Current Psychiatry Reports (2019) 21:123
https://doi.org/10.1007/s11920-019-1105-1

CHILD AND ADOLESCENT DISORDERS (TD BENTON, SECTION EDITOR)

Understanding Chronic Aggression and Its Treatment in Children and Adolescents

Selena R. Magalotti[1] · Mandy Neudecker[1] · Solomon G. Zaraa[1] · Molly K. McVoy[1,2,3]

Abstract

Purpose of review Youth aggression is common and has a significant burden on individuals, families, and society. However, its treatment is often a challenge for clinicians. Thus, this review will examine the current understanding of youth aggression, conceptualize aggression as a symptom rather than its own disorder, and provide an overview of treatment strategies.

Recent findings Youth aggression is associated with complex genetic, neurobiological, and environmental risks. Prevention strategies are of the utmost importance for at-risk families and youth. Psychosocial interventions are the first line treatment. But if not fully effective, then pharmacologic interventions—including psychostimulants, alpha-2 agonists, atomoxetine, and risperidone—have shown benefits. Other medications, such as SSRIs, can be useful in certain scenarios.

Summary It is important to conceptualize youth aggression as being a trans-diagnostic symptom in psychopathology. Determining the underlying cause of aggression will help to guide treatment.

Keywords Aggression · ADHD · Conduct · ODD · Antipsychotic · Stimulant · Pediatric · Treatment

Introduction

Maladaptive aggression is one of the most common reasons for youth mental health referrals [1–3]. Although aggression can be common developmentally in the first several years of life, it typically decreases by the time children start school and further decreases into adulthood [2, 4–7]. When aggression remains beyond what is appropriate developmentally, consequences arise for the person, society, and the healthcare system [8–12]. Maladaptive childhood aggression puts youth at risk for higher levels of poverty, unemployment, substance use, negative health outcomes, criminality and continued aggression, social isolation, poor school performance, impaired parenting, psychiatric comorbidity, suicidality, and death [13, 14•, 15, 16] .

Though the treatment of aggression in youth is commonly sought [1–3], clinicians often feel underprepared and struggle to treat severe behavioral issues in children [17]. The goal of this review is to examine the current understanding of aggression in youth, conceptualize aggression as a symptom rather than its own disorder, and provide an overview of treatment strategies based on common underlying psychopathology causing aggression.

Molecular and Neuropathology

Aggression has complex neurochemical, genetic, epigenetic, and hormonal underpinnings. Neuroimaging studies have also found morphologic brain changes linked to aggressive behavior. Research continues developing and has some inconsistent findings—thus, broad strokes are used here regarding the neuropathophysiology of aggression.

Heritability

The use of aggression has been evolutionarily important in multiple contexts, such as defending oneself against attack,

This article is part of the Topical Collection on *Child and Adolescent Disorders*

✉ Molly K. McVoy
molly.mcvoy@uhhospitals.org

[1] Department of Psychiatry, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

[2] Case Western University School of Medicine, Cleveland, OH, USA

[3] W. O. Walker Building, Division of Child and Adolescent Psychiatry, 10524 Euclid Ave, Suite 1155A, Cleveland, OH, USA

Published online: 18 November 2019

being a successful predator, attracting a mate and reproducing, and having dominance in society [8, 11, 12, 18, 19••]. Because aggression is important for survival, it is believed that certain gene variants may have been selected in the genome to promote aggression [19••].

Twin studies show that approximately 50% of aggression variance may be due to genetics, both for trait aggression and categorical psychopathology [8, 19••, 20] The non-shared environment, i.e., the differences in experiences for children within the same family, has been shown to have a moderate effect [19••, 20, 21]. There are mixed results regarding the influence of the shared environment, with results varying depending on context from negligible influence to moderate influence [19••, 20, 21–23]. Heritability appears comparable between males and females, though results vary.

Candidate gene studies have found possible associations for aggression in serotonergic/dopaminergic genes and with hormone-related genes [8, 19••]. Genome-wide association studies have suggested that aggression may be associated with genes that are involved in neurodevelopment and synaptic plasticity [8, 19••]. Variants in single nucleotide polymorphisms (SNPs) on the 2p12 chromosome appear to be associated with childhood aggression, with near genome-wide significance [6].

Neurochemicals, Hormones, and other Molecules Linked with Aggression

Serotonin is an evolutionarily well-conserved signaling molecule that has been consistently described to be involved in aggression [24–26]. Serotonergic cells represent a very small fraction of CNS neurons but have wide-reaching effects, including executive processing, motor functioning, and autonomics [25•, 26]. The serotonin system also plays downstream effects with the catecholinergic system, noradrenergic system, oxytocinergic system, excitatory glutaminergic system, and the inhibitory GABA-ergic system [25•, 26]. Both high and low serotonin, and several serotonin receptor subtypes, have been linked with aggression [24].

In addition, elevated dopamine has been implicated in aggression, likely due to its involvement in executive functioning, cognition, and reward processes [24].Variants of the enzymes that break down catecholamines have been implicated in aggression, namely monoamine oxidase A (MAO-A) and catechol-O-methyltransferase (COMT) [8, 10, 24, 27].

Several other systems are also believed to play a role in aggression. The hypothalamic-pituitary-adrenal system and the hypothalamic-pituitary-gonadal systems have been shown to have a role in aggressive behavior, including effects of cortisol and testosterone [10, 24, 27]. Vasopressin affects behavior and oxytocin affects social interactions including bonding and empathy—high vasopressin and low oxytocin have both been associated with aggression [8, 25•, 28]. Alterations in thyroid hormones [27], inflammatory markers [27], and cholecystokinin neuropeptide [10] have also been linked with aggression.

Brain Morphology Changes

Several brain regions have been implicated in aggressive behavior, and aggression is likely due to the interaction across different regions of the brain [24]. Aggression has been associated with reduced volume, labile activity, and both hyper- and hypo-responsiveness to threats in the amygdala [24].

