Practitioner Review: Definition, recognition, and treatment challenges of irritability in young people

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Background: Irritability is one of the most common reasons for referral to child and adolescent mental health services and is the main characteristic of the new diagnosis of disruptive mood dysregulation disorder (DMDD). However, the recognition and management of irritability presents a major challenge in clinical practice and may be partly responsible for the dramatic increase in antipsychotic prescribing in recent years. Methods: In this review, we provide up-to-date information on the definition and mechanisms underlying irritability, and its assessment in clinical practice. We aim to discuss the latest research on DMDD, and the presence of severe irritability in the context of other disorders, as well as to recommend a treatment algorithm. Results: Severe irritability is associated with aberrant reward processing and bias toward threatening stimuli. Several measures are available to easily assess irritability. The recent diagnosis of DMDD captures children whose main problem is severe irritability and differ from those with bipolar disorder in longitudinal outcomes, family history, and behavioral and neural correlates. Treatment of irritability might depend on the context it appears. Indirect evidence suggests that parent management training (PMT) and cognitive behavioral therapy (CBT) are the most supported psychological treatments for irritability. Conclusions: Irritability, recognized as a mood problem rather than a purely behavioral manifestation, is a common condition for young people. Practitioners should not ignore irritability as it is associated with substantial morbidity and impairment. Although there are no trials with irritability as main outcome, clinicians can apply several existing pharmacological and psychological interventions for its treatment. Also, new promising approaches relying on pathophysiological findings, such as exposure-based cognitive behavioral therapy techniques and interpretation bias training (IBT), are being currently investigated. Keywords: Emotional dysregulation; temper tantrums; mood disorder; assessment; intervention.

Introduction

Irritability is a very common reason for referral to child and adolescent mental health services (Mikita & Stringaris, 2013; Peterson, Zhang, Santa Lucia, King, & Lewis, 1996). It is linked strongly to psychiatric morbidity both cross-sectionally and longitudinally (Brotman et al., 2006; Copeland, Angold, Costello, & Egger, 2013; Stringaris & Goodman, 2009a, 2009c; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016). It is also associated with long-term adverse outcomes, including educational and financial underachievement (Stringaris, Cohen, Pine, & Leibenluft, 2009; Stringaris & Taylor, 2015). Several lines of evidence suggest that irritability presents a management challenge to clinicians and that this may underlie the widespread use of antipsychotic medication in children for illnesses for which it has little or no evidence base (Correll & Blader, 2015). This underscores the public health relevance of research in irritability and related behaviors. In the last decade, there has been a marked increase in irritability research, most notably neuroscience and treatment-related investigations, with a recent meta-analysis (Vidal-Ribas et al., 2016) and the proposal of a translational model (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017). Moreover, disruptive mood dysregulation disorder (DMDD), a categorical construct meant to capture severe irritability, has been introduced in DSM-5. Yet, there have been few attempts to synthesize information about irritability for clinicians.

The aim of this article is to survey the literature, extract information relevant to clinical practice, and identify areas in need of further clinical research. We begin with trying to resolve some terminological confusion, and then discuss briefly the possible mechanisms underlying irritability. We then discuss the measurement of irritability; concerns and controversies surrounding DMDD; and the presence of severe irritability in other disorders. We conclude with recommending a treatment algorithm.

Irritability: Definition and terminology

Irritability can be defined as an increased proneness to anger relative to peers at the same developmental level (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017). In Table 1, we briefly define a set of key
terms that are either used interchangeably with irritability or are mentioned in clinical practice and research. The table defines three broad groups: terms that refer primarily to the characteristic emotion, such as anger; terms that denote a temporal profile, such as chronic; and terms that imply pathophysiological mechanisms, such as dysregulation or instability.

As with many terms in psychiatry, and science more generally, all definitions have a degree of imprecision. In keeping with Karl Popper, the philosopher of science, we see the role of a definition as ‘cutting a long story short’ rather than as condensing all knowledge on the subject (Popper, 1935). As in all other areas of science, the defining terms are in themselves hard to define – neither ‘irritability’ nor ‘anger’ are semantically unequivocal.

We choose to use irritability for a number of reasons. First, it is the term widely used in the literature to describe the range of phenomena we report on here. Second, it is enshrined in the DSM-5 in three ways: as a dimensional construct, as a subgroup of oppositional defiant disorder (ODD) and, in its extreme form, as the main characteristic of DMDD. Third, there is a historical background to the use of the term, going back to at least Bleuler (1918). Fourth, we cannot find a better term to summarize things; using DMDD would have the downside of referring only to the extremes of a common phenomenon. Moreover, DMDD is a relatively new and little-tested term. It is for those reasons that we prefer to use the term irritability. In addition, irritability (as opposed to, say, anger or rage) is broad enough to include nonpathological phenomena, such as temperamental variability. This is an advantage given the increasing recognition that common psychiatric symptoms are on a continuum (Plomin, Haworth, & Davis, 2009). Finally, the definition of pathological irritability has been operationalized and defined in several recent reviews (Brotman et al., 2017; Leibenluft, 2011, 2017). The conceptualization of irritability in the present manuscript is consistent with these definitions in the literature.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Terminology associated with irritability in clinical practice and research</th>
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<tbody>
<tr>
<td><strong>Emotion</strong></td>
<td><strong>Irritability</strong></td>
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<tr>
<td>Increased proneness to anger compared with peers at same development level, and defining mood of DMDD (see below). As a symptom it is present in the criteria of several psychiatric disorders, including generalized anxiety disorder (GAD), depression, and post-traumatic stress disorder (PTSD)</td>
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<tr>
<td><strong>Anger</strong></td>
<td>The emotion that characterizes irritability. It is often a feeling, i.e. consciously processed. It has received considerable research in psychology (Blair, 2012), but is not classified separately in the DSM</td>
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<tr>
<td><strong>Rage</strong></td>
<td>Typically denotes intense anger often with a propensity to aggression. Not classified in its own right in the DSM, though used in the literature (Carlson &amp; Dyson, 2012) to refer to the behavior of severely irritable children</td>
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<tr>
<td><strong>Frustration</strong></td>
<td>The emotional state induced by blocked goal attainment, analogous to frustrative nonreward which elicits increased aggression and activity in animals (Amsel, 1958; Brotman et al., 2017). Often used synonymously to irritability and anger in clinical practice</td>
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<tr>
<td><strong>Time</strong></td>
<td><strong>Chronic irritability</strong></td>
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<tr>
<td>Irritability that, while severe compared to others, constitutes no change from a child’s baseline. Operationalized in DSM-5 DMDD as the presence of clinically significant irritability for at least 12 months</td>
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<tr>
<td><strong>Episodic irritability</strong></td>
<td>In contrast to chronic irritability, episodic irritability constitutes a change to an individual’s baseline. A cardinal mood for bipolar disorder (BD) and, for children and adolescents only, also for major depressive disorder (MDD)</td>
</tr>
<tr>
<td><strong>Tonic irritability</strong></td>
<td>The persistent irritable mood in between temper outbursts as per DMDD criteria, typically operationalized as persistently angry, grumpy, or grouchy mood; it has received little attention so far</td>
</tr>
<tr>
<td><strong>Phasic irritability</strong></td>
<td>The temper outbursts that occur on top of persistent irritability, according to DMDD criteria, operationalized as behavioral outbursts of intense anger</td>
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<tr>
<td><strong>Mechanism</strong></td>
<td><strong>Emotion/mood dysregulation</strong></td>
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<td>A supradordinate term which can include irritability but also any other dysregulated emotion, e.g. elation, anxiety, and depression. In clinical usage, there is typically no distinction made between the epithets emotion (typically short-lived and elicited by specific event) and mood (an enduring and typically precipitated state)</td>
<td></td>
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<tr>
<td><strong>CBCL dysregulation profile</strong></td>
<td>Another supradordinate category defined as two or more standard deviations away from the mean on the Child Behavior Checklist (CBCL) subscales of anxiety/depression, aggression, attention subscales. It may capture irritability, but appears to be a robust and more general index of poor outcomes including suicidality</td>
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<tr>
<td><strong>Severe mood dysregulation disorder</strong></td>
<td>A category created specifically to test the (by now falsified) notion that chronic irritability may be an early-development form of BD. Severe mood dysregulation (SMD) is characterized by severe tantrums occurring on top of chronically negative mood (Table 2)</td>
</tr>
<tr>
<td><strong>Disruptive mood dysregulation disorder</strong></td>
<td>DSM-5’s categorical diagnosis for severe irritability classified under the depression section to emphasize the close links with MDD. Developed out of SMD, it is narrower by excluding symptoms of hyperarousal (Table 2)</td>
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Mechanisms underlying irritability and their clinical relevance

