Chapter 4
Affective Disorders—Current Status and Controversies

Kandasamy Preeti, Rajeev Jairam and Shoba Srinath

Abstract Affective disorders are common during childhood and adolescence and often pose a challenge in clinical settings. The clinical presentation of affective disorders varies with the developmental age of the child and the classical symptoms increase with age and severity. From a developmental perspective, the disruptive mood dysregulation disorder as a new diagnostic category in DSM 5 addresses this concern as well as the unparalleled increase in pediatric bipolar diagnoses. Use of developmentally appropriate assessments has helped address some of the controversies centred around diagnosis of depression in the young. However, there is sparse evidence of effectiveness of pharmacological and psychological means of treatment and controversies continues to exist regarding effective management of affective disorders in children and adolescents in bringing about a more favourable outcome. This chapter focuses on the current status and particularly controversies related to diagnosis of preschool depression, disruptive mood dysregulation disorder, pediatric bipolar and the differences in pattern of comorbidities across western and Indian literature; current insights into the course and outcome of affective disorders and controversies regarding management of affective disorders.

K. Preeti · S. Srinath (✉)
Department of Child and Adolescent Psychiatry, National Institute of Mental Health and Neurosciences, NIMHANS, P. O. Box 2900, Bangalore 560029, Karnataka, India
e-mail: shobasrinath@gmail.com

K. Preeti
e-mail: preetikandasamy@gmail.com

R. Jairam
ICAMHS, Mental Health, SWSLHD
Campbelltown Hospital, Therry Road, Campbelltown, NSW 2560, Australia
e-mail: rajeev.jairam@sswahs.nsw.gov.au

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4.1 Introduction

Affective disorders are a group of disorders with pervasive mood disturbance as the predominant presentation. They are common during childhood and adolescence and the functional consequences of the disorder can interfere with social, emotional and cognitive development. With significant developmental differences in presentation and comorbidities (Demeter et al. 2013; Axelson et al. 2006), controversies centred around diagnosis and pharmacological interventions, affective disorders often pose a challenge in clinical settings.

4.2 Current Status and Controversies in Diagnosis

Clinical presentation of affective disorders varies with the developmental age of the child and classical symptoms increase with age and severity. For example, younger children with depression express more irritability, frustration, temper tantrums and other behaviour problems with poor verbalization of feelings while adolescents present with sleep and appetite disturbances, somatic complaints, social withdrawal, school refusal, suicidal ideation and attempts, with greater impairment in functioning and with fewer melancholic symptoms and delusions (Rao and Chen 2009).

4.2.1 Preschool Depression

Over the past few years, studies have begun to systematically investigate depression among preschool-aged children and have shown that depressive syndrome can present in this population (Stalets and Luby 2006). Although the controversy regarding diagnosis of depression in young children still exists, age-appropriate mental status evaluation and age-adjusted symptom translations can facilitate diagnosis of depression in young children (Luby 2010).

Longitudinal prospective studies examining the trajectories and continuity of preschool depression have found that even after accounting for other risk factors including maternal depression, preschool depression predicted major depressive disorder in later childhood highlighting the importance of early interventions (Luby et al. 2014).

4.2.2 Disruptive Mood Dysregulation Disorder and Related Controversies

Disruptive mood dysregulation disorder (DMDD) was introduced in DSM-5 to describe children with chronic, severe and persistent irritability and frequent episodes of extreme behavioural dyscontrol. The introduction of this concept as a disorder has been controversial with the primary aim being to address the astronomical increase in pediatric bipolar diagnoses over the past two decades. This rise in diagnosis was largely fuelled by researchers considering severe, non-episodic irritability as a characteristic of bipolar disorder in children (American Psychiatric Association 2013; Tourian et al. 2015). Preliminary, largely post hoc, research has so far demonstrated that children with DMDD usually do not go on to have bipolar disorder in adulthood but are more likely to develop depressive or anxiety disorders. Its placement under depressive disorders emphasizes the disorder's mood component and its distinction from bipolar disorder (Roy et al. 2014).

