Irritability in children: what we know and what we need to learn

Irritability can be defined as increased proneness to anger, relative to peers. Clinically, it manifests as developmentally inappropriate temper outbursts and sullen, grouchy mood; thus, it includes both behavioral and mood components. Related constructs are mood dysregulation, which is broader than irritability, and aggression, which encompasses only behavioral manifestations.

Anger proneness has a defined developmental trajectory, peaking in the preschool period and declining thereafter, with a modest increase during adolescence¹. Irritability is a common reason for mental health evaluation in children, and pediatric irritability is associated with both concurrent and future impairment.

In the 1990s, American researchers suggested that pediatric bipolar disorder does not present with distinct manic episodes as in adults, but instead with severe, chronic irritability. However, *post-hoc* analyses of epidemiological studies found associations between pediatric irritability and risk for subsequent anxiety and depression, but not for bipolar disorder². Similarly, in studies comparing the two dimensions of oppositional defiant disorder (ODD) (i.e., irritability and headstrong behavior), irritability predicts subsequent anxiety and depression, while headstrong behavior predicts attention-deficit/hyperactivity disorder (ADHD) and conduct disorder². Thus, the diagnosis of bipolar disorder should be reserved for youth (and adults) with distinct manic episodes, rather than chronic irritability.

Genetically informative studies link irritability and depression³. Twin studies document that longitudinal associations between irritability and both anxiety and depression have a genetic component. These studies also find that the heritability of irritability is approximately 40-60%, similar to anxiety or unipolar depression.

Irritability is a diagnostic criterion for multiple disorders in youth, including anxiety disorders, major depressive disorder, and ODD. It is also common in youth with ADHD, bipolar disorder, conduct disorder, and autism. However, for children and adolescents, the validity and clinical utility of a diagnostic category characterized primarily by irritability remains an important and unanswered question. Historically, that category has been ODD, which is conceptualized as a disruptive behavior disorder. However, ODD consists of two dimensions, only one of which, irritability, has genetically mediated longitudinal associations with depression and anxiety. Also, severe irritability has significant cross-sectional associations with anxiety disorders. These considerations call into question the appropriateness of combining irritable and headstrong features into one disorder, and of categorizing a diagnosis characterized primarily by irritability as an externalizing, disruptive behavior disorder, rather than as a mood disorder.

Given these complexities, it is not surprising that DSM-5 and ICD-11 take different approaches to diagnosing youth whose primary problem is severe irritability. Reflecting the

American controversy about pediatric bipolar disorder, the mood disorder section of DSM-5 includes a new diagnosis, disruptive mood dysregulation disorder (DMDD), characterized by severe, chronic irritability. DMDD captures youth whose irritability causes impairment comparable to that of youth with bipolar disorder and, hence, is more severe than that of most youth with ODD. Given overlap between DMDD and ODD, ICD-11 instead includes a specifier to the diagnosis of ODD denoting chronic irritability. To evaluate these different nosologic strategies, future research should focus on their utility in predicting treatment response.

Two neuroscience-based formulations can guide research on the pathophysiology of irritability. One conceptualizes irritability as an aberrant response to frustration, the emotion elicited when goal attainment is blocked, as when an expected reward is withheld². The second conceptualizes irritability as an aberrant approach response to threat: whereas healthy organisms approach a threat (i.e., attack) only when it is inescapable, irritable individuals may attack in a broader range of contexts. In an animal model with translational potential for studying irritability, threat and frustration were found to interact in determining an animal's behavior. Specifically, compared to non-frustrated rodents, those who experienced "frustrative non-reward" (i.e., did not receive an expected reward) showed increased motor activity and were more likely to attack a conspecific⁴. Such hyperactivity and increased propensity for aggression may be analogous to the behavior exhibited by a frustrated child experiencing a temper outburst.

Functional magnetic resonance imaging research has examined associations between irritability and neural responses to frustration (e.g., rigged games) and threat (e.g., angry faces). Work with frustrating tasks shows associations between irritability and dysfunction in striatum, anterior cingulate cortex, amygdala, and parietal lobe, consistent with irritable youths' deficits in reward processing and in maintaining attentional control when frustrated^{5,6}. Irritable youth are also more likely than their non-irritable peers to view ambiguous faces as angry and, like youth with anxiety disorders, to attend preferentially to angry faces^{7,8}. One direction for future research would be identifying the extent to which abnormalities in reward or threat processing differentiate subtypes of irritable youth. Also, an important question is whether the brain mechanisms mediating irritability vary across diagnoses and/or when irritability co-occurs with another trait, such as anxiety. Early data suggest that the pathophysiology of irritability varies across such contexts⁹.

