CHILDHOOD DYSREGULATION:
Diagnostic Considerations and Treatment

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It is quite common to see children described as "chronically irritable," "explosive," or "dysregulated" in both inpatient and outpatient psychiatric settings. These children are often highly impaired, have difficult to characterize symptoms and multiple diagnoses, and can be especially challenging to treat. The characteristic affective instability led clinicians to conceptualize this presentation as a juvenile form of bipolar disorder.[1] In recent years, however, there have been three lines of research that have argued against classification of these children as having bipolar disorder: 1) children with chronic irritability or broad dysregulation rarely grow up to exhibit symptoms supportive of adult bipolar disorder;[2-4] 2) neurobiological differences are found between chronically irritable youth and those who meet criteria for Bipolar Disorder;[5-6] and 3) pharmacologic agents thought to be effective in bipolar disorder are less effective for symptom management in dysregulated youth.[7] Several potential solutions have been proposed to better characterize these children, including the concepts of Severe Mood Dysregulation (SMD)/Disruptive Mood Dysregulation Disorder (DMDD) and the Child Behavior Checklist–Dysregulation Profile (CBCL-DP). Here, we delineate similarities and differences among SMD, DMDD, and CBCL-DP and describe how they came to be defined. We then describe what is currently known about prevalence, longitudinal course, and treatment. Finally, we explore the relationship between DMDD and CBCL-DP with an eye towards issues of comorbidity and how diagnosis affects treatment.

PHENOMENOLOGY

The diagnosis of pediatric bipolar disorder became more prevalent following the work of Wozniak and Biederman in the mid-1990s.[8-9] As rates of juvenile bipolar disorder continued to increase,[10] Leibenluft and colleagues proposed the concept of Severe Mood Dysregulation (SMD).[11] SMD was characterized by frequent and severe episodes of emotional reactivity, a negatively valenced (i.e. irritable) mood more than half of the time in between episodes, and a component of hyperarousal. This new characterization of a familiar entity sparked a novel area of research. When the workgroup convened to design a diagnosis for the *DSM-5* that might formally capture children with emotional dysregulation, SMD was used as a starting point. The new diagnostic category that emerged was Disruptive Mood Dysregulation Disorder (DMDD). It differs from its predecessor, SMD, in two key ways in that it no longer involves hyperarousal as a criterion and the requirement for minimum age of onset was lowered from

Table 1: Differences in SMD, DMDD, and CBCL-DP

Severe Mood Dysregulation (SMD)

Profile includes:

1. Negatively valenced mood (sad or angry) at least half of the day, most days, observable by others
2. Emotional reactivity, (such as temper outbursts) at least 3 times a week
3. Hyperarousal, which includes 3 of the following: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness

Duration: Symptoms listed above must have been present for at least 12 months, without a symptom-free period of more than 2 months.

Age: Between 7 and 17 years, symptom onset before 12 years

Context: Symptoms must occur as severe in one setting and be at least mildly present in one other context.

Diagnosis: Based on a clinical interview using a symptoms checklist. A clinician decides if the child meets the criteria, taking into account duration and context of symptoms.

Disruptive Mood Dysregulation Disorder (DMDD)

DMDD is similar to SMD, but differs in the following regards:

- Hyperarousal is not a criterion.
- Duration allows for a symptom-free period of up to 3 months.
- Age range is 6-18 years with symptom onset before 10 years.
- Exclusion included for distinct periods of one or more days of elevated/expansive mood accompanied by 3 of the B criteria for mania.

Child Behavior Checklist-Dysregulation Profile (CBCL-DP)

Diagnosis is made based on empirically-based questionnaires from multiple informants using the CBCL, Youth Self Report and/or Teacher Report Forms, which are broad symptoms inventories. CBCL-DP is present when a child is reported to have symptoms of attention problems, aggressive behavior, and anxious-depression that are significantly elevated compared to population norms.

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12 to 10 years of age (see Table 1). Both SMD and DMDD represented a new diagnostic entity in the standard DSM framework – the criteria were set by experts (a "top-down" approach) and diagnosis is made categorically by raters checking off criteria (see Table 2).

Parallel to work on SMD, a more "bottom-up" approach was being investigated, using the Child Behavior Checklist (CBCL), a parent-report instrument used around the world with excellent validity.[12] The CBCL-Dysregulation Profile (CBCL-DP) is an empirically-based profile derived through statistical operations.[13,14] Children with this profile have symptom endorsement resulting in pathologic elevations on the "Anxious/Depressed," "Attention Problems," and "Aggressive Behavior" scales of the CBCL. These scales were initially chosen based on a meta-analysis of children in studies of pediatric bipolar disorder[15] but it soon became clear that children with this profile did not meet criteria for bipolar disorder.[4,16] Many children with the CBCL-DP also meet criteria for the diagnosis of DMDD, but not all. SMD and CBCL-DP have traveled a somewhat parallel research path over the years, with many similar research questions posed using each characterization, and no single study examining the diagnostic overlap or phenotypic distinctions between the two. It could be that the "top-down" DMDD and the "bottom-up" CBCL-DP are two methods of characterizing the same entity, or they may describe distinct phenotypes, similar to how dimensional measures of attention do not measure exactly the same thing as attention-deficit/hyperactivity disorder (ADHD).