Figure 1 summarizes key putative mechanisms involved in youth irritability, both at the level of the child, but also that of the family. It represents an attempt to condense the knowledge that we have gained from neuroscience (Brotman et al., 2017) and from longitudinal (Vidal-Ribas et al., 2016) and treatment research (Patterson, 1975).

From a neuroscientific perspective, irritability can be defined as aberrant responding to frustrating nonreward and threat (for an in-depth review, see Brotman et al., 2017). Both types of response are preserved across several species and rely on effective instrumental learning; that is, learning when to anticipate rewards and punishments and how to adapt one’s behavior to obtain such rewards or avoid such punishments. The concept of frustrating nonreward refers to the normative emotional state associated with increased activity and aggression when attainment of a goal is blocked. Mounting evidence suggest that irritable youth have aberrant responses to frustrating nonreward. The brain correlate of such deficits include decreased striatal activity during tasks when rewards are omitted (Deveney et al., 2013) and decreased activation of frontal regions (Perlman et al., 2015) in irritable youth compared with controls. Threats, however, are situations or objects that signal harm and which an organism works to avoid or to fight against (Fanselow, 1994; LeDoux & Pine, 2016; Rolls, 2014). Threats that are imminent and inescapable are more likely to lead to angry fight reactions (Blair, 2012; Panksepp, 1990). Severe irritability has been associated with increased orientation toward threatening stimuli. For example, there is evidence that irritable children are more likely to direct attention to angry faces than are healthy volunteers (Hommer et al., 2014; Salum et al., 2016). Moreover, compared with healthy children, irritable children tend to interpret ambiguous or neutral facial stimuli as threatening (Brotman et al., 2010; Stoddard et al., 2016). Difficulties in modulating amygdala responses may underlie some of these aberrations in threat processing (Thomas et al., 2012).

The increased anger that arises from exaggerated responses to frustrating nonreward and aberrant threat processing will have downstream effects in the form of transactional problems within the family. A child’s anger when frustrated is often met by parental negative affect, often also in the form of anger or aggression, leading to a self-reinforcing pattern of what Patterson termed mutually coercive relationships (Patterson, 1982). Often, a parent will eventually acquiesce to a child’s request if the child has a temper outburst – an indication of inconsistent parenting – and thus reinforce angry behavior. Aberrant parent–child interaction cycles have been extensively described in relation to the etiology and maintenance of ODD (Barkley, 2013a); it seems plausible that similar mechanisms operate for irritability too. However, this should be further tested. These interpersonal patterns are rooted in social learning and are targeted by parenting interventions that we discuss below.

Measurement

Measurement assumptions

An implicit assumption underlying the assessment of irritability is that it is a unitary construct. This assumption is supported by current evidence showing the unidimensional structure and high internal consistency (Cronbach’s $\alpha = .90$) of instruments specifically measuring irritability (Stringaris, 2016).
Goodman et al., 2012). The unidimensional structure and good reliability of assessment of irritability have been found in youth with high-functioning autism (Mikita et al., 2015), youth with SMD/DMDD, youth with bipolar disorder (BD), youth at-risk of BD, and healthy volunteers (Meffert, Vidal-Ribas, Leibenluft, Brotman, & Stringaris, 2017). This suggests that irritability is a transdiagnostic feature that can be reliably measured regardless of its psychopathological context.

However, it is still unclear whether the irritability observed in, for example, attention-deficit/hyperactivity disorder (ADHD) is explained exactly by the same mechanisms than the irritability observed in, for example, autism spectrum disorder (ASD). It is possible that other mechanisms (e.g. attentional processes in ADHD or social cognition in ASD) interact with common mechanisms mentioned earlier (i.e. responses to frustrative nonreward and threat) to give place to the expression of irritability. Indeed, recent studies suggest differences in the pathophysiology of irritability in the context of BD (Wiggins et al., 2016) or anxiety symptoms (Stoddard et al., 2017). This is important and needs to be tested across several disorders, especially because it may have implications for treatment development. For example, the identification of common mechanisms is helping us to develop transdiagnostic interventions focusing in such core dysfunctions; yet, the identification of distinct mechanisms across disorders might facilitate the tailoring of such interventions for each case (Marchette & Weisz, 2017).

Some early findings also suggest differences in the etiological underpinnings of irritability between childhood and adolescence (Riglin et al., 2017), which we discuss in more depth in the next section.

Reporting source and reporting age

As with other psychological constructs, information on irritability will vary by informant. The agreement between parent and child ratings of irritability on a questionnaire is about 0.4 (Aebi, Plattner, Metzke, Bessler, & Steinhausen, 2013; Roberson-Nay et al., 2015; Stoddard et al., 2014; Stringaris, Goodman et al., 2012), which is in the upper range of correlation coefficients reported in meta-analyses of other scales (Achenbach, McConaughy, & Howell, 1987). There are no published data on the agreement of teacher reports with other informants. Data from a UK community sample (Stringaris & Goodman, 2009b) suggest that self-reported irritability is more strongly associated with other emotional problems, while parent-reported irritability is more tightly linked with externalizing problems. As in other psychiatric disorders, young people themselves may have access to feelings that are not obvious to parents who can only see resultant behaviors.

Since reporting on symptoms by very young children tends to be unreliable, parent- or teacher-rated irritability will be the only source for that age group. Similarly, children with intellectual disability or severe autism will have difficulties reporting on their own irritability; however, findings so far suggest that boys with high-functioning ASD do not report on their own irritability differently to typically developing boys of the same age (Mikita et al., 2015). Some findings (Riglin et al., 2017) suggest that early-life irritability is associated with ADHD in prepubertal boys. The extent to which this may be confounded by reporting source remains to be established, as prepubertal reports mostly come from parents, whereas most reports after puberty come from adolescents themselves.

Another point to consider related to reporting age is the conscious experience of irritability and how that changes across development. Unfortunately, there are sparse data on this topic; future studies should examine how this experience might impact reports on irritability.