Given the very recent inclusion of DMDD in DSM-5, limited controlled trials exist. However, tentative recommendations stem from studies focused on treating irritability in the context of other disorders, including ADHD and major depressive disorder. Considerable data indicate that stimulants reduce irritability in youth with ADHD². This suggests that, while

stimulants are relatively contraindicated in bipolar disorder, they may be helpful for DMDD. Data support the use of atypical antipsychotic medication in youth with autism and irritability, and in youth with aggression². However, recent increases in antipsychotic prescriptions may have resulted in part from attempts to treat pediatric irritability, perhaps without adequate exploration of alternative pharmacologic and psychotherapeutic approaches¹⁰. Selective serotonin reuptake inhibitors (SSRIs) may treat irritability in adults; such an approach in children is supported by the high comorbidity and longitudinal associations among irritability, anxiety and depression². SSRIs are now being tested in youth with DMDD.

Psychotherapeutic approaches are likely to be important in the treatment of irritability. Parent training can decrease a child's aggression and might also decrease irritability¹¹. Cognitive behavioral approaches are being tested, as is implicit training designed to alter irritable children's tendency to view ambiguous faces as angry⁸.

In conclusion, the recent focus on irritability has yielded considerable knowledge about its longitudinal course and associations with psychopathology. Ongoing work is aimed at identifying the brain mechanisms mediating irritability and at

using that knowledge to inform novel treatment approaches.

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1. Leibenluft E, Stoddard J. *Dev Psychopathol* 2013;25:1473-87.
2. Leibenluft E. *Am J Psychiatry* 2011;168:129-42.
3. Savage J, Verhulst B, Copeland W et al. *J Am Acad Child Adolesc Psychiatry* 2015;54:377-84.
4. Burokas A, Gutierrez-Cuesta J, Martin-Garcia E et al. *Addict Biol* 2012;17:770-82.
5. Deveney CM, Connolly ME, Haring CT et al. *Am J Psychiatry* 2013;170:1186-94.
6. Perlman SB, Jones BM, Wakschlag LS et al. *Dev Cogn Neurosci* 2015;14:71-80.
7. Hommer RE, Meyer A, Stoddard J, et al. *Depress Anxiety* 2014;31:559-65.
8. Stoddard J, Sharif-Askary B, Harkins EA et al. *J Child Adolesc Psychopharmacol* 2016;26:49-57.
9. Wiggins JL, Brotman MA, Adelman NE et al. *Am J Psychiatry* 2016;173:722-30.
10. Correll CU, Blader JC. *JAMA Psychiatry* 2015;72:859-60.
11. Pilling S, Gould N, Whittington C et al. *BMJ* 2013;346:f1298-301.

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Are there new advances in the pharmacotherapy of autism spectrum disorders?

Autism spectrum disorders (ASD) are heterogeneous neurodevelopmental disorders beginning early in childhood and characterized by social communication deficits and restricted patterns of repetitive/stereotypic behaviors. Associated symptoms such as hyperactivity, irritability, insomnia, seizures, gastrointestinal and immunological disturbances may be present. Some ASD children have exceptional (savant) abilities in isolated cognitive areas such as mathematical, artistic or musical skills. ASD are more common in boys than girls (ratio 4:1), but are under-diagnosed in the latter.

The etiology of ASD is quite complex. Genetic, epigenetic, infectious, autoimmune-immunologic, metabolic, nutritional and toxic factors may be involved. Different brain areas, neural circuits, neurotransmitters, neuropeptides, cytokines, synaptic and signal transduction molecules and processes may be affected.

Because of this complexity, the development of pharmacotherapy for ASD has proven quite challenging. The marked heterogeneity of these disorders suggests that different treatments will likely be beneficial for different patients. There is a need for early detection and intervention when the brain is more plastic and changes may be more easily reversible; however, some studies suggest that pharmacotherapy may also be useful in adults. Biomarkers may help stratify subgroups and predict response to therapy. The ultimate goal is to target the ASD core symptoms; however, most current pharmacotherapies target ASD-associated symptoms.

The atypical antipsychotics risperidone and aripiprazole are approved in the US for the treatment of disruptive behaviors (aggression, self-injury, temper tantrums) in childhood ASD. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and citalopram, have been studied in ASD: single-site trials demonstrated efficacy for repetitive behaviors in ASD children and adults^{1,2}, but multi-site trials failed to document efficacy, except in a subgroup of subjects with high irritability. Anticonvulsants have been studied for disruptive behaviors such as impulsivity, self-injury and aggression, common in ASD: valproate, acting by potentiating the inhibitory effect of the GABAergic system and by epigenetic effects, has shown benefit in reducing irritability and impulsive-aggressive behavior in ASD children³. Medications approved for attention-deficit/hyperactivity disorder (ADHD) have been studied in ASD: they have modest efficacy on symptoms such as hyperactivity (methylphenidate, dextroamphetamine, atomoxetine) and irritability (clonidine).

Newer ASD experimental pharmacotherapies target core ASD symptoms and are developed on the basis of knowledge of the molecular neurobiology and genetics of ASD.

One group of such drugs aims to restore the balance of excitation and inhibition in brain cortical regions. They include those targeting metabotropic glutamate receptors (such as mGlu5 antagonists), NMDA receptors (such as the NMDA receptor antagonist memantine), or AMPA receptors (such as