An adolescent twin study of typically developing 14-year olds demonstrated several differences in brain structures thought to be associated with aggression. Enlargement of the striatum (caudate nuclei, putamen, and nucleus accumbens) was associated with aggression, with this region being associated with behavioral regulation [15]. Higher levels of aggression were correlated with smaller medial frontal cortex volume and larger orbitofrontal cortex, suggesting frontal lobe cognitive and executive dysfunction [15]. Aggression was associated with changes in thickness of the middle frontal cortex, superior frontal cortex, anterior cingulate cortex, and temporal regions [15]. These results suggest that the fronto-limbic-striatal circuit is involved in adolescent aggression.

Familial, Environmental Risks, Protective Factors

A person's genetic susceptibility for aggression is affected not only by genetics, but also by the environment and its interaction with gene expression. Fetal exposures related to development of disruptive and aggressive behaviors include maternal smoking and drug use during pregnancy [5•, 29•]. Epigenetic changes due to maternal stress can affect a developing fetus' risk of youth aggression [29•]. Maternal depression and parental substance use have been associated with aggression [5•, 14•, 29•].

Environmental risk factors include low socioeconomic status, exposure to violence, and youth perception of neighborhood disadvantage [5•, 29•, 30]. Harsh and rejecting parenting, conflict and chaos within the family unit, being abused and witnessing interpersonal violence have been associated with an increased risk of aggression [5•, 8, 29•, 31]. In addition, children with aggressive behaviors may be more likely to affiliate with deviant peers [29•]. Research results regarding the correlation of exposure to violent media is widely variable from reports of nearly no effect to large effects [32, 33].

Alternatively, there are several factors that can reduce the risk of youth developing aggressive behaviors. Positive parenting skills and styles reduce the risk of children developing disruptive behavioral issues and supports the development of secure attachments [5•, 29•, 31]. Youth resilience, positive

perceptions of one's neighborhood, and living in a safe neighborhoods can also mitigate risks [29•, 30].

Definitions and Subtypes

Extensive variability for the concept of aggression exists within the literature. For example, aggression can be seen as a trait or due to a diagnostic entity. Because aggression is often defined differently based on the study, it makes it challenging to compare and interpret the literature [19••]. Further, the broad category of aggression is an often amorphous and heterogeneous construct that is not well specified, making studying aggression particularly challenging [10, 24]. Consequently, some of the main subcategorizations of aggression will be reviewed here.

Research Domain Criteria (RDoC)

The National Institutes of Mental Health developed the RDoC to guide researchers into studying the underlying issues in psychopathology. In RDoC, aggression has been broken down into three types: 1) frustrative non-reward: aggression associated with not getting a reward after making an effort; 2) defensive aggression: aggression in response to a threat; 3) offensive aggression: aggression to achieve a goal [19••].

Reactive versus proactive aggression

Reactive aggression is described as overt, abrupt, hot headed, affective, hostile, and associated with anger and rage [24, 34]. It is an explosive, defensive, retaliatory, and uncontrolled response to frustration or the perception of a threat or provocation [24, 34, 35]. It is accompanied by a fight-or-flight reaction and a high level of physiologic arousal [34]. Reactive aggression is associated with a history of abuse, impulsivity, attention issues, anxiety, peer relationship problems, and a negative emotional state [24, 35, 36]. It is associated with limited social competence and carries the risk of developing depression and substance use [35, 36]. A medium-sized association has been shown between reactive aggression and youth suicidal behaviors and completed suicide [35].

Proactive aggression is often described as covert, premeditated, predatory, and goal oriented [7•, 24, 34]. It is done with the planned goal of obtaining a certain favorable result, such as personal power or an item of value [24, 36]. There is minimal associated physiologic arousal, with low heart rate and skin conductance [24, 34]. Proactive aggression is associated with psychopathy, is a risk factor for delinquency, and is associated with over-estimation of social competence [24, 35, 36]. Callous-unemotional traits, which have a strong genetic basis [11], are highly associated with proactive aggression [12]. Callous-unemotional traits are described as having reduced empathy and remorse for behaviors [37••], and can occur under the specifier of "with limited prosocial emotions" in DSM-5's conduct disorder or can occur in the absence of conduct disorder [38, 39].

Reactive and proactive aggressions are highly correlated and often co-exist [1, 7•, 24, 34, 36]. In twin studies, research has suggested common genetic factors and non-shared environmental factors between proactive and reactive aggressions, and different shared environmental factors with proactive versus reactive aggression [7•].

Aggression as a Symptom

Though there is much literature on the treatment of aggression, it is important to emphasize that aggression is not a disorder in itself, but rather a symptom secondary to some other etiology or diagnostic entity [11]. Addressing aggression requires treating the underlying primary disorder, much like treating a fever requires assessing and attending to the underlying cause [3, 34, 41–44]. Some common causes of aggression in youth include attention deficit hyperactivity disorder (ADHD) [3, 15, 34], anxiety [3], mood disorders [3], conduct disorder (CD) [3, 15, 34], and oppositional defiant disorder (ODD) [3, 15]. Aggression is also often associated with trauma, regardless of whether full criteria for post-traumatic stress disorder are met [3, 24, 45, 46, 47•]. Aggression is a transdiagnostic entity [6, 10], and it should improve when the underlying cause is treated. If it does not, as with other psychiatric treatment, it is important to reassess the working diagnosis. Thus, the therapeutic treatment modality for aggression is different for each child and is based on the most likely contributing etiology.

Assessment of aggressive behaviors in youth should include thorough evaluation with the patient and parent prior to prescribing [48]. If clinically indicated, objective rating tools (see Table 1 for examples) and neuropsychological testing can be helpful for evaluation and monitoring of aggression [44, 48].

