent depressive disorder(RDD). Clinic-based studies have shown that the risk for developing bipolar disorder in children with MDD ranges between 20-40% (Birmaher, 1996a). Bipolar disorder type II can be misdiagnosed as MDD when history of hypomanic episodes are not systematically evaluated. In one study 12 (20%) of 61 youngsters with MDD had past history of hypomania, which was undiagnosed in routine clinical assessment (Bhargava Raman et al, 2007).

The average duration of a depressive episode is about 7–9 months. Most episodes remit 1 to 2 years after onset. 6-10% of the episodes tend to become chronic. MDD is a recurrent condition with a cumulative probability of recurrence of 40% by 2 years and 70% by 5 years (Warner et al., 1992). Short-term outcome studies from India have indicated a remission rate of 84% in clinic-based studies with average duration ranging from 7-24 weeks (Mean-27.4±15 weeks) (Raghunandan, 2005 unpublished).

#### **COMORBIDITY:**

Clinical & epidemiological investigations have shown that 40 to 70 % of depressed children and adolescents have co-morbid psychiatric disorders and at least 20 to 50 % have two or more co morbid diagnoses (Birmaher et al, 1996a, b). The most frequent co-morbid diagnoses are dysthymic disorder and anxiety disorders (both at 30 to 80%), disruptive disorders (10% to 80%), and substance abuse (20% to 30%). Conduct problems may develop as a complication of the depression and persist after the depression remits.

#### **RECOMMENDATIONS:**

##### **1. SCREENING:**

Detailed enquiries have to be done about periods of low moods in the youngster with special emphasis on the context in which the symptoms occur. Evaluation of associated stressors, family history of mood disorders and substance dependence is important.

##### **2. USE OF DIAGNOSTIC CRITERIA:**

Diagnostic criteria from either DSM-IV or ICD-10 or the NICE guidelines (2005) can be used. These systems require at least one of the key symptoms to be present on most days, most of the time, for at least 2 weeks: persistent sadness or low (irritable) mood, loss of interests and/or pleasure and fatigue or low energy along with subsidiary symptoms like sleep/appetite disturbances, poor concentration or indecisiveness, low self-confidence, suicidal thoughts or acts, guilt or self-blame and agitation or psycho-motor retardation.

Instruments like Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (Ambrosini, 2000) and Mini International Neuropsychiatry Interview for

Children and Adolescents (MINI-KID) can be used for assessment of depression. Severity rating using Child Depression Inventory (CDI) (Kovacs, 1985) or Childhood Depression rating Scale- Revised (CDRS-R) (Poznanski and Mokros, 1996) can help assess improvement with treatment.

##### **3. EVALUATION OF COMORBIDITY:**

Evaluation of comorbid disorders such as disruptive behaviour disorders and anxiety disorders is essential

since they can influence treatment decisions and also help understand possible long-term course. Conduct symptoms can occur in the background of a dysphoric mood where treating the depressive illness can reduce conduct symptoms.

#### 4. Treatment:

##### **MILD DEPRESSION:**

Medication is not the first choice of treatment in mild depression. However, in settings where resources for delivery of psychological therapies are limited medication can be considered. Psychotherapeutic interventions alone are enough in most of the mild cases.

##### **MODERATE AND SEVERE DEPRESSION:**

A combination of an antidepressant and psychotherapy is the recommended treatment. Fluoxetine and individual psychological therapy is the first line of management. When fluoxetine is prescribed, the starting dose should be 10 mg daily. This can be increased to 20 mg daily after 1 week if there are no side-effects, although lower doses should be considered in children of lower body weight. There is little evidence regarding the effectiveness of doses higher than 20 mg daily (NICE, 2005). Escitalopram or Sertraline are the next medications that can be tried if a child does not respond to Fluoxetine.

In children who respond to treatment, fluoxetine should be continued for at least 6 months after remission (defined as no symptoms and full functioning for at least 8 weeks). Data to show the efficacy of SSRIs in this population though meager is emerging. The results of the first 12 weeks of the Treatment for Adolescents with Depression Study (TADS), conducted at 13 sites in the US, show that in 439 adolescents aged 12-17 years, 71 % responded to the combination of fluoxetine and CBT, 60.6 % to fluoxetine-only, 43.2 percent for those receiving only CBT and 34.8 percent for a group that received a placebo. The difference in response rates for the latter two treatment groups was not statistically significant (March et al, 2004).