Table 2: "Top-Down" Versus "Bottom-Up" Approaches

Top-Down: Expert-opinion. DMDD, like most *DSM* disorders, was designed by experts sharing clinical observations to define a disorder. Criteria were written through a process of consensus and then field trials were conducted to arrive at a classification.

Bottom-Up: Data driven. The CBCL-DP was identified statistically using broad symptom inventories administered to thousands of parents reporting on their children. The statistical operation involves finding naturally occurring symptom clusters present in a significant proportion of children. The CBCL-DP corresponds to a profile defined by clinically significant elevations on 3 subscales: attention problems; anxious-depression; and aggressive behavior. Clinical correlations to other classification systems and outcome studies were then performed.

PREVALENCE

The prevalence of dysregulation varies from about 0.8% to 5% depending on the conceptualization used (SMD, DMDD, or CBCL-DP) and the population studied. An article by Copeland et al.[17] compared the prevalence of DMDD in three studies. The Great Smoky Mountain study[18] was a population-based study of 1,420 kids, ages 9 to 16 and the lifetime prevalence of DMDD was found to be 1.1%. The Duke Preschool Study studied 3,424 children between ages 2 and 5 and found a slightly higher prevalence of 3.3% in these younger children.[19] The Caring for Children in the Community Study[20] looked at lifetime prevalence among 920 youth ages 9 to 17 and found a lower estimate: 0.8%. For the CBCL-DP, the prevalence ranges from 1%[13] to 4-5%,[21] depending on statistical method used. A variety of techniques have been used to define the threshold for the profile. Some grouping strategies such as latent curve analysis (LCA) or receiver operating characteristic (ROC) are used to determine naturally occurring clusters of subscale scores, while other methods predetermine a t-score cutpoint based 1-2 standard deviations above the mean for each of the attention problems, aggression, and anxious-depression subscales. When two standard deviation cutpoints are used, lower prevalence estimates are found, as one would expect. Studies by Biederman et al.[22] and Peyre et al.[23] suggest that while there may be minor differences in the nature of comorbidities and response to treatment, the different symptom cut-points likely represent levels of severity of the same syndrome.

CO-OCCURRING DIAGNOSES

Although DMDD criteria specifically do not allow for the concurrent diagnosis of defiant disorder (ODD), comorbidity estimates from the three DMDD data sets presented by Copeland showed highest overall levels of ODD, ranging from 57-71%. Anxiety diagnoses were common in preschoolers, but less so in the older cohorts, while the opposite was true of depression. Up to one third of the adolescents with DMDD had a depression diagnosis. Younger children also showed lower percentages of ADHD diagnoses, but this was higher in the older children. Estimates of comorbidity for the CBCL-DP typically come from studies of clinical populations, such as children who have already been diagnosed with ADHD or ODD/conduct disorder (CD). In an ADHD sample, the frequency of CBCL-DP was 36%.[22] In a more recent study by Peyre et al.,[23] CBCL-DP was frequently present (90%) in a sample of children with ODD or CD. However, none of the aforementioned studies used CBCL-DP as a starting point to examine co-occurring disorders. A preschool study of CBCL-DP demonstrated higher rates of depression and opposition.[24]

LONGITUDINAL OUTCOME

Researchers have been particularly interested in the abil-

ity of dysregulation to predict adult outcomes. Copeland and colleagues followed 1,273 children with DMDD into adulthood, and showed higher rates of anxiety, depression, worse health outcomes, and more poverty.[25] In the Great Smoky Mountain Study, children with SMD followed into adulthood had higher rates of depressive disorders.[2] Likewise, a study of children with significant irritability showed increased adult depression and anxiety.[26] Althoff and colleagues examined 2,076 Dutch children over 14 years into adulthood and demonstrated that those with CBCL-DP showed higher rates of adult drug abuse, mood disorders, anxiety disorders, and disruptive behavior disorders, but not bipolar disorder. A smaller study of 101 at-risk individuals with CBCL-DP, followed over 23 years, demonstrated similar findings with slight deviations.[27] Children of mothers with a mood disorder exhibited higher rates of later anxiety, ADHD, suicidality, and "cluster B" personality disorders (i.e., antisocial, histrionic, narcissistic, and borderline). In a similar study with a high-risk sample, Biederman and colleagues showed higher rates of bipolar disorder at follow-up,[28] while a German study of 325 at-risk subjects, followed over 19 years, reported increased risk for substance use disorders, higher suicidality, and poorer general functioning, rather than a specific set of *DSM* disorders.[29] Given these findings, it appears that DMDD, SMD, and 'irritability' are more highly linked to adult depression and anxiety, while the CBCL-DP is related to a greater spectrum of disorders and overall general impairment.