Psychiatric Diagnoses Associated with Aggression and Their Treatment

In this section, we will review common psychiatric diagnoses from which aggression may arise in youth, and discuss associated treatment modalities. The bulk of the aggression literature focuses on ADHD, ODD, and CD—thus, this is where the majority of the review will focus. To a lesser extent, other common considerations for aggression in youth will be reviewed, including disruptive mood dysregulation disorder (DMDD), anxiety, depression, sleep issues, and trauma. Of note, aggression can also occur due to substance use, autism

Table 1 Objective tools for evaluating and monitoring aggression [3, 52, 57]

Name	Acronym
Aberrant Behavior Checklist	ABC
Antisocial Behavior Scale	ABS
Brief Psychiatric Rating Scale–Children	BPRS-C
Buss-Perry Aggression Questionnaire	
Child Behavior Checklist	CBCL
Children's Aggression Scale	CAS
Children's Hostility Inventory	CHI
Children's Inventory of Anger	ChIA
Conners' Parent and Teacher Rating Scales	
Impulsive/Premeditated Aggression Scale	
Modified Overt Aggression Scale	M-OAS
Nisonger Child Behavior Rating Form	NCBRF
Outburst Monitoring Scale, Adolescent Anger Rating Scale	AARS
Pediatric Anger Expression Scale	PAES
Rating of Aggression Against People and Property	RAAPP

spectrum disorder, bipolar disorder, intellectual disability, psychosis, personality disorders, and medical and neurologic issues [3, 10, 15, 34, 49]—however, these topics are outside the scope of this review.

ADHD, ODD, and CD

Due to the extensive overlap in comorbidity and treatment, the diagnoses of ADHD, ODD, and CD will be reviewed together.

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is defined as an impairment in functioning due to inattention and/or hyperactivity-impulsivity [38]. ADHD is a common childhood disorder, with a reported 5% childhood prevalence [38], and is often a reason for seeking mental health services [50•]. Neurologically, children with ADHD show reduced total brain volume, possible delay in cortical maturation, and demonstrate increased slow waves on electroencephalograms [38]. ADHD symptomatology changes as children age—over time, hyperactivity transitions to restlessness and inattention becomes more prominent [38]. However, impulsivity typically remains a problem throughout the lifecycle [38]. There is high heritability in ADHD, and environmental risks include very low birth weight, maternal smoking and alcohol use during pregnancy, history of abuse, lead exposure, and infections [38].

Aggression has been often associated with ADHD, whether due to hyperactivity-impulsivity, a trait innate to with ADHD, or from a comorbid diagnosis [10, 37••, 41]. This is consistent with the impulsivity, hyperactivity, and difficulty with executive functioning that are core features of ADHD. There is evidence that aggression in childhood ADHD is more predictive of future criminality, rather than risk of criminality being due to the typical core symptoms of ADHD such as hyperactivity [13, 51]. Overall, if it is deemed that the underlying psychopathology in a child with aggression is ADHD, then treatment of ADHD (typically starting with a psychostimulant unless clinically contraindicated) should ensue [52••].

Oppositional Defiant Disorder (ODD)

ODD is a pattern of disruptiveness, behavioral problems, and vindictiveness [38]. ODD has an approximate prevalence of about 3.3% [38]. It is challenging to classify neurobiological attributes of ODD, as it is often combined in studies with CD [5, 38, 53•]. ODD is very highly comorbid with ADHD and CD [38, 50•, 54], and thus its treatment as discussed in this review will be related to those others disorders.

Conduct Disorder (CD)

CD is defined as a pattern of behavior that disregards societal rules and norms, and violates the basic rights of others [38]. CD is highly heritable and occurs with a prevalence of approximately 4% [38, 50•, 53•]. Peer relationships are typically limited in childhood onset CD (< 10 years old), but not in adolescent onset CD. Individuals with CD may have poor frustration tolerance, suspiciousness, and recklessness [38]. Early onset CD is more likely to continue into adulthood, and is more likely associated with criminality and substance use [38]. It is common for ODD to precede CD or co-occur with CD, and a little less than 50% of people with CD develop antisocial personality disorder [38]. CD is more likely to persist if there is an associated ADHD or substance abuse [38]. ADHD and ODD are commonly comorbid in CD, and predict a worse prognosis [38].

CD is associated with certain physiologic and neurologic changes. On the whole, autonomic responses are blunted in CD, including slower resting heart rate and low skin conductance [38]. However, when CD is associated with internalizing issues such as anxiety, the person tends to have autonomic hyper-arousal and dysregulation; this is in contrast to CD with callous-unemotional traits, when there is more often autonomic hypo-arousal [55].

Aggression is a common occurrence in CD [38]. Physical fighting, physical cruelty to people, and physical cruelty to animals are diagnostic criteria of CD [38]. Less than half of people with CD has the specifier of "with limited prosocial emotions," in which there may be lack of remorse or guilt, a callous lack of empathy, lack of concern about performance in important life activities, or a shallow deficient affect [38, 50•]. Limited prosocial emotions is often described as "callous and

unemotional (CU) traits" in the literature [38, 50•, 54]. Aggression is particularly common in childhood-onset CD and in CD with limited prosocial emotions [38]. CD can manifest with both proactive and reactive aggression [38]. Impulsivity is more related to reactive aggression in youth with CD, whereas CU traits are linked with proactive aggression in youth with CD [54, 56].

Treatment of ADHD, ODD, and CD

Psychotherapeutic techniques Psychotherapeutic interventions are an important first-line treatment of aggression in youth with ADHD, ODD, or CD, and should continue throughout care [5•, 43, 52••]. Evidence supports the use of group parent training, multisystem therapy (combining parent training, interpersonal skills, and classroom management), cognitive behavioral therapy (CBT), and brief family therapeutic interventions [50•, 57, 58, 59••]. These programs improve parent-child interactions, lead to more positive parenting styles, provide education on appropriate discipline, and improve communication [5•, 29•]. Evidence shows that interventions with a parent component, with or without other components, have the largest effect for the treatment of youth disruptive behavioral disorders [60•]. Psychological treatments can show small but significant improvement in CD, but a 2017 meta-analysis showed that no one form of psychological treatment was superior for the treatment of CD [61•]. Psychosocial interventions tend to have a less robust response for CU traits, though research is ongoing and certain strategies appear preferable for treating CU traits (i.e., emotion-regulation training in tandem with parent training had better response than parent training alone) [54].

Psychopharmacology After psychosocial interventions have been implemented, pharmacologic treatments should be considered for remaining symptoms [43, 52••]. Pharmacologic agents with notable evidence are reviewed here [52••].

For all of the following medication classes, refer to Table 2 for commonly used medications and dosage; refer to Table 3 for common and severe side effects to monitor during treatment; visit the United States Food and Drug Administration (FDA) and medication inserts for more details about specific medication warnings and contraindications, including black box warnings (https://www.fda.gov/).

Psychostimulants Psychostimulants act by increasing release and blocking reuptake of catecholamines, mainly norepinephrine and dopamine [62]. Stimulants are available in short and long acting formulations, and are effective first-line treatments for ADHD [40, 41, 63]. Stimulants are also effective for the treatment of ADHD in the context of oppositional behaviors, conduct problems, and aggression, whether or not there is a formal diagnosis of ODD or CD [2, 52••, 64]. Methylphenidate and amphetamine preparations have similar efficacy and side effect profiles [41, 52••]. It is recommended to optimize stimulant dosing, and to trial the alternate stimulant class, prior to starting other medications [52••].

In the landmark 14-month Multimodal Treatment of ADHD study, it was shown that children in the combined treatment of medication (methylphenidate) and intensive behavioral treatment group and in the medication (methylphenidate)-only group showed significant improvement over the intensive behavioral treatment alone group or community care medication group [63]. The combined group may have had greater secondary improvements (such as functionality and aggression) compared to the medication only group [63]. Thus, optimized treatment of ADHD should include both psychotherapeutic interventions and medication.

In a 2013 study, pretreatment callous-unemotional traits and proactive aggression were reported to decrease in children with ADHD and CD or ODD treated with optimized stimulant medication regimen and family-focused behavioral interventions [37••]. However, a 2018 systematic review and meta-analysis of the treatment of CD reports that there is not enough evidence to determine the effect of CU on pharmacologic treatment [65••].

Guanfacine and Clonidine (alpha-2 agonists) Guanfacine and clonidine are alpha-2 adrenergic agonists at presynaptic receptors [62]. Both of these medications can be a useful second-line treatments for ADHD [66–68••]. These medications have also been shown to have some benefit in treating oppositional behavior in youth with ADHD, with or without formal ODD or CD diagnosis, either in monotherapy or combined with a stimulant [62••, 69]. Guanfacine or clonidine can be considered for monotherapy when stimulants did not prove beneficial or when stimulant side effects were intolerable, and can be considered in combination when stimulants have provided partial improvement [52••]. Both medications are available in short and long acting formulations [40].

Atomoxetine (Norepinephrine Reuptake Inhibitor) Atomoxetine is a selective norepinephrine reuptake inhibitor [62]. Atomoxetine may be a useful second- or third-line treatment for ADHD [66, 68••, 70••]. Atomoxetine has been shown to have some benefit in treating oppositional behavior in youth with ADHD, with or without formal ODD or CD diagnosis [52••, 70••]. Atomoxetine can be considered after patients have inadequate response to stimulants or could not tolerate stimulants [52••].

Risperidone (Atypical Antipsychotic) After treating a youth's primary disorder with medication and therapy, the use of an antipsychotic may be indicated [9••, 43, 44, 71]. Among the antipsychotics, risperidone has the most data supporting its use in the treatment of aggression in youth [9••, 52••, 71,

Table 2 Dosing information for selected medications in the treatment of youth aggression [48, 62••]

Medication class	Generic name	Brand name	Typical dosage range
Psychostimulants	Dexmethylphenidate	Focalin, Focalin XR	5–30 mg/day
	Dextroamphetamine	Dexedrine, ProCentra, Zenzedi	2.5–40 mg/day
	Lisdexamphetamine	Vyvanse	20–70 mg/day
	Methylphenidate	Ritalin, Ritalin LA, Metadate, Metadate CR, Methylin, Quillivant XR	5–60 mg/day
	Methylphenidate OROS	Concerta	1–72 mg/day
	Methylphenidate, transdermal	Daytrana	10–30 mg/9h
	Mixed amphetamine salts	Adderall, Adderall XR, Evekeo	2.5–40 mg/day
Norepinephrine reuptake inhibitor	Atomoxetine	Strattera	40–100 mg/day
Alpha-2 agonists	Clonidine	Catapres, Kapvay	0.025–0.4 mg/day
	Guanfacine	Tenex, Intuniv	0.5–4 mg/day
Atypical antipsychotic	Risperidone	Risperdal	0.5–4 mg/day

72••]. Risperidone is an atypical antipsychotic that is a dopamine-2 (D2) receptor antagonist and also has effects on other neurotransmitters including serotonin [73]. If risperidone is ineffective, there is limited evidence for the use of other antipsychotics, except possibly for aripiprazole [9••, 71]. Risperidone has good evidence and may be considered an option for treating disruptive and aggressive behavior in youth with ODD or CD with average IQ, with or without ADHD [52••, 71]. When an antipsychotic is deemed clinically necessary, it should be trialed on a short-term (< 3 month) basis, with attempts to wean off over weeks to months when behaviors are under control [71].