FDA sponsored reevaluation of data on 4582 pediatric patients in 24 antidepressant trial indicated an increased risk of 1-3% of suicide although no suicides occurred (Hammad et al, 2006). The committee concluded that a causal link exists and mandated a black box labeling of all antidepressants used with pediatric patients. Currently the only SSRI that is approved by the USFDA for the treatment of depression in this population is fluoxetine with a ban on the use of other antidepressants especially paroxetine and venlafaxine. Tricyclic antidepressants are generally found to be less efficacious in the child and adolescent population compared to adults (Murrin et al, 2007).

It is very important to take parental consent and assent from the youngster whenever medication is being started and educate them about possible adverse effects and the need for good compliance. Regular monitoring at weekly intervals initially, biweekly after one month and again after 12 weeks is essential.

It has been found that most studies evaluating efficacy of antidepressants in this population have used very small sample sizes, with only mild to moderate depression being taken and excluding those children and adolescents with comorbid disorders. Also seriously ill patients like ones with suicidal attempts, with catatonia or those with recurrent episodes do not get taken into clinical trials. It is very important for the clinician to take a decision based on the individual case and use medication judiciously. Withholding medication when a youngster needs it is a serious lapse in care.

##### **CLINICAL VARIANTS:**

In psychotic depression there is a need to add an antipsychotic with the anti-depressant and the antipsychotic needs to be tapered and stopped gradually. There might be a role for ECT in psychotic depression. In bipolar depression the initial strategy would be to hike the dose of the mood stabilizer. An antidepressant like fluoxetine can be added later (after 2-3 weeks with careful monitoring of symptoms during this period) if there

is no response or if the depressive episode is moderate to severe. A risk for switch to mania/hypomania and worsening of cycling has to be kept in mind when adding an antidepressant.

## **5. PSYCHOTHERAPEUTIC INTERVENTIONS:**

The therapies that have been used are psychodynamic therapies which help youth understand themselves, help improve self-esteem and cope with ongoing and past conflicts. Cognitive Behaviour Therapy (CBT) helps identify and counteract the cognitive distortions that contribute to depressive cognitions and mood. Interpersonal therapy (IPT) has also been used. This therapy focuses on grief, interpersonal role disputes, role transitions and personal difficulties (Birmaher, 1998).

A specific goal of psychological therapies are stopping of suicidal behaviour and/or verbalisation of the desire to die. The steps to be taken are to assess the cognitive messages that the client gives to him/herself that reinforce helplessness and hopelessness, teach and reinforce positive cognitive messages that facilitate growth of the clients self confidence and self acceptance, monitor the potential for self harm and refer when needed / use protective setting. Contract with youngster for no self-harm also needs to be taken (Jongsma et al 1996).

An important part of individual therapy would be to get the youngster acknowledge unhappiness with life and specify what in the past or present contributes to sadness or what is missing from his life. The level of the youngster's self-understanding about self-defeating behaviours linked to depression has to be assessed and a connection between symptoms and the underlying depression has to be built. Reinforcement of open expression of underlying feelings of anger, hurt & disappointment is important (Jongsma et al 1996).

Other therapies like Contextual emotion-regulation therapy (CERT) are in the process of evaluation and have shown some initial positive response. This therapy focuses on self-regulatory responses to distress and dysphoria, which unfolds across development and are important for adaptive functioning and appear to be dysfunctional in individuals with depressive disorders across the life span (Kovacs et al, 2006).

In conclusion, depressive disorders in the child and adolescent population needs early recognition and intervention to avoid morbidity and mortality. Psychosocial forms of therapy are the mainstay of treatment in the milder forms and a combination of psychological therapies with medication especially SSRIs are useful in the moderate and severe forms of depression. Appropriate modifications are necessary in the other clinical variants of depression. A collaborative approach between the treating team, the youngster and his/her family is essential to ensure treatment compliance.

## **BIPOLAR DISORDER:**

The occurrence of mania in youngsters is well documented.