Measuring the severity of irritability

The severity of irritability is determined by the intensity of angry responses, their frequency, the duration of irritable mood, and the context and its consequences, including resulting impairment. It is worth assessing youth both for temper outbursts and for chronic negative mood that may persist between temper tantrums. This distinction, highlighted in Table 1, is reflected in the DMDD diagnostic criteria.

In general, behavioral expressions of anger will be seen more commonly early in development during the preschool period and then decline with a slight increase in adolescence (Leibenluft & Stoddard, 2013). This will have implications when setting the threshold for normality, since severe irritability is defined as relative to peers. In the study by Wakschlag et al. (2012), tantrums occurred in over 80% of preschoolers over the preceding month and close to 9% had daily tantrums. One major finding was that temper outbursts appear to be on a continuum. Temper outbursts in disruptive children tend to be very intense (loud and with forceful movements), easily elicited, progressively reaching a crescendo. They also tend to occur in more than one situation and to be persistent, with slow recovery (Wakschlag et al., 2012). In later childhood and adolescence, temper outbursts are still common in the general population but diminish with age (Copeland, Brotman, & Costello, 2015; Wiggins, Mitchell, Stringaris, & Leibenluft, 2014). Normative outbursts in later childhood and adolescence tend to be relatively short-lived, generally lasting between 5 and 7 min and occurring at an average frequency of no more than once a week. Importantly, an increased number of tantrums is associated with an increased risk for...
future psychosocial impairment, with those scoring in the 90th percentile being at the highest risk for future impairment (Copeland et al., 2015).

There is little research on the characteristics of the irritable mood that can be present between tantrums. Results in the general population suggest that irritable mood, while less common than tantrums, rarely occurs in their absence (Copeland et al., 2015).

There is even less research on how contextual factors may influence irritability. It is well known from the literature on oppositional defiant disorder (ODD) that it is common for children to express symptoms such as anger in only one setting – for example, the home as opposed to the school (Gadow & Drabick, 2012).

The most dramatic consequence of irritability is aggression. This, however, is neither a certain nor unavoidable outcome of irritability. Data suggest that aggression occurs in a minority of those with irritability; only 12% of general population subjects who report temper outbursts also report aggressive behavior (Vidal-Ribas et al., unpublished observation). The expression of irritability can also have other consequences in the environment that might help to maintain it. For example, in Figure 1, we provide an illustration of how parent-child transactions may influence the intensity and maintenance of irritability. It is, therefore, part of a good clinical assessment to tease apart what leads to temper outbursts and what may alleviate them, not least because this will be useful therapeutically (see below under psychological interventions). To this end, a functional analysis of antecedents and consequences may be very helpful.

Family accommodation, for example, the modification of parental behaviors to reduce the negative consequences of symptoms in the young person, is typically seen in anxiety disorders. Similarly, parents of an irritable child frequently report ‘walking on eggshells’ and reducing any demands (such as having to go to school) on the child in order to reduce the probability of a temper tantrum. Recent data on anxious children show moderate associations between family accommodation and irritability, with correlations ranging 0.3–0.4 (Monzani et al., Unpublished observation).

**Instruments for assessing irritability**

**Questionnaires.** Recently, several instruments have been developed to assess irritability. The Affective Reactivity Index (ARI) is a concise scale (six items) which allows for self, parent, and teacher report on a young person’s irritability. It has good reliability and validity for both parent- and self-reported scales (Stringaris, Goodman et al., 2012). It is short by design to enable busy clinicians to capture changes in irritability and for use in large studies, in which participants are often asked hundreds of questions about other problems. A comprehensive alternative is the Multidimensional Assessment of Preschool Disruptive Behavior (MAP-DB) Questionnaire, which is a valid instrument to assess irritability features in preschool children (Wakschlag et al., 2010). The MAP-DB Temper Loss subscale contains 20 items that assess features of tantrums and anger regulation with excellent reliability and covering a broad range of behaviors.

More specific consequences of irritability, such as aggressive behaviors, can be assessed with the Retrospective-Modified Overt Aggression Scale (R-MOAS), an adaptation of the Modified Overt Aggression Scale (MOAS). This is a parent-rated instrument that covers the frequency of 16 aggressive behaviors during the preceding week grouped in four areas: verbal aggression; physical toward others; physical toward oneself; and toward property. It has a good internal consistency (Cronbach’s α = .82) and has been employed in several trials (Blader, Schooler, Jensen, Fliszka, & Kafantaris, 2009; Donovan et al., 2000).

**Semi-structured interviews.** The most widely used clinical interview is a version of the DMDD K-SADS developed by Leibenluft and colleagues at NIMH. It follows the typical format used for the assessment of DSM disorders, for example, depression or generalized anxiety disorder. After the publication of DSM-5, the K-SADS DMDD module was shortened, making it easier to use in clinical practice.

**Structured interviews.** The DMDD module of the Development and Wellbeing Assessment (DAWBA) is a structured interview for the ascertainment of DMDD that assesses the full range of symptoms and impairment. It is set up for convenient online completion and provides space for open-ended comments by the respondent.

**Change measures.** The Clinical Global Impression (CGI) scale for irritability is a clinician-rated instrument to assess the severity of irritability. It works analogously to the CGI for depression or BD. It is the primary outcome measure in drug and psychological treatment trials of irritability that are currently underway (ClinicalTrials.gov identifiers NCT00794040, NCT01714310, NCT02531893). The Clinician ARI is another clinician-rated instrument that focuses on a number of irritability domains that include aggression. It is one of the first clinician-rated instruments to assess specific behaviors in depth, requesting examples and also enquiring about the context in which these problems occur.

**Other measurement approaches**

**Content.** Clinical experience suggests that recurrent and intrusive angry thoughts are important in the maintenance of angry feelings. It seems plausible
that angry ruminations may underlie the maintenance of negative mood, in that negative thoughts rekindle feelings and imagery related to angry events. Measuring angry rumination in irritable youth has not yet been done and may prove particularly useful.

Technology. Ecological mood monitoring has been used with relative success in other domains of psychopathology (Trull & Ebner-Priemer, 2009) and a project is under way to examine daily fluctuations in irritability using mobile-phone-based sampling in adolescents. This may elucidate the extent to which tantrums and persistent mood are independent events, or whether mood between episodes is simply a concatenation of less severe outbursts. Preliminary data suggest that the method works well and may concur with observer reported mood states (Forbes et al., 2009). Another promising way of measuring affect is through automated facial emotion recognition. Applying machine learning algorithms to classify facial expressions into valences and specific emotions is increasingly used in advertising and by the gaming industry to assess products.

Disruptive mood dysregulation disorder
Disruptive mood dysregulation disorder is a new category in the DSM-5 classified under the section of depressive disorders. DMDD is characterized by persistent irritable mood and severe (i.e. out of proportion in intensity or duration) and frequent (i.e. three or more times per week) temper outbursts. These features should have been present for at least 1 year and begun before age 10, although the diagnosis should not be made before age 6 or after age 18. The irritability must be severely impairing in at least one setting (home, school, peers) and at least be present in a second setting. Much of our knowledge about severe irritability as a category comes from research on the precursor to DMDD, that is, severe mood dysregulation (SMD). The two are compared in Table 2.