TREATMENT

Despite the diagnosis of DMDD appearing in the *DSM-5*, treatment studies targeted specifically at dysregulation are sparse. There is, however, a growing body of evidence that suggests psychosocial interventions are particularly effective for this constellation of symptoms. Evidence comes from direct trials of psychotherapy interventions,[30-31] as well as from the psychopharmacologic studies that involve behavioral treatment prior to medication intervention. For example, in a study of lithium to target symptoms of SMD, Dickstein and colleagues utilized a design including a lead-in period of two weeks on an inpatient unit.[7] When the time came to randomize the participants, 20 of the original 45 no longer met criteria for SMD. It appears that the structured environment of the inpatient unit was a strong intervention in itself. Of the 20 patients who were then able to be randomized, lithium was not found to offer extended benefit. Likewise, a study examining valproate as an adjunct to stimulant therapy with ADHD plus aggression (a pool of subjects who would likely have a high percentage of DMDD/CBCL-DP) noted a high rate of aggression remission in the group receiving family therapy as well as a stimulant (31 of 70). Of the 27 that were eventually randomized, valproate was found to further ameliorate aggression.[32]

Within the limited number of strictly pharmacologic studies, methylphenidate was found to be well tolerated in SMD and equally effective in decreasing externalizing symptoms in both the ADHD + SMD and ADHD-only groups, although the children with SMD remained more impaired, with higher rates of manic behavior and oppositionality.[33] Another recent study examining treatment of ADHD in children with and without CBCL-DP replicated the finding that ADHD symptoms were similarly treated by methylphenidate regardless of dysregulation status. There was no decreased response by the dysregulated children, nor were there increased numbers of side effects.[23] In 2011, an open label trial of risperidone for irritability symptoms in 21 children with SMD yielded a positive result of diminished irritability following eight weeks of medication.[34] A very small trial of micronutrients was piloted in adults with ADHD plus SMD with findings that point to neurocognitive benefits; however, the number was small, and the design lacked a control group.[35]

For psychotherapy, there has been one trial of individual CBT for children with OCD plus CBCL-DP showing that both OCD symptoms and dysregulation decreased following CBT. Similar to the findings with stimulants and ADHD, the improvement of OCD symptoms with CBT was the same among those with and without CBCL-DP. CBCL-DP status did, however, predict a higher attrition rate.[36] The majority of therapy research, notably, has emphasized family-based interventions. In a trial of Parent Management Training (PMT) for children with oppositionality, Scott and O'Connor showed higher susceptibility for improvements among children with co-occurring emotional dysregulation than those without.[31] Another study involved CBT groups for children with SMD and PMT groups for their parents run in parallel.[30] After nine weeks, this study demonstrated significant improvements in depressive symptoms, mood lability and global functioning in children. The success of family-based interventions makes sense on several levels given that there is evidence that parents of children with CBCL-DP are more punitive and controlling in their parenting style.[24,37] Further, there is evidence that the CBCL-DP is heritable, implying that many households contain dysregulation across generations.[13,21] Thus, directing intervention at the level of the family seems appropriate.

Summary

It is still too early to place too much significance on the differences and similarities between the CBCL-DP and

DMDD. The population prevalence range is fairly similar, depending on the source of the estimate, hovering around 3% of the general population, placing dysregulation as a more prevalent condition than, for instance, pediatric bipolar disorder.[38] The longitudinal outcomes between children presenting with CBCL-DP and DMDD seem relatively similar with DMDD perhaps leading more specifically to adult depressive disorders and the CBCL-DP being associated with a broader range of adult pathology. Regardless, both of these conceptualizations appear related to broad and significant global impairment that needs treatment. Unfortunately, the treatment research is limited for both DMDD and CBCL-DP and too scarce to make meaningful comparisons. The clearest theme thus far appears to be that psychosocial interventions involving the entire family may be more effective than medication for the core aspects of dysregulation. Furthermore, treatment of co-occurring symptoms such as attention problems, OCD, or depressive symptoms does not appear to differ in the context of dysregulation. There are two trials currently underway focused on sequential use of stimulant and SSRI, which may result in new clinical guidance.

For now, what can we do when we see these kids in the clinic? It is always helpful to employ empirically-based questionnaires that involve multiple informants, such as the CBCL, to identify symptoms that can be treated. Stimulants for attention problems may be useful and are unlikely to exacerbate dysregulation systematically. Based on the side effect profiles of atypical antipsychotics and the lack of evidence of efficacy, these agents should always be used as a last resort. Parent management training appears to have a role as does involving family in cognitive behavioral therapy. Keeping in mind that dysregulation runs in families and has been shown to be related to a broad range of adult pathology, it is always important to identify and recommend treatment for family members if needed. It appears that the family environment, while important for all children, is especially important for children with dysregulation. Finally, the results of large trials are around the corner, and we can best serve our patients by keeping a close eye on the literature.

Take Home Summary

Dysregulation can be conceptualized from a "top-down" (SMD or DMDD) or "bottom-up" approach (CBCL-DP). There appears to be significant overlap in the phenotypes described by the varying diagnoses in terms of prevalence, longitudinal outcome, and treatment. While treatment research is sparse, psychosocial interventions involving the family appear to be most effective.

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