## **EPIDEMIOLOGY:**

Community-based studies have shown a prevalence rate of approximately 1% for bipolar disorder in adolescence (Lewinsohn et al, 2000). Large-scale studies of bipolar adults found that approximately one fifth of cases retrospectively had evidence of the illness before age 19 years (Carlson et al., 1977; Joyce, 1984; Loranger and Levine, 1978). Although historically considered rare, childhood onset bipolar disorder is now being diagnosed much more commonly, including in preschool children (Wilens et al., 2003).

In clinic based studies at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, the prevalence rates of bipolar disorders was found to range between 3-6% (Srinath and Bavle, 1987, Jairam et al, 2004).

## **CLINICAL PRESENTATION:**

In the past, children with this disorder were often misdiagnosed as suffering from other conditions such as attention deficit – hyperactivity disorder (ADHD), conduct disorder and childhood onset schizophrenia. This

was partly due to variations in clinical presentation and also because of being less sensitive in considering a diagnosis of mania in this population.

Phenomenology of juvenile mania, especially in younger children, can vary from the classic descriptions of bipolar disorder in adults (Bowring and Kovacs, 1992). Mania in adolescents is frequently associated with psychotic symptoms, markedly labile moods, and/or mixed manic and depressive features (Pavuluri et al., 2005). The presence of irritability and emotional instability in children in comparison to euphoria, elation seen in adolescents and adults is seen as a developmental modulation of symptom expression (Carlson, 1983). In a study from NIMHANS it was found that the most common symptoms were pressure of speech, irritability, elation, distractibility, increased self-esteem, expansive mood, flight of ideas and grandiose delusions (Reddy et al, 1997) in a largely adolescent population.

The early course of bipolar disorder in adolescents appears to be more chronic and refractory to treatment than adult onset (Perlis et al., 2004), whereas the long-term prognosis is either similar to that of adults (McClellan et al., 1993; Werry et al., 1991) or worse (Carter et al., 2003). However this has not been seen in clinic based studies from India, where it has been seen that the recovery rates from the index episode has ranged between 96-100% with shorter time taken to recover. Relapse rates in the first two years have been higher compared to the west (Srinath et al, 1998, Jairam et al, 2004).

#### **CO-MORBIDITY:**

Juvenile mania is co-morbid with other psychiatric disorders the rates of which have varied in studies. The lifetime co-morbidity was estimated to be 69% with conduct disorder (CD) and the rate of episode co-morbidity was found to be 54% in a study by Kovacs and Pollock (1995). The authors also suggested that co-morbid CD might identify a sub-type of early onset bipolar disorder.

Rates of disruptive behaviour disorders (DBD) have been found to be as high as 86.5% (Geller et al, 2002) in studies from the west. However studies from NIMHANS have found a very low co-morbidity rate. Reddy et al. (1997) found that no patient had ADHD and only two patients had CD in a sample of 21 patients. A retrospective chart review of 151 subjects with bipolar disorder found that 31 (26%) had a comorbid diagnosis, with 16 (11%) having ADHD, 13(9%) having ODD and 11 (8%) having CD (Rajeev et al, 2004). In a subsequent study 10 (14%) of the subjects had one or more comorbid DBD. ODD, ADHD and CD were present in 8(11%), 3 (4%) and 2 (3%) subjects, respectively. Those with DBD had earlier onset of bipolar disorder and spent more time ill compared to those without DBD (Jaideep et al, 2006). This difference in rates could be because of differing sample characteristics. Substance abuse and anxiety disorders are the other two important co-morbid diagnoses.

#### **RECOMMENDATIONS:**

##### **1. SCREENING:**

Detailed enquiries have to be done about periods of mood changes in the youngster with specific questions about symptomatology as discussed. Histories of depression and family histories of mood disorders are also important to assess. Symptoms across different settings have to be assessed to rule other contextual causes for behavioural problems.

##### **2. USE OF DIAGNOSTIC CRITERIA:**

Specific criteria for diagnoses from either DSM-IV or ICD-10 can be used with special emphasis on the duration of symptoms. It is important to look at developmental influences on symptom presentation. One has to be careful while applying the criteria in pre-schoolers.

Instruments like Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (Ambrosini, 2000) and Mini International Neuropsychiatry Interview for

Children and Adolescents (MINI-KID) can be used for diagnosis and Young's Mania rating Scale (YMRS) (Young et al, 1978) for severity rating can be used in certain settings.

### **3. EVALUATION OF COMORBIDITY:**

A thorough workup can rule out other confounding illnesses and identify comorbid disorders that need to be addressed as part of a comprehensive treatment plan.

Disorders that need to be specifically checked for are disruptive behaviour disorders (ADHD, ODD, CD), substance use disorders and anxiety disorders.

### **4. PSYCHOPHARMACOLOGICAL INTERVENTIONS:**

Most of the treatment recommendations for early-onset bipolar disorder are derived from the adult literature for acute mania because of lack of controlled studies in this population. Standard therapy, based on the adult literature, typically includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (Kowatch et al., 2005; Suppes et al., 2002).

The choice of medication(s) should be made based on (1) evidence of efficacy, (2) the phase of illness, (3) the presence of confounding presentations (e.g., rapid cycling mood swings, psychotic symptoms), (4) the agent's side effect spectrum and safety, (5) the patient's history of medication response, and (6) the preferences of the patient and his or her family. A history of treatment response in parents may predict response in offspring (Duffy et al., 2002).

All of the mood stabilizers and antipsychotic agents are commonly used for early-onset bipolar disorder in clinical settings, although none of the agents has been well studied in juveniles. The few double-blind, placebo-controlled studies of lithium (Carlson et al., 1992; DeLong and Aldershof, 1987; Geller et al., 1998) are generally positive, but they are limited by small sample sizes and diagnostic variability. However, one controlled discontinuation trial randomized adolescents acutely stabilized on lithium to either ongoing lithium therapy or placebo (Kafantaris et al., 2004). High rates of relapse were found in both groups in patients stabilized on lithium, raising questions about its ongoing efficacy.

In a short-term study done at NIMHANS 20 children and adolescents (mean age 14.1 years) with mania were treated with lithium (mean dose  $1125 \pm 106$  mg). At follow up (15 days), the recovery rate was 63.5%. Longer duration and greater severity of the episode predicted a poorer response (Somashekhhar, 1999 unpublished). In another study from the same centre there was 100% recovery from the index episode and 16 out of 25 (64%) patients relapsed after  $18 \pm 16.4$  months. Of these 11 patients relapsed despite the patient being on "adequate" treatment (Rajeev et al, 2003).

A retrospective chart review of 139 consecutive juvenile bipolars (age < 16 years) showed that 96% of them had recovered from the index episode. 90% were on a mood stabilizer (usually lithium or valproate). A relapse rate of 35% (n=47) was found, with 89% of the relapses (n=42) occurring in the first two years following the index episode. Of these, 28% (n=17) relapsed despite being on adequate, "therapeutic" doses of lithium. This raises doubts about the efficacy of this drug in juvenile bipolar disorder (Jairam et al, 2004). Srinath et al(1998) note that there may be some justification for considering long term maintenance medication, at least for all young hospitalized bipolar patients. Indefinite prophylaxis may be used when a family history of affective disorders is present, when the child has had multiple bipolar episodes or needed multiple medications for the index episode or if subsyndromal symptoms persist

Most studies so far have looked at bipolar I disorder in children and adolescents.

Evidence for the treatment of other softer forms of bipolar disorders is lacking, though thymoleptics, and/ antipsychotics have been used.

There are very few studies to date that document the efficacy of the anticonvulsants for bipolar disorder in

youths. Open-label trials, case reports, and retrospective chart reviews describe the effectiveness of valproate, carbamazepine, and topiramate (as an adjunctive agent) for juvenile mania, and lamotrigine for adolescents with bipolar depression.

The USFDA has approved the use of risperidone for the short-term treatment of manic or mixed episodes of bipolar disorder in children and adolescents aged 10-17 years based on data from a randomized double-blind controlled study (USFDA, 2007). Open-label trials and retrospective chart reviews also support the effectiveness of olanzapine, quetiapine and aripiprazole for pediatric bipolar disorder. When used as mood stabilizers, the atypical antipsychotic agents are prescribed with the same dose ranges and have the same spectrum of side effects as when used for psychotic illnesses. Weight gain has been a particular concern for this class of agents, especially in youths (Smarty and Findling, 2007).

Case reports indicate that ECT may be beneficial for youths with bipolar disorder (Hegde et al, 1997) (including mania, rapid cycling, and depressed phases), although the literature at this time is extremely limited. The guidelines for use of ECT in this population are given in detail by the American Academy of Child and Adolescent Psychiatry (2004). ECT should only be considered for adolescents with well characterized bipolar I disorder who have severe episodes of mania or depression and are nonresponsive (or unable to take) standard medication therapies.

#### **5. DURATION OF TREATMENT AND MONITORING:**

An adequate trial of a mood stabilizer has to be given before changing or augmenting with another drug. A 6- to 8-week trial of an appropriate dose is generally considered adequate. Although more definitive studies are needed, current evidence suggests that the regimen needed to stabilize acute mania should be maintained for 12 to 24 months with high rates of relapse in the first two years of the first episode (Rajeev et al, 2004). Maintenance therapy is often needed for youths with bipolar disorder, with some individuals needing lifelong therapy when the benefits of continued treatment outweigh the risks. This should be decided on a case-by-case basis after discussing the risks and benefits of continued treatment (Kowatch et al., 2005).

Baseline investigations like renal function tests, thyroid functioning, complete blood counts have to be done before initiating lithium. A 300mg test dose can be given in adolescents and if well tolerated can be increased to 900mg per day in divided doses (or 25 to 30mg per kg of body weight) and a serum lithium level has to be done after 5 days when steady state concentration is reached. The dose is subsequently adjusted to a maximum extent of the suggested therapeutic range (1-1.2 meq/litre) as side effects permit. Slightly lower doses can be used in children to avoid or reduce emergent side effects. Liver function tests, complete blood counts have to be done before starting Valproate. A target dose of 1000-1500 mg in adolescents and 1000 mg in children can be reached according to the response and side effect profile. The initial dose could be 500-750mg in divided doses (Kutcher, 1997).

Regular monitoring of parameters checked at baseline subsequently (once in 3-6 months) along with serum drug levels is important. Monitoring for metabolic side effects with atypical antipsychotics especially weight gain and insulin resistance cannot be over-emphasized.

#### **6. PSYCHOTHERAPEUTIC INTERVENTIONS:**

A comprehensive, multimodal treatment approach that combines medication management with adjunctive psychosocial therapies is almost always indicated for early onset bipolar disorder since the disorder causes disruption in the developmental processes of the child (Kowatch et al, 2005). Preexisting behavior disorders, substance abuse disorders, learning problems, and confounding psychosocial issues may require specific treatments related to those problems once the affective episode is stabilized. Psychotherapeutic interventions are needed to promote medication compliance and avoid relapse. Finally, interventions are needed to help youths and families cope with the developmental impact on peer relationships, academic performance, and psychological health.

Some of the interventions that have been tried in this population and whose efficacy has been proven in adults (Craighead and Miklowitz, 2000) are: 1) Psychoeducation to the family and youngster regarding the symptoms and course of the disorder, treatment options, the potential impact of the illness on psychosocial and family functioning;

2) Relapse prevention strategies especially the impact of noncompliance with medications, the recognition of emergent relapse symptoms, and other factors that may precipitate relapse (e.g., sleep deprivation, substance abuse). Stress reduction and the promotion of stable social and sleep habits also need emphasis; 3) Individual psychotherapy to support psychological development, skill building, and close monitoring of symptoms and progress in addition to correcting cognitive errors during periods of remission; 4) Efforts to enhance family and social relationships, including therapies directed at communication and problem-solving skills, are likely to be helpful; 5) Academic needs must be adequately addressed to help promote long term academic growth, especially given the high rates of comorbid disruptive behavior disorders. School consultation and an individual educational plan are often necessary to help develop an appropriate educational environment.

In conclusion, lithium has been the most studied psychopharmacologic agent and the first line of management in juvenile bipolar disorder though doubts about its efficacy as a prophylactic agent has been raised. Other mood stabilizers like anticonvulsants and antipsychotics have been used in this condition though controlled studies supporting their usefulness is lacking. A combination of psychopharmacological methods and appropriate psycho-social therapies are currently the mainstay of management.

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