DMDD have symptoms that overlap with many other disorders including Attention deficit hyperactivity disorder (ADHD), anxiety disorder, depressive disorder and bipolar disorder and poses difficulties in diagnosis. In a recent study, the 3-month prevalence of DMDD was found to be 8.2 % among 6-year-old children. DMDD co-occurred with behavioural and emotional disorders in about 60.5 % of children. Some of the predictors of DMDD at age 3 years included ADHD, oppositional defiant disorder (ODD), temperamental factors such as high urgency, negative emotional intensity and lower effortful control, parental lifetime substance use and higher parental hostility. At age of 6 years, there was association with depression and ODD apart from temperamental and parental factors (Dougherty et al. 2014).

While the DSM 5 criteria has addressed the concern for better diagnosis both for clinical and research purposes, management of DMDD is still a concern as there is paucity of literature in terms of interventions. Current treatment plans are often individualized based on the target symptoms. Treatment options include selective norepinephrine reuptake inhibitors, mood stabilizers, psycho-stimulants, antipsychotics and alpha-2 agonists (Tourian et al. 2015).

Notwithstanding the controversies surrounding its validity, the criteria when applied to a cohort of children followed through to adulthood revealed DMDD to be a hetero-typically continuous disorder with poor outcomes and significant psychosocial morbidity in adulthood (Copeland et al. 2014).

4.2.3 Pediatric Bipolar Disorder

More articles have been published on pediatric bipolar disorder than any other topic in child psychiatry over the last 20 years. Major controversies have been regarding its diagnosis, comorbidities and management. Prominent irritability and

difficulty in differentiating it from other disorders (which are sometimes comorbid), the high rates of comorbidities, chronicity and rapid cycling makes diagnosing pediatric bipolar in the young challenging. Indian studies on pediatric bipolar have revealed a lesser prevalence of comorbidities with conditions like Attention deficit hyperactivity disorder, conduct disorder and substance abuse (Jairam et al. 2004) as compared to western literature (Yen et al. 2015). Studies have also found that Bipolar II disorder is often misdiagnosed as Major depressive disorder in about 20 % of children (Bhargava Raman et al. 2007).

4.3 Comorbidities

A thorough assessment of comorbid disorders as part of evaluation is essential, as they can influence treatment decisions and also help understand possible long-term course. 40–70 % of children with depressive disorder suffer from another psychiatric disorder and many have two or more comorbid diagnoses (Rao and Chen 2009; Angold et al. 1999; Essau et al. 2008). Common comorbid disorders include Disruptive behaviour disorders 21–83 %, attention deficit hyperactivity Disorder 0–57 %, anxiety disorder in 20–75 %, substance abuse in 20–30 % (Angold et al. 1993, 1999). While western studies shows an increased prevalence of comorbid behavioural disorders, studies from Indian subcontinent shows an increased prevalence of Anxiety disorder—18 % and obsessive compulsive disorder—7 % and lesser comorbidity with disruptive behaviour disorders and attention deficit hyperactivity disorder (Krishnakumar et al. 2006). Conduct symptoms comorbid with depression can sometimes be misdiagnosed as irritable mania in children and treating the depressive illness can reduce conduct symptoms (Srinath et al. 2008).

4.4 Current Status and Controversies in Treatment

4.4.1 Depressive Disorder

Standard treatment guidelines provided by AACAP practice parameter (2007) and NICE Guidelines (2005) recommend that management of a child and adolescent with mild depressive disorder should include psycho-education and supportive therapy for 4–6 weeks. Both child and parents must be taught to develop concept of depression as an illness, identify and label the affect, learn importance of compliance and reduce feelings of stigmatization. Children and adolescents with moderate to severe depression should be provided the cognitive behavioural therapy, interpersonal therapy or short-term family therapy for at least 3 months duration. Antidepressants are indicated to treat those children who do not respond to first line psychotherapeutic interventions or whose level of risk warrants the

use of medication; even in these instances, it should be used in combination with psychotherapy.

Studies on psychotherapy for depressed youth have shown modest effect. Duration of therapy did not affect outcome indicating brief interventions may be as efficacious and cost-effective (Weisz et al. 2006).Other forms of therapy that have been reported to be helpful include attachment therapy (Diamond et al. 2002) and contextual emotion-regulation therapy (Kovacs and Lopez-Duran 2012).

Choice of therapeutic modality depends on severity, number of previous episodes, chronicity, subtype, comorbidity, age, contextual issues, previous treatment and response, child's and family's motivation and therapist's orientation and expertise. Choice of treatment may also be dependent on availability of trained professionals and patient and family preference. Children who are actively self harming or suicidal, agitated/psychotic or have low motivation, poor concentration, sleep disturbances or with comorbid developmental disorders may have difficulty in participating in psychotherapy and may need medication in the first instance.

Fluoxetine is approved by US FDA for children 8 years and older and Escitalopram is approved in youth 12 years and older. Fluoxetine is the most studied SSRI and recent reviews indicate that Fluoxetine should be considered as the first line drug treatment for adolescents with Major depressive disorder. In children who cannot tolerate Fluoxetine, Sertraline can be considered.

Treatment of Adolescents with Depression Study (TADS) found that combination of Fluoxetine and CBT was superior to monotherapy at 12 and 36 weeks (March et al. 2007) as shown in Table 4.1.

It also found that suicidal ideation decreased with treatment, but less so with fluoxetine therapy than with combination therapy or CBT. The study concluded that adding CBT to medication would enhance the safety of medication.

Continuation therapy for at least 6–12 months is recommended for all patients. Children and adolescents who have experiences at least two episodes or one severe/chronic episode require maintenance for more than one year. Children and adolescents with double depression may need to continue medication indefinitely. Trial discontinuation when considered should be during a stress free period (AACAP 2007).

Treatment of resistant depression in adolescents (TORDIA) study found that with use of alternate SSRI or combined therapy 38.9 % remission rate was achieved by 24 weeks. Remission was higher (61.6 % vs. 18.3 %) and faster among those who had shown clinical response by week 12. Factors that predicted remission includes lower severity rates of depression, hopelessness, anxiety, suicidal ideation, family conflict and absence of comorbid dysthymia, drug/alcohol use, anxiety and impairment (Emslie et al. 2010).

Table 4.1 Treatment of adolescents with depression study

TADS	Fluoxetine + CBT (%)	Fluoxetine (%)	CBT (%)
12 weeks	73	62	48
36 weeks	86	81	81

Electroconvulsive therapy (ECT) is reserved for children and adolescent with severe, persistent depressive symptoms, disabling or life-threatening symptoms, associated with catatonic symptoms or when there is lack of treatment response (AACAP 2004). Independent evaluation by a psychiatrist who is knowledgeable about ECT is suggested and ECT can be given to children and adolescents only after approval by the Mental Health Review Boards per current recommendations of Mental health care bill, India, 2013 (Narayan and Shekhar 2015). Cognitive assessment and written informed consent should be part of the ECT protocol.

4.4.2 Controversies Regarding Selective Serotonin Reuptake Inhibitor (SSRI) and Suicidality

US FDA in 2004 issued a black box warning to all antidepressant's labelling, that children taking these medications are at increased risk for suicidality. Further review showed suicidal ideation with few attempts and no completed suicide in 4300 subjects. The number needed to harm (NNH) was found to be 125 as compared to the number needed to treat (NNT) 10. The Risk: Benefit has been found to be 1:14.

The possible increase in suicidality could be attributed to roll back phenomenon—decreasing psychomotor retardation, akathisia, induction of anxiety and panic attacks and insomnia, behavioural activation or stage shifts as antidepressants may lead to a switch from depression into mixed states in bipolar depressed patients. However, paradoxical worsening of depression is quite a rare effect.

Evidence that favours administration of SSRI is that SSRIs continue to be the first line pharmacotherapy for depression in children. A declining trend in suicide rates was noted after widespread availability of SSRI and it ended with the decrease in antidepressant prescriptions following official warnings (McCain 2009). Warnings are therefore not meant to decrease the use of SSRIs in children but to emphasis on proper education and regular monitoring.

Clinical recommendations to address safety issues includes (Cheung et al. 2006)

1. Patients and their families need to be fully informed about the risks and benefits.
2. History of suicidal behaviours to be clarified and monitored at all subsequent visits.
3. To start at a low dose (equivalent of 5–10 mg of fluoxetine) and increase every 2 weeks.
4. To monitor closely for worsening depression, worsening or new suicidal ideation or behaviours, and other behavioural side effects. These are most likely to occur in the first four to 6 weeks.
5. The FDA therefore suggests weekly monitoring at least for the first 4 weeks after the introduction of antidepressant therapy.

4.4.3 Pediatric Bipolar Disorder

Prepubertal bipolar disorder had been found to have a more malignant course (Geller et al. 2004). Greater baseline severity, comorbid attention deficit hyperactivity disorder and conduct disorder was noted to predict poorer treatment response (Masi et al. 2003, 2006). Comorbid ADHD had also been associated with poor long-term recovery (Biederman et al. 2004). A retrospective application of criteria for the subjects of some of these studies may indicate that they would fulfil criteria for DMDD rather than bipolar type I.

Valproate, Lithium, Risperidone, Olanzapine, Aripiprazole and Quetiapine remained first line treatments for acute manic or mixed episodes. The lack of medium to long-term studies to ratify this is astonishing and subsequently, their efficacy in maintenance treatment remains unclear (Jairam et al. 2012). Long-term prophylaxis may be indicated in children with family history of affective disorders, multiple bipolar episodes, when multiple medications were needed to treat the index episode or if subsyndromal symptoms were present (Jairam et al. 2004). We could not find more recent studies which gave direction on prophylaxis.

A recent review of acute treatment for mania in children and adolescents found consistent evidence favouring the use of second-generation antipsychotics (SGAs), limited evidence favouring the use of combinations of SGA with a mood stabilizer (MS), and no evidence supporting the use of MS monotherapy in this context. Various SGAs are not clearly separated in terms of efficacy, but differ in their side effect profiles. There are insufficient data to comment on the benefit of alternative treatments, psychological treatments and electroconvulsive therapy. Gaps remain about expected time to recovery, and when to augment or change treatment when there is lack of effect (Hazell and Jairam 2012).

In a retrospective chart review, 96 % recovered from the index episode and 90 % were either on lithium or valproate (Rajeev et al. 2003, 2004). The relapse rate was 35 and 89 % of the relapses occurred in the first 2 years following the index episode, 28 % of whom relapsed despite being on adequate therapeutic doses of lithium. This raised doubts about the efficacy of this drug in relapse prevention (Rajeev et al. 2004, Pravin et al. 2005). However, earlier studies have reported a threefold higher relapse rate in those who discontinued medications and that early relapse predicted a higher risk of later relapse (Strober et al. 1990).

Based on the evidence and current understanding, the recommendation is for an acute episode of mania or mixed affective state in an adolescent be treated with SGA with lithium/valproate/lamotrigine added for prophylaxis. The decision about prophylaxis including choice of agent is based on several factors including the type and duration of episode, the number of episodes, comorbidities, family history, response to treatment and functional impairment. At all times, the need to include the family in the discussion regarding treatment must be remembered. The efficacy of specific psychotherapeutic treatments in mania is unclear, but they may have a role in prophylaxis and enhancing the quality of life (Hazell and Jairam 2012).

4.4.4 Biomarkers of Treatment Response

Recent studies have focused on the identification of biomarkers related to the pathophysiological mechanisms underlying the development, clinical presentation, course and treatment response of bipolar disorder. The importance of clinically applicable biomarkers has been pursued and reviews have shown promising evidence for brain-derived neurotrophic factor and pro-inflammatory markers as clinically relevant biomarkers in Bipolar disorder. The adolescent population has been of particular focus in identifying biomarkers before onset of comorbid medical conditions and to enable early intervention (Goldstein and Young 2013). Sleep changes as a biomarker of bipolar disorder to predict the occurrence of an episode has also been examined (Lopes 2013). Identifying dysfunctional biochemical processes and neuronal circuits in mood disorders can help plan effective treatment strategies (Bredt et al. 2015).

Meta-analysis of amygdala volumes in children and adolescents with bipolar disorder has concluded that structural, functional and neurochemical amygdala differences may be useful as age-specific biomarkers of illness and treatment response (Pfeifer et al. 2008).

4.5 Course and Outcome

4.5.1 Depressive Disorder

Mean length of a depressive episode is around 7–9 months, with 90 % remission rates at the end of 2 years. Risk of Recurrence is about 40 % by 2 years and 70 % by 5 years. 5–10 % may have a protracted episode, lasting longer than 2 years. It is also found to be persistent into adulthood with a recurrence rate of 70 % (Lewinsohn et al. 1994; Kovacs et al. 1997; Rao and Chen 2009).

20–40 % of children and adolescents with MDD develop bipolar disorder within 5 years (Rao and Chen 2009). Predictors of bipolarity in depressed children include: rapid onset, presence of psychotic symptoms, psychomotor retardation, family history of affective disorders and drug induced hypomanic symptoms (Strober et al. 1993; Akiskal et al. 1995).

Suicide attempts and completion is one of the most significant sequelae of MDD. 60 % report having thought about suicide and 30 % attempt suicide. The risk of suicidal behaviour increases if there is a history of suicide attempts, comorbid disruptive disorders, substance abuse, impulsivity and aggression, availability of lethal agents, exposure to negative events and a family history of suicidal behaviour (AACAP 2007).

4.5.2 Pediatric Bipolar Disorder

With the introduction of DMDD, there is a need to review the literature to tease out those studies whose finding may have been 'contaminated' by the addition of those children who would now be diagnosed as DMDD. This leaves those studies that had applied the DSM criteria strictly in order to generate either a bipolar type I or type II disorder. A review of the available literature on the course and outcome of pediatric bipolar disorder revealed 12 outcome studies. Six were retrospectively designed, while six were prospective studies. In essence, with treatment, the mean index manic/mixed episode length was 10–14 weeks; 81–100 % showed episodic recovery with 50–80 % of them experiencing one or more recurrences over a 5-year period. Majority of recurrences occurred in the first 2 years following the index episode (Srinath et al. 1998; Jairam et al. 2004). The retrospective studies demonstrated that the majority of bipolar disorder (BD) in the adult population had its onset in adolescence. There is some preliminary evidence to indicate that the phenotype of BD becomes more classical as the person becomes older and additionally, that adolescent onset BD may have a poorer prognosis than adult onset BD. A number of predictors of both negative and positive outcomes were identified in prospective studies. Living with an intact biological family was positively associated with a faster time to recovery whereas the presence of previous affective episodes, comorbid ADHD, low SES and poor treatment adherence predicted a longer duration of index episode. In Strober et al.'s (1995) study those who had a mixed affective state were more likely to have relapses of their BD. Other factors associated with relapse were low maternal warmth, alcohol use, antidepressant treatment, no psychotherapeutic intervention post hospitalization and longer duration of index episode. These adolescents had high rates of hospitalization and health service utilization, high unemployment, legal problems and poor academic and psychosocial functioning (Geller et al. 2008; Jairam et al. 2008).

4.6 Conclusion

The developmental differences in the presentation of affective disorders in children and adolescents has received a greater focus over the years and the introduction of DMDD as a new diagnostic category in DSM 5 is indicative of the same. Using developmentally appropriate assessments has helped address some of the controversies centred around diagnosis of depression in the young. Research has provided insights into the course and outcome of affective disorders; however, controversies exists regarding their effective management in bringing about a more favourable outcome.

The current research is moving towards identifying reliable and clinically relevant biomarkers. This will inform clinical practice by providing a better understanding and predictability of treatment responses and thereby address some of the current unaddressed concerns related to management of affective disorders.

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