DMDD and the BD controversy
An important motivation for the American Psychiatric Association (APA) to generate a pediatric diagnosis centered on severe, chronic irritability was the so-called pediatric bipolar debate (Leibenluft, 2011). In the recent past, the rates of BD diagnoses in US youth have risen sharply in both inpatient units (Blader & Carlson, 2007) and outpatient services (Moreno et al., 2007). Changes in how BD was diagnosed seem to be the most plausible explanation for this increase (Leibenluft, 2011; Mikita & Stringaris, 2013), and irritability appears to have been central to this matter. The idea that mania may present differently in early-life prompted researchers to suggest that, whereas mania in adults presents in an episodic form, pediatric BD is instead characterized by chronic, nonepisodic irritability (Wozniak et al., 1995). Of note, the DSM-IV (and DSM-5) criteria for mania require a ‘distinct period of abnormally and persistently elevated, expansive or irritable mood’ which we discuss below. It seems likely that ignoring this requirement for an episodic mood change has led to many children with chronic irritability being misdiagnosed with BD. The APA attempted to tackle the dramatic increase of bipolar diagnoses in youth by introducing DMDD. It should be emphasized here that this increase may be related to the concomitant increase in the use of antipsychotic medication to treat illnesses for which there is little or no evidence base of antipsychotic treatment –

Table 2 From severe mood dysregulation (SMD) to disruptive mood dysregulation disorder (DMDD)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>1. Compared with his/her peers, the child exhibits markedly increased reactivity to negative emotional stimuli that is manifested verbally or behaviorally. For example, the child responds to frustration with extended temper tantrums (inappropriate for age and/or precipitating event), verbal rages, and/or aggression toward people or property. Such events occur, on average, at least three times a week.</td>
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<tr>
<td>2. Abnormal mood (specifically anger or sadness), present at least half of the day most days, and of sufficient severity to be noticeable by people in the child’s environment (e.g. parents, teachers, and peers).</td>
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<td>3. Hyperarousal, as defined by at least three of the following symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, and intrusiveness.</td>
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<td>4. The symptoms in 1, 2, and 3 are currently present and have been present for at least 12 months without any symptom-free periods exceeding 2 months.</td>
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<td>5. Aged 7–17, with the onset of symptoms before age 12d</td>
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<tr>
<td>6. The symptoms are severe in at least one setting (i.e. violent outbursts, assaultive behavior at home, school, or with peers). In addition, there are at least mild symptoms (distractibility, intrusiveness) in a second setting.</td>
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<tr>
<td>1. Exhibits any of these cardinal manic symptoms:</td>
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<td>• Elevated or expansive mood.</td>
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<td>• Grandiosity or inflated self-esteem.</td>
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<td>• Episodically decreased need for sleep.</td>
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<td>2. The symptoms occur in distinct periods lasting more than 1 day.</td>
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<td>3. Meets criteria for schizophrenia, schizoaffective disorder, pervasive development disorder, or posttraumatic stress disorder.</td>
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<td>4. Meets criteria for substance abuse disorder in the past 3 months.</td>
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<td>5. IQ–70.</td>
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<td>6. The symptoms are due to the direct physiological effects of a drug of abuse, or to a general medical or neurological condition.</td>
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Changes from SMD to DMDD: “Replaced with Irritable mood; aLeft out; bReplaced with 3 months; cReplaced with age 6–17, with the onset of symptoms before age 10; “Replaced with Symptoms must be present in at least two of three settings.”
a recent survey from prescriptions in a US state showed that over 10,000 children of 6 years of age or less (over 4% of all children of that age enrolled in Medicaid) received a prescription for antipsychotic medication and that 75% of those prescriptions were for a diagnosis of BD (Lohr, Chowning, Stevenson, & Williams, 2015). This underscores the profound public health implications of research differentiating chronic irritability from pediatric BD.

Indeed, there is now compelling evidence against the notion that severe irritability is an early-life form of bipolar disorder. First, follow-up studies in community samples do not show a link between dimensional measures of irritability and later BD (Brotman et al., 2006; Leibenluft, Cohen, Gorrindo, Brook, & Pine, 2006; Stringaris et al., 2009). A clinical follow-up study (median time 28.7 months) demonstrated a stark difference in the rate of manic symptoms between youth with SMD and those with classical bipolar disorder (i.e. distinct manic episodes). Only one of 84 SMD subjects (1.2%) experienced a (hypo-) manic episode, whereas the frequency of manic episodes was over 50 times higher in those with classically defined BD (58/93, 62.4%; Stringaris et al., 2010). Findings were similar in other studies (Axelson et al., 2012; Deveney et al., 2015). Second, SMD and BD were found to differ in family history (Axelson et al., 2012; Brotman et al., 2007). Parents of youth with narrowly defined BD were significantly more likely to have BD (14/42, 33.3%) than parents of youth with SMD (1/37, 2.7%; Brotman et al., 2006). Indeed, a recent study found higher rates of DMDD symptoms in offspring of parents with depression than offspring of parents with BD, and DMDD diagnoses were only present in the former (Propper et al., 2017). Third, behavioral and functional MRI studies have found that while both youths with BD and those with SMD have impairments in labeling facial emotions (Guyer et al., 2007; Rich et al., 2008), the neural correlates of this deficit differ between the two groups (Brotman et al., 2010; Thomas et al., 2012; Wiggins et al., 2016). A similar pattern was found in their response to frustration; that is, although both SMD and BD youth displayed significantly more negative affect than healthy controls in response to negative feedback, patients with SMD differed from those with BD in their event-related potentials (Rich et al., 2007) and brain activation patterns (Rich et al., 2011). In addition, recent evidence suggests that the pathophysiological correlates of trait irritability itself differ between BD and DMDD (Wiggins et al., 2016). Thus, not only pathophysiological mechanisms may differ between DMDD and BD but also the brain mechanisms mediating irritability across diagnoses.

DMDD and oppositional problems

The other reason for the APA to create DMDD was to accommodate diagnostically youth with severe irritability as their main presentation. The irritability of these severely impaired youth was not codable under DSM-IV unless subsumed under oppositional defiant disorder (ODD).

Several researchers and clinicians have argued that it is hard to differentiate DMDD from ODD and that adding an irritability specifier for ODD in the new DSM-5 would have been preferable to the new diagnosis of DMDD (Runions et al., 2016). These views were supported by the high overlap seen between DMDD and ODD (Axelson et al., 2012; Freeman, Youngstrom, Youngstrom, & Findling, 2016; Mayes, Waxmonsky, Calhoun, & Bixler, 2016), and also due to the ample empirical evidence demonstrating that symptoms of ODD can be broken down into three dimensions: irritable, headstrong, and hurtful (Burke et al., 2014; Krieger et al., 2013; Stringaris & Goodman, 2009a, 2009c; Vidal-Ribas et al., 2016). This distinction among ODD has indeed been taken up by DSM-5, which groups ODD symptoms in three categories, namely Angry/Irritable mood, Argumentative/Defiant Behavior, and Vindictiveness.

However, evidence shows that youth with DMDD are extreme cases of the most irritable ODD youth (APA, 2013), resulting in more functional impairment and the need for substantially more services (Conner, Meldrum, Wieczorek, Duberstein, & Welte, 2004; Nock, Kazdin, Hiripi, & Kessler, 2007; Peterson et al., 1996; Pickles et al., 2010; Stringaris et al., 2009). Moreover, diagnostic specifiers are often not used by clinicians. Thus, there was concern that simply adding a specifier would not adequately address the pressing public health need. Also, whereas most youth with DMDD will meet criteria for ODD, the opposite is not the case, since DMDD is much rarer. Importantly, the dimensionality of ODD suggests that it is a heterogeneous construct that encompasses behaviors ranging from temper outbursts to vindictiveness. This may be advantageous for a broad-sweep clinical category, but it may be lumping together important etiological distinctions. Indeed, evidence suggests that oppositionality and irritability, which are both components of ODD, have differential longitudinal and genetic associations (Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012). In that sense, having an irritability-specific category may be advantageous in terms of external validity, and possibly, treatment specificity. Finally, given the significant mood component of DMDD and the longitudinal, genetic, and cross-sectional associations among irritability, anxiety, and depression (Vidal-Ribas et al., 2016), DMDD is appropriately placed in the mood disorders section, whereas ODD is in the disruptive behavior disorders section of DSM-5.

Concerns about DMDD

One of the main concerns about the introduction of DMDD has been pathologizing normal childhood behaviors, such as tantrums (Althoff et al., 2016;
Axelson et al., 2012; Freeman et al., 2016; Mayes et al., 2015; Stringaris, 2011). However, the prevalence of DMDD in epidemiological studies suggests that this was an exaggerated concern; DMDD is relatively rare with a prevalence around 1% and it appears to capture children with severe impairment, rather than the typically developing majority (Copeland et al., 2013). Actually, DMDD prevalence is low (3.3%) even in youth at risk for mood disorders (Propper et al., 2017).

The interrater reliability of DMDD was low in the DSM-5 field trials ($k = 0.25$). Similarly, the temporal stability of the diagnosis of DMDD is low, in that only a small fraction of children with DMDD meet full criteria across time. This is in contrast to the moderate stability of the dimensional measure of irritability, with correlations ranging between 0.29 and 0.88 (Leadbeater & Homel, 2015; Roberson-Nay et al., 2015; Stringaris, 2011; Stringaris, Goodman et al., 2012; Whelan, Stringaris, Maughan, & Barker, 2013). The reasons for the low reliability of the diagnosis are unclear, but are likely to be related to the arbitrarily chosen threshold. Indeed, most of the cases with DMDD who do not meet criteria at follow-up have significant ongoing subthreshold irritability and severe impairment (Deveney et al., 2015).

Association of irritability with other disorders

Cross-sectionally, irritability is present in young people who suffer from a variety of disorders. However, in contrast to the breadth of cross-sectional associations, longitudinal associations of irritability with depression and anxiety seem to be specific. The reasons for the broad cross-sectional overlap between irritability and other disorders are not fully understood, yet a model according to which irritability shares etiological risks — typically genetic in nature — with other disorders is currently the best supported by evidence, as we discuss below. The mechanisms underlying the shared genetic factors are unknown but may include aberrant processing of reward and emotional stimuli. This still needs to be tested.

DMDD and other disorders

Disruptive mood dysregulation disorder co-occurs with another emotional and behavioral disorders in 65%-90% of cases (Brotman et al., 2006; Copeland et al., 2013; Dougherty et al., 2014); these are mainly depression, anxiety, ADHD, and ODD. However, some of this overlap is due to the use of identical items (e.g. ODD) of post hoc analyses and therefore artificial. Similarly, in the Copeland study (Copeland et al., 2013), sadness — a depression criterion — was also used to ascertain DMDD. And also, ODD should not be coded if DMDD criteria are met. In any case, it will be important to establish whether, after excluding such artificial overlap, DMDD shows more comorbidity than is characteristic of other established psychiatric disorders, for example, ADHD.

Irritability in depression and anxiety disorders

There is now meta-analytic evidence about the strength of the longitudinal association between depression and irritability. Vidal-Ribas et al. (2016) found an odds ratio of 1.80 for longitudinal studies. The follow-up of those studies ranges from 1 to 20 years and many of them control for the presence of depression at baseline, meaning that irritability predicts the new onset of depression. Indeed, a recent study suggests that irritability, alongside anxiety, is a major pathway into depression for adolescents at high risk (Rice et al., 2017). Irritability is also associated with anxiety longitudinally in several studies (Vidal-Ribas et al., 2016).

Mechanisms

One hypothesis about how irritable children become depressed is the so-called failure trajectory, whereby irritability creates a depressogenic environment: an irritable person behaves in ways that annoy peers, parents, and teachers, thereby eliciting negative life events (e.g. exclusions from school, involvements with police) which adversely impact on his or her mood. This is a plausible idea, but there is little evidence to support it. Two twin studies of irritability have shown that the overlap between depression and irritability, both cross-sectionally and longitudinally, is best explained by common underlying genetic factors (Savage et al., 2015; Stringaris, Zavos et al., 2012). Against what the failure hypothesis would predict, environmental risks did not explain why irritability is associated with depression. Some evidence suggests that the overlap with anxiety might also be explained by genetic factors (Savage et al., 2015).

Diagnosis

In our experience, depression in young people with chronic irritability is often undiagnosed because in the eyes of clinicians, parents, and teachers, disruptive symptoms overshadow those of low mood. This is problematic given the evidence presented above about the high likelihood for irritable youth to develop depression as they grow up.

Irritability can, of course, occur during a depressive episode — this form of episodic irritability is a cardinal criterion of depression in young people, but not adults (Stringaris, Maughan, Copeland, Costello, & Angold, 2013).

Irritability in ADHD

Irritability — often referred to as emotional or mood lability or dysregulation in the ADHD literature — is
common both in epidemiological and clinical samples according to a systematic review (Shaw, Stringaris, Nigg, & Leibenluft, 2014). More than 35% of children with ADHD in a population-based study showed marked irritability (Stringaris & Goodman, 2009b) – a tenfold higher rate compared with the general population. The presence of irritability was associated with increased impairment, irrespective of ADHD severity and other comorbidity.

**Mechanisms**

It is clinically plausible to consider irritability in ADHD to be a consequence of evocative transactions, whereby hyperactivity or impulsivity in the child evokes a negative response from the environment. This possibility has not been directly tested, although the fact that irritability improves upon treatment of ADHD (Fernandez de la Cruz et al., 2015) argues in favor of this model. However, the alternative model of shared risk factors has more evidence in its favor. A twin study in the general population (Merwood et al., 2014) found that the overlap between irritability and ADHD is mostly accounted for by shared genetic risks, rather than environmental factors. Recent findings support these results (Riglin et al., 2017), in which ADHD and early irritability share genetic liability.

**Diagnosis**

A careful history of the timing of irritability is important. It is not uncommon for irritability severity to fluctuate according to external stimuli in youth with ADHD. Environmental events such as the beginning of a new school year often coincide with worsening of irritability in those with ADHD. Typically, such environmental events are also the ones that place greater demands on concentration and the need to sit still. Assessing this co-variation between environmental demands, ADHD symptoms, and irritability is important diagnostically and is also important for treatment planning, as discussed below. The role of parental responses, understood in the framework of evocative transactions discussed above, is an important component of this assessment.

**Irritability in autism spectrum disorder**

Clinicians often find that irritability is one of the most vexing problems in the management of youth with ASD, and one of the most important reasons for referral to psychiatric services. Data from rigorously ascertained community cases of ASD suggest that severe irritability is present in about 20% of participants, 20 times higher than in a general population comparison sample without ASD (Copeland et al., In preparation). The presence of severe irritability was not related to the severity of the ASD, but rather associated with high comorbidity rates (such as anxiety and ADHD), as well as significant psychosocial impairment, particularly at schools.

**Mechanisms**

The evidence for shared risks comes from findings that youth with severe irritability and autism have more relatives who also suffer from affective disorders, compared with the relatives of children with ASD only (Simonoff et al., 2012). However, this finding could also be explained by evocative transactions within the family. There is currently no twin study studying the overlap between the two phenotypes. Simonoff et al. (2012) found that cognitive rigidity as assessed in a card-sorting task was linked with irritability. It is plausible that such inflexibility is reflected in difficulties with changes in routines or schedules that parents often report as precipitating temper outbursts. However, the magnitude of the association was small. Other factors that might increase the risk of irritability in children with ASD – and need to be carefully assessed – are communication impairments that compromise the child’s ability to express internal states or coexisting physical symptoms such as pain (Malone, Delaney, Luebbert, Cate, & Campbell, 2000). Mikita et al. (2015) also found aberrant stress reactivity in youth with ASD who also suffered from irritability. In particular, boys with ASD and irritability showed a blunting of cortisol responses and decreased heart rate reactivity to a stress test, compared with those without irritability. These findings parallel previous results from typically developing children with ODD, who also showed blunting of stress responses.

**Diagnosis**

According to DSM, the diagnosis of DMDD is exclusionary for those with ASD. This is based on the usual caution displayed by nosological committees when it comes to comorbidities in autism. Whether this exclusion will persist in future versions of the DSM remains to be seen. In any case, clinicians will want to measure irritability carefully. A well-established measure for disruptive behaviors in youth with ASD is the Aberrant Behavior Checklist, which contains an irritability subscale. This scale contains a number of items, such as screaming, yelling, or crying that are not irritability in the strict sense. The Overt Aggression Scale (OAS) and the Child Autism Rating scale have also been used to capture such behaviors. In high-functioning autism, the ARI appears to perform similarly well to typically developed children both by parent and by self-report (Mikita et al., 2015). A key component of irritability assessment in ASD should be a functional analysis, where antecedents, behaviors/feelings, and consequences are carefully evaluated. It is our experience that such an approach can reduce temper outbursts,
particularly as they relate to preparation of routine change or sensory sensitivity.

Irritability in BD

The DSM-5 criteria for BD specify a distinct period of ‘abnormally and persistently elevated, expansive or irritable mood’. Unlike the criteria for major depressive episodes, those for manic episodes and BD make no distinction between children and adults in terms of whether irritability can be a cardinal mood. Under DSM, irritability can be the predominant mood of a manic episode even in the absence of other cardinal mood symptoms. This is in contrast to the practice in other countries, such as the United Kingdom, where advice from the National Institute for Health and Care Excellence is that irritability without elation or grandiosity should not allow a diagnosis of mania in children (NICE, 2014). This decision was made to guard against what was seen as an overdiagnosis of BD in the United States. Even under DSM, there is a requirement that four additional manic symptoms to be present if the cardinal mood is irritability, which contrasts to the requirement for only three manic symptoms if the mood is elated or expansive; this probably reflects an implicit recognition that irritability, even if episodic, is less pathognomonic than elation.

A study in youth with BD demonstrated that, while episodic irritability is common, it is rare in the absence of elation – about 10% of subjects had only irritability as a cardinal symptom (Hunt et al., 2009). Those with irritability-only were significantly younger than those with elation or those with elation and irritability as cardinal symptoms. In our experience, episodic irritability in BD is strongly influenced by the patient’s interactions with the environment. As symptoms of disinhibition become more severe and the patient faces increasing restrictions by their family or mental health professionals, more and more behavioral goals, such as overspending, are blocked leading to frustration. Indeed, it is characteristic in such instances to observe extreme euphoria to turn into very severe irritability, increasing the risk for aggression.

There are several guidelines for the treatment of BD in young people, and it is beyond the scope of this review to discuss them. No treatment trial has examined irritability as an outcome in its own right in bipolar youth.

Irritability in other psychiatric disorders

Irritability can appear in a host of other disorders. One of the most notable is irritability that occurs after trauma, an observation enshrined in the DSM criteria of post-traumatic stress disorder. The extent to which irritability is the most impairing symptom of so-called complex trauma (Stringaris, Smith, Hickin, & Villalta, In preparation), a condition characterized by mood dysregulation resulting from prolonged exposure to severe stressors in developmentally vulnerable times such as early childhood or adolescence still needs confirmation.

Children with obsessive-compulsive disorder (OCD) can also experience severe tantrums, particularly when they suffer from comorbid depression (Krebs et al., 2013). However, tantrums are not an obstacle to treatment of OCD symptoms, which are reduced after CBT (Krebs et al., 2013).

Management of irritability

Increasingly, trials with irritability as the primary outcome are being conducted, but the evidence base remains relatively small. When treating irritable patients, clinicians will often be faced with the decision about whether to treat irritability, the comorbid condition, or both. In Figure 2, we recommend a simple algorithm for the treatment of irritability. In our experience, and based on the findings in the comorbidity section above, it is most sensible for clinicians to start by trying to treat any comorbid condition first using evidence-based treatments. This approach is driven by pragmatic constraints; there have been far fewer trials of irritability than of depression, anxiety, or ADHD, for example. It is in recognition of the existing evidence – and secondary analyses that have been conducted with irritability from those trials – that we recommend this approach. For example, a child with ADHD and irritability ought to be treated with stimulants first, given the solid evidence base about their effectiveness on the core symptoms of the disorder and irritability. In parallel with this approach or as a next step in the treatment of irritability, clinicians can add a psychological treatment, such as a parenting intervention for younger children or CBT for adolescents, for both of which there are encouraging data as discussed later. Pharmacological treatment for irritability should be reserved for later stages. Exceptions to this rule are situations where irritability is extremely acute (as in situations where rapid tranquilization may be required) or when it is very clear from early on that psychological interventions may be futile (Scott & Dadds, 2009).

Psychological treatments

There are several psychosocial interventions that have been developed for irritability-related clinical syndromes, which fall into two broad classes: (a) parent management training (PMT) and cognitive behavioral therapy (CBT; Sukhodolsky, Smith, McCauley, Ibrahim, & Piasecka, 2016).

Parent management training (PMT). Originally derived from operant conditioning behavioral research and parent–child interactions observed by Patterson and colleagues (Patterson, 1975), PMT
targets negative patterns of family interactions underlying children’s aggressive behavior. Specifically, to address irritability and anger, during PMT, parents are taught to reinforce children’s prosocial behavior and not reinforce maladaptive behavior, such as temper outbursts (Barkley, 2013b). Through positive reinforcement, parents are instructed to focus on increasing youths’ positive behaviors by providing praise or a reward after an identified target behavior occurs. Problematic child behavior is addressed through parents using active ignoring, timeouts, and nonreinforcing consequences. Inconsistent patterns of reinforcement and consequences are addressed, with the goal of more consistent contingencies for child behavior. Numerous meta-analytic studies have demonstrated the general efficacy and effectiveness of PMT of decreasing children’s disruptive behavior and conduct problems in youth with disruptive behavior disorders such as oppositional defiant disorder and/or conduct disorder (Comer, Chow, Chan, Cooper-Vince, & Wilson, 2013; Eyberg, Nelson, & Boggs, 2008; Furlong et al., 2012; Knapp, Chait, Pappadopulos, Crystal, & Jensen, 2012; Morrison, Pikhart, Ruiz, & Goldblatt, 2014; NICE, 2013a; Sandler, Schoenfelder, Wolchik, & MacKinnon, 2011), yielding a moderate effect size (around 0.5) for studies that use blinded assessments. Longitudinal evidence suggests that improvements in prosocial behavior are stable and prevent future antisocial behaviors (Scott, Briskman, & O’Connor, 2014). There is increasing evidence for the usefulness of parenting interventions in addressing disruptive behaviors in children with ASD (Bearss et al., 2015). However, it is important to note that there are few studies examining the efficacy of PMT specifically for symptoms of irritability, severe mood dysregulation, or DMDD (Waxmonsky et al., 2008, 2013). PMT has been shown to be effective in both individual- and group-based formats (Pilling, Gould, Whittington, Taylor, & Scott, 2013; Waxmonsky et al., 2016). In a recent study, Waxmonsky et al. (2016) demonstrated the feasibility of a group-based parenting intervention specifically targeting anger and irritability for youth with SMD; preliminary results suggest its efficacy. A secondary analysis of data by O’Connor and Scott suggests that youth with irritability may be particularly responsive to parenting interventions (Scott & O’Connor, 2012).

**Cognitive behavioral therapy.** Cognitive behavioral therapy grows out of both social information processing and behavioral approaches to psychopathology (Sukhodolsky & Scahill, 2012). From a social learning perspective, disruptive behavior can be conceptualized as the result of maladaptive hostile interpretations of social stimuli (Crick & Dodge, 1994; Dodge, 1980). Children learn more adaptive ways to interpret and respond to social situations, leading to fewer anger and aggressive responses. Behavioral approaches posit that aggressive behavior is a learned response. As discussed above, changes in contingent learning are addressed with parents during PMT. There are several CBT

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**Figure 2** An algorithm for the treatment of irritability. Treatments for irritability indicated here should be provided only when the comorbidity labeled above is ascertained after a complete clinical assessment. Continuous arrows show paths to first-line interventions. Dashed arrows show paths to second-line interventions after application of only first-line interventions has proven to be futile. 1NICE (2013b); 2Parent intervention for irritability is effective in children with ODD (Scott & O’Connor, 2012) or ASD (Bearss et al., 2015); it might work in children with ADHD treated with stimulant (Waxmonsky et al., 2016)

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manuscripts for aggressive behavior, anger, and irritability, including Anger Coping Program (Lochman, Powell, Boxmeyer, & Jimenez-Camargo, 2011) and a CBT for Anger and Aggression in Children (Sukhodolsky & Scahill, 2012). In addition, CBT approaches focusing on angry rumination appear promising (Leigh, Smith, Milavic, & Stringaris, 2012), yet more work needs to be done in this regard.

**New psychological treatment approaches.** Given the pathophysiological overlap of irritability with anxiety, as discussed above, and the efficacy of exposure techniques in treating anxiety, ongoing work (ClinicalTrials.gov identifier NCT02531893) is beginning to test the hypothesis that, following graded exposure to frustrating situations, through extinction learning, irritable children will develop increased tolerance for frustration and more adaptive coping strategies. In addition, during joint parent–child sessions, parents are taught typical PMT strategies, as well as how to tolerate their own discomfort if the child has an outburst while the parent is engaging in behavioral strategies (e.g. active ignoring of child’s outbursts).

Given the limited number of effective treatments for irritability, preliminary studies are also exploring novel computer-based treatment interventions leveraging observed pathophysiological deficits observed in youth with severe irritability. Specifically, interpretation bias training (IBT) is a cognitive retraining approach that requires youth to make forced, two-choice (happy/angry) judgments of facial expressions on a linear morph continuum from happy to angry. Patients receive feedback encouraging them to learn new, positive associations to ambiguous face emotions. One clinical trial has demonstrated that over 4 or 5 days, this computer-based training decreased aggression in youth at risk for criminal behavior (Penton-Voak et al., 2013). Consistent with this, an open trial training DMDD youth to perceive ambiguous faces in a more benign manner was associated with decreased irritability and neurobiological changes in a smaller subset (Stoddard et al., 2016). These two studies suggest promise; however, larger-scale RCTs of IBT for DMDD are needed and ongoing (ClinicalTrials.gov identifier NCT02531893).

**Pharmacological treatments**

Only one RCT for the pharmacological treatment of irritability in youth has been completed, but there are several underway.

**Lithium.** There has only been one pharmacological randomized controlled trial for severe irritability in youth (Dickstein et al., 2009). Growing out of controversy as to whether severe irritability is a pediatric manifestation of mania, the authors examined the efficacy of lithium in youth with severe mood dysregulation. In that small study, there was no benefit of lithium over placebo in the treatment of severe irritability in youth. It should be noted that lithium may reduce aggression in children and adolescent with conduct disorder (Campbell et al., 1984, 1995; Malone et al., 2000; Rifkin et al., 1997). However, aggression is only one of the many consequences of irritability.

**Selective serotonin reuptake inhibitors.** Indirect evidence suggests the efficacy of SSRIs in the treatment of irritability in depressed adults with anger attacks (Fava & Rosenbaum, 1999) and those with intermittent explosive disorder (Coccaro, Lee, & Kavoussi, 2009). However, a recent systematic review on the effect of antidepressants on irritability in young people found a small impact on irritability and disruptive behaviors (Kim & Boylan, 2016). Two NIMH-funded studies are ongoing in youth with severe mood dysregulation (ClinicalTrials.gov identifiers NCT00794040 and NCT01714310). One concern for clinicians is whether an increase in episodic irritability during SRI treatment reflects activation that can, in turn, be associated with the increase in suicidality that is occasionally observed during treatment. Clinicians often discontinue SRI treatment out of concern that an adolescent’s irritability may indicate risk for mania or suicidality. Arguing against this practice are good-quality adult trial data that did not find irritability to be associated with an increased liability for a manic switch during treatment (Frye et al., 2009; Perlis et al., 2009). Therefore, while the presence of new onset irritability should always prompt the clinician to consider carefully the emergence of SRI-induced mania, it is not in and of itself a reason to stop treatment.

**Stimulants.** Meta-analyses have demonstrated a medium to large effect sizes in the efficacy of stimulants in treating aggression in youth with ADHD (Connor, Glatt, Lopez, Jackson, & Melloni, 2002). Specially, numerous studies have shown that stimulant monotherapy, in concert with behavioral treatment, decreases aggressive behavior and outbursts (Blader, Pliszka, Jensen, Schooler, & Kafanaris, 2010; Blader et al., 2016; Waxmonsky et al., 2016). A re-analysis of the MTA data suggests that stimulants can reduce irritability (Fernandez de la Cruz et al., 2015) alongside ADHD symptoms. In addition, the authors found that the presence of irritability did not moderate the treatment effects on ADHD symptoms. These findings are in keeping with indirect evidence from a series of other trials (Shaw et al., 2014). There is also evidence against the notion that stimulants increase irritability as a side effect (Ahmann et al., 1993; Manos et al., 2011).

**Antiepileptics.** Drugs such as sodium valproate or carbamazepine are employed as mood stabilizers for the treatment of BD in youth. Evidence for their use in chronic irritability in young people is indirect and
comes mainly from anecdotal experience and the results of an RCT of valproate to treat children with ADHD whose aggression had not responded to stimulant treatment (Blader et al., 2009). Great caution is warranted in their use in young people, particularly for valproate in young females (MHRA, 2016).

**Atypical antipsychotics.** There are several RCTs supporting the role of risperidone for disruptive behaviors in ASD and the drug has FDA approval for this indication (RUPPAN, 2002). Aripiprazole also has an FDA indication for the treatment of such behaviors in ASD, and the effect size \( (d = 0.78) \) is comparable to that of risperidone \( (d = 0.86; \text{Fung et al., 2016}) \). There is also evidence for the utility of olanzapine in ASD. While the evidence is there for robust and sustained (albeit probably nonspecific) effects of antipsychotic drugs, especially indicated to treat irritability in ASD, clinicians must remember the strong adverse effects of these drugs. These include obesity (e.g. 5.5-kg weight gain in children below 12 over a period of several months with risperidone; Findling, Aman, Eerdekens, Derivan, & Lyons, 2004), iatrogenic diabetes, and endocrine abnormalities. These problems may be more pronounced in those with autism (De Hert, Dobbelaere, Sheridan, Cohen, & Correll, 2011) and are more common in young people compared with adults (Correll, Sheridan, & DelBello, 2010; Correll et al., 2006).

The caution in prescribing antipsychotics cannot be overemphasized. There are several lines of evidence indicating the overuse of antipsychotics in those without an illness for which antipsychotic treatment has little or no evidence base. Indeed, the evidence suggests that hard-to-manage irritability underlies many, probably unnecessary, such prescriptions. Irritability, either misdiagnosed as BD or as the presenting problem in disruptive behaviors, prompts clinicians to choose the ostensibly simple solution of antipsychotic prescribing. While results indicate some significant reductions in irritability, it is important to note the significant health risks and side effect burden associated with atypical agents mentioned above, especially in children and adolescents. We urge clinicians to be cautious in using these agents for irritable children.

There has been one open trial examining the efficacy of low doses of risperidone in the treatment of severe mood dysregulation, in youth without autism, that showed reductions in irritability scores (Krieger et al., 2011). Our recommendation is that antipsychotic prescriptions be reserved for those young people who have not responded to a series of other treatments and that the prescription be for a short period of time during which health indicators such as weight are tightly monitored. The clinicians should be upfront with parents and patients about the potentially damaging effects of such treatments.

**Discussion**

The purpose of this paper was to review the evidence on irritability as it relates to clinical practice. Two important and clinically relevant progress in the field have been done. First is the recognition of irritability as a common and impairing condition for young people. This has led to a number of new initiatives ranging from symposia dedicated to irritability (NIMH, Vermont) through to re-analysis of large existing datasets, new measurement instruments, a new diagnostic category (DSM-5), and several clinical trials (Dickstein et al., 2009; Krieger et al., 2011; Stoddard et al., 2016; Waxmonsky et al., 2016). Second is the recognition of irritability as a mood problem rather than a purely behavioral problem. This conceptualization of irritability has shaped not only its nosology (e.g. DMDD classified under section of depressive disorders in DSM-5) but also the development and testing of new and more specific treatments. As we have shown, these advances are beginning to bear fruit and allow us to address key clinical questions.

Perhaps, the most important of such questions concerns the boundaries between irritability and normality. It is now evident that irritability is associated with substantial morbidity and disadvantage even when adjusted for other confounds. The key message to practitioners is that ignoring irritability is not appropriate. Another key message is that irritability can be reliably and easily measured making it clinically possible to document the problem, and communicate it to patients, families, and other practitioners.

There is also reason for clinicians to convey optimism to patients with irritability and their families given what we have learnt about both pharmacological and psychological treatments. While there is dearth of trials with irritability as a primary outcome, improvements in irritability through existing treatments for other conditions is encouraging. It is particularly encouraging that pathophysiological research in irritability and related areas is also pointing at innovative avenues for psychotherapeutic approaches. For example, treatments such as interpretation bias training hold promise because of their low cost and scalability. And the use of exposure treatment – specially adapted to tackle irritability – presents a fascinating adjunct or alternative for youth with irritability based on sound psychological principles.

However, next to these promises, there are also several challenges. From a public health perspective, probably the biggest issue concerns using antipsychotic medication to treat children with irritability. The side effect profile of the commonly used second-generation antipsychotics should compel clinicians to be very careful when prescribing them. It is important for clinicians and policy makers to focus their attention on monitoring the trend in antipsychotic prescribing, educating clinicians about the problems with such prescribing and to roll out efficacious...
psychological treatments for such youth (which could be used as a first line, as per our recommendation above). From a pathophysiological perspective, the most interesting challenge concerns the possible etiological and clinical heterogeneity in irritability – whether irritability in, say, ADHD is similar to the irritability that precedes depression. This work will require a number of different approaches and probably collaboration between sites that will generate large enough samples to tackle this question.

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Key practitioner message
- Regardless of its etiology, irritability is easy to measure across diagnostics. Several reliable instruments are available for use in clinical practice, from short questionnaires to structured interviews. Assessment of irritability is always recommended since it is present in many psychiatric disorders, is associated with increased impairment, and can be treated.
- DMDD was introduced in DSM-5 to tackle the increase of BD diagnosis and antipsychotic medication prescription in children as well as to accommodate youth with severe chronic irritability as the main symptom. There is compelling evidence showing that DMDD and BD differ in longitudinal outcomes, family history, treatment response, and behavioral and neural correlates.
- Severe irritability is present in many psychiatric disorders, yet it is specifically associated with depression and anxiety in longitudinal studies. The overlap between irritability and other disorders is mainly explained by shared genetic factors.
- We recommend that an algorithm be used (such as the one presented in this paper), by which treatment choice for irritability is based on the presence of comorbidities and their type. For example, in patients with ADHD and irritability, solid treatment of ADHD should typically be the first approach.
- There is only one pharmacological RCT in youth with severe irritability that showed no effects of lithium over placebo. However, several trials are underway.
- Parent management training (PMT) and cognitive behavioral therapy (CBT) are the most supported psychological treatments for irritability, albeit mainly through indirect evidence. New promising approaches relying on pathophysiological findings, such as exposure-based techniques and interpretation bias training (IBT), are under development.

Areas for future research
- There is a need to develop new instruments to assess irritability that capture in more detail its different components (i.e. tonic and phasic irritability).
- Future research should examine whether the brain mechanisms mediating irritability vary across diagnoses or when co-occurs with other traits, such as anxiety for example.
- Future studies should look at how aberrant reward processing and bias toward threatening stimuli interact, and whether this might help us to develop more individualized treatments.
- We should examine further the specific association between severe irritability and depression/anxiety; we need to know why this happens in order to prevent it.
- Finally, randomized controlled trials with measures of irritability as primary outcome are needed.

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