In the Treatment of Severe Childhood Aggression (TOSCA) study, it was shown that the addition of risperidone was superior to parent training and stimulant alone in the 9-week treatment of aggression in youth with ADHD and ODD or CD, though the benefit in the non-risperidone group was still significant [64, 74•]. Further, those who improved in either group in the original trial continued to have symptom improvement out to 21 weeks, but there were no between group differences in many clinical outcome measures [75]. Thus, the combination of stimulant and risperidone can cautiously be considered in particularly refractive cases after initial stimulant and psychosocial treatment [64]. Of note, the TOSCA study showed improvement in reactive aggression in the risperidone-augmented group compared to the basic group, but there was no significant treatment effect for proactive aggression [74•].

Disruptive Mood Dysregulation Disorder (DMDD)

DMDD is characterized by temper outbursts with associated verbal or physical aggression, in the context of persistent irritable or angry mood between temper outbursts [38]. DMDD was added in DSM-5, in part, in response to a perceived over diagnosis of bipolar spectrum disorders in youth [76••, 77]. Given that DMDD is a new diagnosis, its prevalence is unclear [38]. Risk factors for developing DMDD are maternal perinatal depression, malnutrition, trauma, and disrupted parental unit [76••]. Youth with DMDD has elevated risk of developing anxiety and unipolar depression in adulthood, having long-term occupational issues, acting in risky or illegal ways, suicidality, worsened health, substance use, risky sexual behaviors, and higher sexually transmitted diseases [38, 76••]. Neurobiologically, DMDD appears to be related to overactivation of the amygdala [76••]. DMDD is often comorbid with ADHD, CD, anxiety disorders, or major depression [38, 76••].

Psychotherapeutic interventions, such as parent training and behavioral therapy, are critical in the treatment of DMDD [76••]. The current understanding of the pharmacologic treatment of DMDD is by targeting core symptoms of irritability and aggression through medications such as selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SNRIs), and psychostimulants [76••, 78, 77]. If treatment response is not achieved with these medications, then other medications to consider are alpha-2 agonists, atypical antipsychotics, other antidepressants, and mood stabilizers [76••]. There is unfortunately minimal guidance in the current literature regarding treatment of DMDD beyond specifically targeting problematic symptoms, such as aggression and irritability, with medications shown to be effective for these symptoms in other disorders [76••].

Anxiety

Anxiety disorders are the most common psychiatric disorders in youth [79••]. Aggression is often comorbid with anxiety disorders [80–82]. However, anxiety is often an unrecognized phenomena, both in the clinical conceptualization of aggression and in its treatment [82]. Parent-child relational problems,

Table 3 Selected possible side effects in common medications used in the treatment of youth aggression [48, 49, 62••, 71••, 83•, 85••, 87]

	Psychostimulants	Alpha-2 agonists	Norepinephrine Reuptake Inhibitor	Atypical Antipsychotics
Cardiac	Heart palpitations, tachycardia, angina, increased blood pressure, increased heart rate	Rebound tachycardia and hypertension with abrupt discontinuation, hypotension or decreased blood pressure, decreased heart rate, changes in QTc interval	Myocardial infarction (rare)	Tachycardia, hypotension, syncope, changes in QTc interval, torsades de pointes
Gastrointestinal	Anorexia, abdominal pain, hepatotoxicity (rare)	Dry mouth, abdominal pain	Decreased appetite, nausea/vomiting, hepatotoxicity and severe hepatic injury (rare)	Dry mouth, dyspepsia, nausea/vomiting, constipation, diarrhea, liver enzyme changes
Metabolic	Weight loss, long-term growth suppression	N/A	N/A	Hyperglycemia, diabetes mellitus, weight gain, cholesterol and triglyceride abnormalities, changes in insulin
Miscellaneous	Fever, rash, urticarial, leukopenia, thrombocytopenia purpura, neuroleptic malignant syndrome (rare), erythema multiforme (rare), exfoliative dermatitis (rare)	N/A	Urinary frequency, sudden death (rare)	Rhinitis
Movement	Motor tics or Tourette's syndrome (rare, conflicting evidence)	N/A	N/A	Extrapyramidal symptoms, including parkinsonism, tardive dyskinesia or dystonia, and akathisia
Neurologic	Headache, blurred vision, dizziness, seizures, cerebral arteritis (rare)	Dizziness, headache, syncope (rare)	Stroke (rare)	Headache, dizziness, visual disturbance, seizures, stroke, transient ischemic attack
Psychiatric	Nervousness, depression, psychosis, dependency/abuse	Irritability, dysphoria, agitation	Suicidal ideation (rare), dysphoria (rare), irritability (rare), severe mood lability (rare), hallucinations (rare), mania (rare), aggression	Agitation, anxiety, neuroleptic malignant syndrome
Hormonal and sexual	N/A	N/A	N/A	Thyroid dysfunction, elevated prolactin, gynecomastia, galactorrhea, menstrual irregularities, infertility, sexual dysfunction, priapism
Sleep	Insomnia	Fatigue, somnolence	Fatigue, somnolence	Insomnia, somnolence, increased dream activity

impaired peer relationships, strained friendships, and rate of teacher turnover have been found to be correlated with aggression and anxiety in a study of rural low-income youth [80]. Interestingly, a secondary analysis of the aforementioned TOSCA study showed that the risperidone group had improvements in anxiety which were found to mediate the improvement in the disruptive behavior disorders [83•].

First-line treatment interventions for anxiety disorders in youth include SSRIs and CBT [79••, 84]. Combined medication and CBT has been demonstrated to be superior to either treatment alone [79••]. For a review on the evaluation and treatment of anxiety in youth, please see the 2015 article by Strawn et al. from this journal [85].

Depression

Aggression and oppositionality can occur in the context of depression in youth [3, 81•, 86, 87]. Aggression related to underlying depression can show improvement with treatment with an SSRI and/or CBT [3, 87]. Further details about the treatment of depression is outside of the scope of this review.

Trauma

Trauma is a common issue encountered in youth seeking mental health treatment. Having a history of trauma can complicate almost any other comorbid psychiatric issue and is correlated with aggression in youth [45, 47•]. Aggressive behaviors are symptoms of post-traumatic stress disorder and traumatized youth demonstrate hormonal and structural neurologic changes that may lead to increased aggressive behaviors [24, 46, 47•]. There are no psychiatric medications currently approved for the treatment of the effects of trauma and traumatic disorders in youth. However, it is important to be aware of a child having a history of trauma, to guide the conceptualization of the clinical picture.

Conclusions

Aggression is a common and detrimental symptom experienced in youth. It is important to conceptualize chronic aggression as a trans-diagnostic symptom in psychiatric pathology, rather than as a disorder in and of itself or as a specific treatment target. The most important step in the treatment of aggression is to determine the underlying psychiatric disorder from which the aggression is stemming. It is expected that with the treatment of the underlying disorder, the aggression will improve. As with other aspects of psychiatric treatment, if symptoms are not improving with appropriate treatment of a disorder, it is important to reconsider the clinical diagnosis and adjust treatment accordingly.

Further research is needed to better understand the cause and treatment of aggression in youth. With the understanding that aggression is a symptom of a variety of disorders, further research is needed to understand what puts youth at risk with underlying impulsive, mood, and anxiety disorders to develop aggression as one of their symptoms. Further developing an understanding of the neurobiologic, psychological, and environmental risks that a youth with underlying mood, anxiety, or impulsive disorders have that go on to develop maladaptive aggression is needed to personalize the treatment and evaluation of these youths.

From a systems perspective, because of the shortage of child psychiatrists and the complexity of aggression in youth, further collaboration with general pediatrician colleagues and adult psychiatrists who may see older adolescents and transitional age youth is needed. Without ongoing collaboration and education regarding the complex issues related to aggression in youth, these at risk children continue to wait for appointments with the most under-served medical specialty in the USA.

Overall, the medical profession can contribute to improved treatment of aggression in youth by expanding the literature via research, taking measures to improve access to care, and judicious prescribing. The effort is worthwhile for these vulnerable youth, their futures, their families, and society.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Smeets KC, Oostermeijer S, Lappenschaar M, Cohn M, van der Meer JM, Popma A, et al. Are proactive and reactive aggression meaningful distinctions in adolescents? A variable- and person-based approach. J Abnorm Child Psychol. 2017;45(1):1–14. https://doi.org/10.1007/s10802-016-0149-5.
2. Saylor KE, Amann BH. Impulsive aggression as a comorbidity of attention-deficit/hyperactivity disorder in children and adolescents. J Child Adolesc Psychopharmacol. 2016;26(1):19–25. https://doi.org/10.1089/cap.2015.0126.
3. Gurnani T, Ivanov I, Newcorn JH. Pharmacotherapy of aggression in child and adolescent psychiatric disorders. J Child Adolesc Psychopharmacol. 2016;26(1):65–73. https://doi.org/10.1089/cap.2015.0167.

4. Tremblay RE, Vitaro F, Cote SM. Developmental origins of chronic physical aggression: a bio-psycho-social model for the next generation of preventive interventions. Annu Rev Psychol. 2018;69:383–407. https://doi.org/10.1146/annurev-psych-010416-044030.
5.• Tandon M, Giedinghagen A. Disruptive behavior disorders in children 0 to 6 years old. Child Adolesc Psychiatr Clin N Am. 2017;26(3):491–502. https://doi.org/10.1016/j.chc.2017.02.005. **This article reviews the genetics, neurobiology, environmental risks, and treatment of disruptive behavior disorders in 0-6 year olds.**
6. Pappa I, St Pourcain B, Benke K, Cavadino A, Hakulinen C, Nivard MG, et al. A genome-wide approach to children's aggressive behavior: the EAGLE consortium. Am J Med Genet B Neuropsychiatr Genet. 2016;171(5):562–72. https://doi.org/10.1002/ajmg.b.32333.
7.• Paquin S, Lacourse E, Brendgen M, Vitaro F, Dionne G, Tremblay RE, et al. Heterogeneity in the development of proactive and reactive aggression in childhood: common and specific genetic-environmental factors. PLoS One. 2017;12(12):e0188730. https://doi.org/10.1371/journal.pone.0188730. **This twin study examined the genetic and environmental factors contributing to the development of proactive versus reactive aggression.**
8. Fernandez-Castillo N, Cormand B. Aggressive behavior in humans: Genes and pathways identified through association studies. Am J Med Genet B Neuropsychiatr Genet. 2016;171(5):676–96. https://doi.org/10.1002/ajmg.b.32419.
9.• van Schalkwyk GI, Lewis AS, Beyer C, Johnson J, van Rensburg S, Bloch MH. Efficacy of antipsychotics for irritability and aggression in children: a meta-analysis. Expert Rev Neurother. 2017;17(10):1045–53. https://doi.org/10.1080/14737175.2017.1371012. **This meta-analysis supports the efficacy of risperidone and aripiprazole for treatment of youth aggression and irritability across diagnoses.**
10. Pompili E, Carlone C, Silvestrini C, Nicolo G. Focus on aggressive behaviour in mental illness. Rivista di psichiatria. 2017;52(5):175–9. https://doi.org/10.1708/2801.28344.
11. Asherson P, Cormand B. The genetics of aggression: where are we now? Am J Med Genet B Neuropsychiatr Genet. 2016;171(5):559–61. https://doi.org/10.1002/ajmg.b.32450.
12. Waltes R, Chiocchetti AG, Freitag CM. The neurobiological basis of human aggression: a review on genetic and epigenetic mechanisms. Am J Med Genet B Neuropsychiatr Genet. 2016;171(5):650–75. https://doi.org/10.1002/ajmg.b.32388.
13. Broidy LM, Nagin DS, Tremblay RE, Bates JE, Brame B, Dodge KA, et al. Developmental trajectories of childhood disruptive behaviors and adolescent delinquency: a six-site, cross-national study. Dev Psychol. 2003;39(2):222–45.
14.• Hendricks KLJ. Maternal depression and childhood aggression: literature review. MCN Am J Matern Child Nurs. 2012;37(4):253–61. https://doi.org/10.1097/NMC.0b013e3182482c5e. **This twin study examined brain morphology differences in proactive and reactive aggression.**
15. Yang Y, Joshi SH, Jahanshad N, Thompson PM, Baker LA. Neural correlates of proactive and reactive aggression in adolescent twins. Aggress Behav. 2017;43(3):230–40. https://doi.org/10.1002/ab.21683.
16. Hart SR, Van Eck K, Ballard ED, Musci RJ, Newcomer A, Wilcox HC. Subtypes of suicide attempters based on longitudinal childhood profiles of co-occurring depressive, anxious and aggressive behavior symptoms. Psychiatry Res. 2017;257:150–5. https://doi.org/10.1016/j.psychres.2017.07.032.
17. Pringsheim T, Andrade B, Doja A, Gorman DA. Assessment and treatment of oppositional behaviour, conduct problems, and aggression in children and adolescents: creation and dissemination of a national curriculum. Can J Psychiatry. 2017;62(6):431–2. https://doi.org/10.1177/0706743716679818.
18. Coccaro EF, Sripada CS, Yanowitch RN, Phan KL. Corticolimbic function in impulsive aggressive behavior. Biol Psychiatry. 2011;69(12):1153–9. https://doi.org/10.1016/j.biopsych.2011.02.032.
19.•• Veroude K, Zhang-James Y, Fernandez-Castillo N, Bakker MJ, Cormand B, Faraone SV. Genetics of aggressive behavior: an overview. Am J Med Genet B Neuropsychiatr Genet. 2016;171b(1):3–43. https://doi.org/10.1002/ajmg.b.32364. **This article provides a comprehensive review of the heritability of aggression, including twin studies, candidate genes, and genome wide association studies.**
20. Tuvblad C, Baker LA. Human aggression across the lifespan: genetic propensities and environmental moderators. Adv Genet. 2011;75:171–214. https://doi.org/10.1016/B978-0-12-380858-5.00007-1.
21. Tucker-Drob EM, Harden KP. Gene-by-preschool interaction on the development of early externalizing problems. J Child Psychol Psychiatry Allied Discip. 2013;54(1):77–85. https://doi.org/10.1111/j.1469-7610.2012.02578.x.
22. Fujisawa KK, Yamagata S, Ozaki K, Ando J. Hyperactivity/inattention problems moderate environmental but not genetic mediation between negative parenting and conduct problems. J Abnorm Child Psychol. 2012;40(2):189–200. https://doi.org/10.1007/s10802-011-9559-6.
23. Porsch RM, Middeldorp CM, Cherny SS, Krapohl E, van Beijsterveldt CE, Loukola A, et al. Longitudinal heritability of childhood aggression. Am J Med Genet B Neuropsychiatr Genet. 2016;171(5):697–707. https://doi.org/10.1002/ajmg.b.32420.
24. Rosell DR, Siever LJ. The neurobiology of aggression and violence. CNS Spectr. 2015;20(3):254–79. https://doi.org/10.1017/S109285291500019X.
25.• de Boer SF, Olivier B, Veening J, Koolhaas JM. The neurobiology of offensive aggression: revealing a modular view. Physiol Behav. 2015;146:111–27. https://doi.org/10.1016/j.physbeh.2015.04.040. **This article provides a very detailed description of the neurobiology of aggression in animals and humans.**
26. Olivier B. Serotonin: a never-ending story. Eur J Pharmacol. 2015;753:2–18. https://doi.org/10.1016/j.ejphar.2014.10.031.
27. Hagenbeek FA, Kluft C, Hankemeier T, Bartels M, Draisma HH, Middeldorp CM, et al. Discovery of biochemical biomarkers for aggression: a role for metabolomics in psychiatry. Am J Med Genet B Neuropsychiatr Genet. 2016;171(5):719–32. https://doi.org/10.1002/ajmg.b.32435.
28. de Jong TR, Neumann ID. Oxytocin and Aggression. Curr Top Behav Neurosci. 2018;35:175–92. https://doi.org/10.1007/7854_2017_13.
29.• Labella MH, Masten AS. Family influences on the development of aggression and violence. Curr Opin Psychol. 2018;19:11–6. https://doi.org/10.1016/j.copsyc.2017.03.028. **This article provides a detailed overview of familial environmental factors affecting the risk of aggression in youth**.
30. Romero E, Richards MH, Harrison PR, Garbarino J, Mozley M. The role of neighborhood in the development of aggression in urban African American youth: a multilevel analysis. Am J Community Psychol. 2015;56(1-2):156–69. https://doi.org/10.1007/s10464-015-9739-6.
31. Hentges RF, Shaw DS, Wang MT. Early childhood parenting and child impulsivity as precursors to aggression, substance use, and risky sexual behavior in adolescence and early adulthood. Dev Psychopathol. 2018;30(4):1305–19. https://doi.org/10.1017/S0954579417001596.
32. Ferguson CJ, Kilburn J. The public health risks of media violence: a meta-analytic review. J Pediatr. 2009;154(5):759–63. https://doi.org/10.1016/j.jpeds.2008.11.033.
33. Anderson CA, Shibuya A, Ihori N, Swing EL, Bushman BJ, Sakamoto A, et al. Violent video game effects on aggression,

empathy, and prosocial behavior in eastern and western countries: a meta-analytic review. Psychol Bull. 2010;136(2):151–73. https://doi.org/10.1037/a0018251.

34. Vitiello B, Stoff DM. Subtypes of aggression and their relevance to child psychiatry. J Am Acad Child Adolesc Psychiatry. 1997;36(3):307–15. https://doi.org/10.1097/00004583-199703000-00008.
35. Hartley CM, Pettit JW, Castellanos D. Reactive aggression and suicide-related behaviors in children and adolescents: a review and preliminary meta-analysis. Suicide Life Threat Behav. 2018;48(1):38–51. https://doi.org/10.1111/sltb.12325.
36. Polman H, Orobio de Castro B, Koops W, van Boxtel HW, Merk WW. A meta-analysis of the distinction between reactive and proactive aggression in children and adolescents. J Abnorm Child Psychol. 2007;35(4):522–35. https://doi.org/10.1007/s10802-007-9109-4.
37.•• Blader JC, Pliszka SR, Kafantaris V, Foley CA, Crowell JA, Carlson GA, et al. Callous-unemotional traits, proactive aggression, and treatment outcomes of aggressive children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2013;52(12):1281–93. https://doi.org/10.1016/j.jaac.2013.08.024. **This study showed that pretreatment CU traits and proactive aggression declined in youth with aggression who had ADHD, CD, or ODD that were treated with stimulants and family-focused behavioral interventions.**
38. American Psychiatric A. Diagnostic and statistical manual of mental disorders. Arlington: American Psychiatric Publishing; 2013.
39. Eisenbarth H, Demetriou CA, Kyranides MN, Fanti KA. Stability subtypes of callous-unemotional traits and conduct disorder symptoms and their correlates. J Youth Adolesc. 2016;45(9):1889–901. https://doi.org/10.1007/s10964-016-0520-4.
40. Zaraa SGCN, Pappadopulus E, Jensen PS. Disruptive behavior disorders and aggression. In: McVoy MFR, editor. Clinical Manual of Child and Adolescent Psychopharmacology. Arlington: American Psychiatric Association Publishing; 2017.
41. Patel BD, Barzman DH. Pharmacology and pharmacogenetics of pediatric ADHD with associated aggression: a review. Psychiatr Q. 2013;84(4):407–15. https://doi.org/10.1007/s11126-013-9253-7.
42. Robb AS, Schwabe S, Ceresoli-Borroni G, Nasser A, Yu C, Marcus R, et al. A proposed anti-maladaptive aggression agent classification: improving our approach to treating impulsive aggression. Postgrad Med. 2019;131(2):129–37. https://doi.org/10.1080/00325481.2019.1574401.
43. Scotto Rosato N, Correll CU, Pappadopulos E, Chait A, Crystal S, Jensen PS, et al. Treatment of maladaptive aggression in youth: CERT guidelines II. Treatments and ongoing management. Pediatrics. 2012;129(6):e1577–86. https://doi.org/10.1542/peds.2010-1361.
44. Pappadopulos E, Macintyre Ii JC, Crismon ML, Findling RL, Malone RP, Derivan A, et al. Treatment recommendations for the use of antipsychotics for aggressive youth (TRAAY). Part II. J Am Acad Child Adolesc Psychiatry. 2003;42(2):145–61.
45. Nuttman-Shwartz O. Children and adolescents facing a continuous security threat: aggressive behavior and post-traumatic stress symptoms. Child Abuse Negl. 2017;69:29–39. https://doi.org/10.1016/j.chiabu.2017.04.008.
46. Aebi M, Mohler-Kuo M, Barra S, Schnyder U, Maier T, Landolt MA. Posttraumatic stress and youth violence perpetration: a population-based cross-sectional study. Eur Psychiatry. 2017;40:88–95. https://doi.org/10.1016/j.eurpsy.2016.08.007.
47.• Fragkaki I, Cima M, Granic I. The role of trauma in the hormonal interplay of cortisol, testosterone, and oxytocin in adolescent aggression. Psychoneuroendocrinology. 2018;88:24–37. https://doi.org/10.1016/j.psyneuen.2017.11.005. **This article describes the hormonal effects of trauma and its hypothesized relation with aggression.**
48. Knapp P, Chait A, Pappadopulos E, Crystal S, Jensen PS, Group TMS. Treatment of maladaptive aggression in youth: CERT guidelines I. Engagement, assessment, and management. Pediatrics. 2012;129(6):e1562–76. https://doi.org/10.1542/peds.2010-1360.
49. Austerman J. Violence and aggressive behavior. Pediatr Rev. 2017;38(2):69–80. https://doi.org/10.1542/pir.2016-0062.
50.• Blair RJ, Leibenluft E, Pine DS. Conduct disorder and callous-unemotional traits in youth. N Engl J Med. 2014;371(23):2207–16. https://doi.org/10.1056/NEJMra1315612. **This article reviews the biology of CD and CU, and includes related descriptions of often co-occurring psychopathology.**
51. Pingault JB, Cote SM, Lacourse E, Galera C, Vitaro F, Tremblay RE. Childhood hyperactivity, physical aggression and criminality: a 19-year prospective population-based study. PLoS One. 2013;8(5):e62594. https://doi.org/10.1371/journal.pone.0062594.
52.•• Gorman DA, Gardner DM, Murphy AL, Feldman M, Belanger SA, Steele MM, et al. Canadian guidelines on pharmacotherapy for disruptive and aggressive behaviour in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, or conduct disorder. Can J Psychiatry. 2015;60(2):62–76. https://doi.org/10.1177/070674371506000204. **This article provides the evidence based on systematic review and meta-analyses for the pharmacologic treatment of aggression in youth with ADHD, ODD, or CD.**
53.• Noordermeer SD, Luman M, Oosterlaan J. A systematic review and meta-analysis of neuroimaging in oppositional defiant disorder (ODD) and conduct disorder (CD) taking attention-deficit hyperactivity disorder (ADHD) into account. Neuropsychol Rev. 2016;26(1):44–72. https://doi.org/10.1007/s11065-015-9315-8. **This systematic review and meta-analysis showed neuroanatomy differences in individuals with ODD or CD, irrespective of comorbid ADHD diagnosis**.
54. