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When parents and caregivers refer their children because of increased energy levels and rapid mood changes clinicians are confronted with the task of ruling out a manic or hypomanic episode (see also Chapter E.2). The diagnosis of juvenile mania, the *sine qua non* of bipolar illness, is often complicated in children because of its rather unspecific symptoms (e.g., episodes of anger, elation and irritability, often accompanied by aggressive behavior).

Kraepelin's 100-years-old legacy, the unambiguous distinction between *dementia praecox* (schizophrenia) and manic depressive illness (bipolar disorder), has been questioned increasingly (Lichtenstein et al, 2009). Not only the distinction between schizophrenia and bipolar disorder but also the construct of bipolar disorder itself are coming under attack (Parker, 2009). Against this shifting background, considerable controversy has arisen during the last 20 years about the prevalence and characteristics of bipolar disorder in the young.

The traditional view is that bipolar disorder can occur in pre-pubertal children – but rarely – becoming increasingly prevalent during adolescence, and that symptoms in the young are largely the same as in adults. A contrasting stance asserts that bipolar disorder is not uncommon in children, even among toddlers and preschoolers, and that symptoms are quite different from those observed in adults. According to the latter view, the episodic nature of bipolar disorder is often absent in young patients; mood changes – even within the hour – are much more common than in adults and aggressiveness, irritability, sleep disturbance and increased energy are the symptoms observed more often in children with bipolar disorder that in adults with the illness (Danielyan et al, 2007). Proponents of this view also maintain that bipolar disorder is often misdiagnosed as, or co-morbid with attention deficit hyperactivity disorder (ADHD) (Biederman et al, 1998). Indeed, ADHD does show a significant symptom overlap with bipolar disorder in children and adolescents as can be seen in Figure E.3.1 (Zepf, 2009).

The pediatric bipolar disorder controversy

Clinical diagnoses of bipolar disorder have increased dramatically in children in the last 20 years, especially in the US, accompanied by an explosion in publications – more articles were published on pediatric bipolar disorder in January 2008 than in the decade from 1986 to 1996 (Leibenluft, 2008). For example, in the US between 1993 and 2003 the number of adults diagnosed with bipolar disorder doubled, but increased *40 times* in people younger than 20 years (Blader & Carlson, 2007; Moreno et al, 2007). This means that clinicians are either better able to detect the illness or that many have adopted a controversial widening of the construct – if an epidemic of bipolar disorder is excluded.

Although an uncommon diagnosis in many countries apart from the US, a growing body of research shows that some pre-pubertal children show symptoms consistent with DSM-IV criteria for bipolar disorder, demonstrate continuity with adult bipolar disorder and have poor outcomes. The controversy refers to the view that bipolar disorder may present differently in children than in adults – this type of dispute is not new; a similar process occurred in relation to depression half a century ago, and was settled by acknowledging that adult diagnostic criteria were applicable with minor modifications to children. Differences refer to the definition of episode and mood abnormality.
Figure E.3.1: Diagnostic overlap in manic episodes and ADHD

**DSM-IV symptoms of ADHD that can also be observed in a manic episode**

- Trouble keeping attention
- Not giving attention to details/makes careless mistakes
- Often easily distracted
- "On the go", acts as if "driven by a motor"
- Fidgets with hands or feet
- Gets up from seat when remaining in seat is expected
- Excessive talking
- Trouble playing or enjoying leisure activities quietly
- Runs about/climbs when it is not appropriate/restlessness.
- Interrupts or intrudes on others
- Blurt out answers
- Trouble waiting one's turn

**DSM-IV symptoms of a manic episode that can also be observed in ADHD**

- Increased talking
- Distractibility
- Heightened activity
- Reduced social inhibition

Episode

According to DSM-IV, an episode is characterized by a distinct period of mood change distinguishable from baseline, lasting at least one week for mania or four days for hypomania. These discrete episodes are separated by periods of euthymia or sub-syndromal symptoms. Several research groups have contended that this criterion fails to detect a proportion of children with bipolar disorder because such children have episodes shorter than four days or have symptoms that are chronic (i.e., non-episodic).

Mood abnormality

Some clinicians and researchers believe that the typical symptoms of a manic episode (abnormal, persistently elevated, expansive, or irritable mood and increased activity or energy) are often absent in children. An important question is whether or not children with bipolar disorder, like adults with the illness, have episodes and, if severe, non-episodic irritability is a developmental presentation of pediatric mania (while euphoria would be most characteristic of adult mania).

It could be concluded that there is a group of severely impaired children who show symptoms that overlap with bipolar disorder (and in many cases with ADHD) but who do not meet strict criteria for either diagnosis – this could potentially be a new, different disorder. The present chapter focuses on children with these emotional and behavioral problems, which are different from those typical of hypomania or mania. These children are characterized by chronic unstable mood and heightened irritability. A term frequently used to describe this phenotype has been severe mood dysregulation (SMD), largely equivalent to “disruptive mood dysregulation disorder” proposed for DSM-5.

The concept of SMD has been proposed by Leibenluft et al in 2003. Research findings providing neurobiological support for this phenotype have been published only within the last nine years. Because of this, only preliminary information can be given on epidemiological aspects and prevalence as well as evidence-based treatment strategies and pathways to care.

SEVERE MOOD DYSREGULATION (SMD)

SMD encompasses symptoms of hyper-arousal (as observed in manic episodes, but also sometimes in ADHD) accompanied by severe chronic and, above all, non-episodic irritability. Whereas some researchers argue that children and adolescents with bipolar disorder present with a rather narrow behavioral phenotype, which resembles bipolar disorder in adults, with clear episodes of depressed mood and of mania or hypomania, patients with SMD do not show well defined episodes. However, bipolar disorder in children and adolescents and SMD show comparable levels of impairment. Evidence suggests that SMD increases the risk of early adulthood depressive disorders (Brotman et al, 2006) and anxiety disorders (Stringaris et al, 2009) but not for bipolar disorder, which is less frequently observed in families of children with SMD than in families of children with bipolar disorder in both community and clinical populations (Brotman et al, 2007; Leibenluft, 2011).
Prevalence

An epidemiologic study found a lifetime prevalence of 3.3% for a retrospectively assigned proxy diagnosis of SMD in children 9 to 19 years of age (Brotman et al, 2006), and SMD was associated with depressive and anxiety symptoms in later adulthood (Brotman et al, 2006; Stringaris et al, 2009); no further research is available so far apart from studies on a psychometric profile in the Child Behavior Checklist (CBCL; Achenbach, 1991) that can characterize such mood problems (see below). Overall, these preliminary data suggest that SMD is relatively common in childhood.

Neurobiology

The work conducted so far suggests that children and adolescents with SMD and bipolar disorder differ from healthy controls and patients with anxiety or depressive disorder in facial expression recognition tasks, but patients with SMD and bipolar disorder do not differ from each other in these tasks although both groups seem to get more frustrated than controls on a rigged task (Guyer et al, 2007). Behavioral and psycho-physiological performance differ between SMD and bipolar patients, with children with SMD showing a diminished N1 event-related potential amplitude when compared to controls and children with bipolar disorder, and patients with bipolar disorder showing a decreased parietal P3 (Rich et al, 2007).

Children with ADHD show increased activation of the left amygdala, a region of the brain that is particularly important for emotion, when compared to controls and patients with SMD and bipolar disorder when rating the subjective fear of faces with neutral expressions, while participants with SMD show an underactivation (Brotman et al, 2010). In regard to altered reward and punishment processing, a feature that is relevant for a variety of neuropsychiatric conditions, preliminary research suggests that youths with SMD (and also individuals with bipolar disorder) do not differ from healthy people, in contrast to individuals with psychopathy (Rau et al, 2008).

With respect to motor inhibition, a feature that is relevant for heightened activity in patients, neural recruitment during failed motor inhibition differentiates children with SMD and bipolar disorder from each other (Deveney et al, 2012a). One study on emotional prosody labeling deficits (as indexed by the inability to identify nonverbal emotional cues) indicated that such impairments were larger in people diagnosed with SMD than in controls (Deveney et al, 2012b). It can be concluded at this stage that underlying brain mechanisms of several processes that are related to the symptomatology of SMD are different between patients with SMD, bipolar disorder and healthy people. This section will be updated regularly when more data become available.

Clinical presentation and diagnostic criteria

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is currently undergoing a major revision, with SMD being discussed as a possible new diagnostic category. The label currently proposed for the new condition is “disruptive mood dysregulation disorder”, grouped under the depressive disorders. Table E.3.1 summarizes the proposed diagnostic criteria for disruptive mood dysregulation disorder for DSM-5 as they stood at the time of writing.
Table E.3.1 Summary of diagnostic criteria for disruptive mood dysregulation disorder proposed for DSM-5.

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<table>
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<tbody>
<tr>
<td>A</td>
<td>Severe recurrent temper outbursts in response to common stressors, which are: • Manifest verbally or behaviorally, such as in the form of verbal rages, or physical aggression towards people or property. • Grossly out of proportion in intensity or duration to the situation or provocation. • Inconsistent with the child’s developmental level.</td>
</tr>
<tr>
<td>B</td>
<td>Temper outbursts occur, on average, three or more times per week.</td>
</tr>
<tr>
<td>C</td>
<td>Mood between temper outbursts is persistently negative (irritable, angry, and/or sad) nearly every day.</td>
</tr>
<tr>
<td>D</td>
<td>Criteria A-C have been present for at least 12 months and symptoms have been absent for less than 3 months at a time.</td>
</tr>
<tr>
<td>E</td>
<td>Symptoms in at least two settings (at home, at school, or with peers) and must be severe at least in one setting.</td>
</tr>
<tr>
<td>F</td>
<td>Aged 6 years or older.</td>
</tr>
<tr>
<td>G</td>
<td>Onset before 10 years of age.</td>
</tr>
<tr>
<td>H &amp; I</td>
<td>Does not meet criteria for another mental disorder (e.g., bipolar, major depression, psychosis) but it can coexist with oppositional defiant disorder, ADHD, conduct disorder or substance use disorder.</td>
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</tbody>
</table>

Diagnostic criteria for research on SMD have been used to characterize young people with this type of problem, which are summarized in Table E.3.2. It is of note that age of onset differs between the two: before 10 years of age for disruptive mood dysregulation disorder and before 12 for SMD. Moreover, a diagnosis of SMD requires symptoms of hyperarousal, whereas disruptive mood dysregulation disorder does not, with the rationale that clinicians can also assign a concurrent diagnosis of ADHD if warranted.

**Child Behavior Checklist dysregulation profile (CBCL-DP)**

An additional line of research has used the CBCL (Achenbach, 1991) to capture a phenotype showing broad overlap with the clinical presentation of SMD. A profile has been identified that captures the mixed phenotype of severe behavioral and affective dysregulation, including irritability, aggression, “affective storms”, hyperarousal and mood instability. This profile is characterized by simultaneous extreme values on the syndrome scales “anxious/depressed”, “attention problems”, and “aggressive behavior”. This profile was initially coined the CBCL-pediatric bipolar disorder phenotype because it is commonly seen in children with bipolar disorder (Biederman et al, 1995). However, the specificity of the association with bipolar disorder has recently come into question (Diler et al, 2009; Holtmann et al, 2008; Volk & Todd, 2007). Therefore, Althoff et al (2008) suggested to change the name to the “CBCL-dysregulation profile” (CBCL-DP), a proposal which is adopted in this chapter. About 1-2% of youth in epidemiological samples (Volk & Todd, 2007; Holtmann et al, 2007; Hudziak et al, 2005), 6-7% in child psychiatric clinical samples and 13-20% of children with ADHD meet criteria for this behavioral phenotype (Holtmann et al, 2008).

The CBCL-DP may be a valuable tool to identify patients with severe mood problems. High scores may indicate persisting problems and poor outcomes, such
Table E.3.2  Research diagnostic criteria for severe mood dysregulation (adapted from Leibenluft, 2011; Leibenluft et al, 2003)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>1. Age 7–17 years, with onset of the syndrome before age 12</td>
<td>Exhibits any of these cardinal manic symptoms:</td>
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<td></td>
<td>• Elevated or expansive mood</td>
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<td></td>
<td>• Grandiosity or inflated self-esteem</td>
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<td></td>
<td>• Episodically decreased need for sleep</td>
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<tr>
<td>2. Abnormal mood (specifically, anger or sadness), present at least half of the day</td>
<td>Symptoms occur in distinct periods lasting more than one day</td>
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<td>most days, and of sufficient severity to be noticeable by people in the child's</td>
<td></td>
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<td>environment (e.g., parents, teachers, peers)</td>
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<tr>
<td>3. Hyper-arousal (defined by at least three of the following: insomnia, agitation</td>
<td>Meets criteria for schizophrenia, schizoaffective disorder, pervasive developmental</td>
</tr>
<tr>
<td>, distractibility, racing thoughts or flight of ideas, pressured speech, and</td>
<td>disorder, or posttraumatic stress disorder</td>
</tr>
<tr>
<td>intrusiveness)</td>
<td></td>
</tr>
<tr>
<td>4. Compared to peers, the child exhibits markedly increased reactivity to negative</td>
<td>Meets criteria for substance abuse disorder in the past 3 months</td>
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<td>emotional stimuli that is manifest verbally or behaviorally. For example, the</td>
<td></td>
</tr>
<tr>
<td>child responds to frustration with extended temper tantrums (inappropriate for</td>
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<tr>
<td>age or precipitating event), verbal rages or aggression toward people or property.</td>
<td></td>
</tr>
<tr>
<td>Such events occur, on average, at least three times a week.</td>
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<tr>
<td>5. The symptoms in 2, 3 and 4 are currently present and have been present for</td>
<td>IQ &lt; 70</td>
</tr>
<tr>
<td>at least 12 months without any symptom-free periods exceeding 2 months.</td>
<td></td>
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<tr>
<td>6. The symptoms are severely impairing in at least one setting (home, school or</td>
<td>Symptoms are due to the direct physiological effects of a drug of abuse, or to a</td>
</tr>
<tr>
<td>with peers) and are at least mildly impairing in a second setting.</td>
<td>general medical or neurological condition</td>
</tr>
</tbody>
</table>


Comorbidity

It is essential for clinicians to be able to make a differential diagnosis between SMD and bipolar disorder. Importantly, bipolar disorder should not be diagnosed in the absence of episodes characterized by a distinct change in mood and concurrent changes in behavior and cognition (Baroni et al, 2009). Regarding the differential diagnosis of ADHD and mania, symptoms such as distractibility, agitation, etc. should only be considered to be symptoms of mania if these symptoms are clearly worse than the patient’s baseline symptomatology and occur in tandem with mood changes and other symptoms of mania (see Table E.3.1). In youths with bipolar disorder, co-morbid ADHD should be only diagnosed based on observations made while the patient is euthymic (Baroni et al, 2009).

TREATMENT

Only very few studies addressed specific treatment approaches for SMD. One study in hospitalized patients with SMD investigated the effect of lithium. Because in this study a significant proportion of participants with SMD experienced clinical improvement during an initial two-week, single-blind, placebo run-in
M was 7.5 years of age when his parents became increasingly aware and worried because of his frequent temper outbursts, which seemed to happen without a noticeable or minor trigger, such as after arguing with his older sister over which TV channel they would watch. These outbursts had increased in intensity and frequency over time, with verbal and physical aggression towards his classmates as well as objects. Between these outbursts M mostly showed a negative mood. He once mentioned to his friends and parents that he was thinking about what would happen if he was no longer alive. His peers wondered why M was always so cranky and irritable; minor provocations leading to aggressive reactions far out of proportion. The mentioned outbursts happened on average 3-4 times per week; initially, however, frequency was lower. Outbursts led to frequent fights at school, and soon teachers contacted the parents to come and discuss M’s behavioral problems. Before the current presentation M had been taken to a community health center because teachers had raised the possibility that M was suffering from ADHD. However, the diagnostic process was lengthy as M frequently refused to participate in an evaluation and only rarely showed up for clinical appointments.

A diagnosis of severe mood dysregulation disorder was made. A diagnosis of major depression as well as conduct disorder were ruled out based on self-, parent and teacher reports obtained through interviews and/or additional diagnostic questionnaires. Treatment with risperidone was initiated based upon clinical experience because of the frequent temper outbursts. In addition, M received behavioral psychotherapy with a local psychologist in order to identify potential triggers and stressors leading to temper outbursts and negative mood, and to develop strategies to cope with stressful situations that could easily impact M’s mood. Further, M and his parents had several meetings with teachers and community health workers to plan strategies for prevention and constructive management of his temper outbursts (such as time-out strategies, understanding and avoiding triggers for aggression and management/coping strategies for stressful situations), frequency and intensity of M’s outbursts gradually decreased from the initiation of treatment; he became more cooperative and willing to participate in further treatment and assessment, which lead to the diagnosis of ADHD (based on clinical observations, self-, -parent and teacher-reports as well as cognitive and neuropsychological testing). Subsequently, treatment with methylphenidate was initiated leading to a further improvement of his scholastic performance and, with only a short latency, to a further improvement of his outbursts. M currently only receives treatment with methylphenidate as treatment with risperidone was discontinued after approximately six months in which he was able to significantly reduce his temper outbursts and aggressive problems. However, treatment for ADHD symptoms needed to be continued, but his mood dysregulation problems improved significantly.

Given the high comorbidity with ADHD, there has been a focus on stimulants as a possible treatment approach (Waxmonsky et al, 2008). Significant improvements have been reported following stimulant medication, indicating a decrease of ADHD, ODD, and mood symptoms. A combination treatment including varying intensities of behavior modification therapy and stimulant medication (methylphenidate) was developed for subjects with ADHD and SMD. Results showed that methylphenidate and behavior modification therapy were effective and acceptable treatments for children presenting with both disorders. The authors, however, stated that SMD subjects were more likely to remain significantly impaired than non-SMD subjects after an intervention period of 3 weeks. In another treatment trial, Waxmonsky et al (2012) developed a novel group-based therapy. Children with ADHD and SMD were randomized to either psychosocial community treatment or group therapy for 11 weeks while maintained in an optimal dose of stimulant medication prior to randomisation. The group therapy program consisted of concurrent 90-minute sessions for parent and children. With this treatment, children showed a significant decline in levels
of suicidal ideation whereas parents showed more positive parenting behaviors.

In the absence of sound empirical evidence, medications that may improve symptoms such as irritability and depressed mood may be valuable – all used “off label”. In this line, antidepressants (e.g., SSRIs) as well as mood stabilizers (e.g., lithium, valproic acid) may be considered. Second generation antipsychotics such as risperidone, aripiprazole, olanzapine and ziprasidone, have also been suggested to be beneficial. However, prescribing practices have been under scrutiny due to the marked increase of on-label and off-label use, and concerns regarding medication safety. Antipsychotic medication may cause adverse effects such as sedation, cognitive impairment, extrapyramidal symptoms, weight gain and metabolic changes. Therefore, discussion with parents and patients as well as a careful monitoring of potential side effects by an experienced clinician are warranted when prescribing these medications.

Apart from medication, educational aspects are highly relevant. In particular, clinicians, teachers and parents need to work closely together to address and meet these patients’ special needs (e.g., classroom support, more time to complete school tests, etc.). This also refers to the adverse effects of medication; teachers should be made aware of them. Patients and families should also receive education about the disorder, co-morbid symptoms and related impairments as well as strategies for intervention and coping. Finally, changes in lifestyle can be addressed together with the help of allied health professionals. Such changes could include, for example, strategies for coping with crises and identifying potential stressors and triggers for such situations. A plan to manage emergencies (e.g., suicidal behaviour, extreme loss of control) needs to be put in place also. Moreover, parenting programs and family therapy need to be considered as many of these children come from problematic families with poor parenting and communication skills, or whose parents suffer from psychiatric disorders themselves. In that case a referral to a psychiatrist should be considered.

OUTCOME

Not surprisingly, there is limited evidence on the long term outcome of patients with SMD. One study involving a 2-year follow-up of youths with SMD showed that they had lower rates of manic, hypomanic or mixed episodes than patients with bipolar disorder (Stringaris et al, 2010). There is also evidence that patients with SMD have an increased risk for depressive and anxiety disorders in later adulthood (Brotman et al, 2006; Stringaris et al, 2009). Long term follow-up of children captured by the CBCL-DP phenotype suggest that young adults with a positive CBCL-DP in childhood are at increased risk for substance use, conduct and mood disorders, suicidal ideation and suicide attempts. In addition, they showed a marked impairment in overall functioning (Althoff et al, 2010; Holtmann et al, 2011).

CONCLUSIONS

SMD represents a potentially new diagnostic entity based on recent clinical observations and research evidence. Irrespective of whether SMD is accepted as a new disorder, it remains to be conclusively demonstrated whether children with these symptoms suffer from a new condition or from severe forms of widely known
psychiatric disorders (in particular bipolar disorder, conduct disorder, oppositional defiant disorder, ADHD) or their combination (Carlson, 2007). It would appear that many of the children diagnosed with bipolar illness, particularly in the US, might have suffered in fact from a combination of ADHD and oppositional defiant disorder or conduct disorder. Experienced clinicians know that many of these children come from very disturbed families in which abuse, neglect and separation from attachment figures is often the norm. However, this is sometimes ignored in taxonomic and research studies. This adds another layer of complexity, in particular because it becomes very difficult to establish which of the child’s behaviors are due to a “biological” disorder and which ones are the result of, or response to family dysfunction.

According to the guidelines of the British National Institute for Health and Clinical Excellence (NICE, ) as well as of the American Academy of Child and Adolescent Psychiatry (AACAP, 2007) summarized in a recent overview for clinical practitioners (Baroni et al, 2009), the diagnosis of bipolar disorder in children should only be applied if the patient presents with a history of manic or hypomanic episodes in line with relevant diagnostic criteria (e.g., as regards the duration and frequency of such episodes).

Current treatment approaches to SMD comprise psychopharmacology (although there is limited evidence available), parenting programs, family support, psychotherapy, and psychoeducation. Research is currently underway that will hopefully ascertain which interventions are effective.

REFERENCES


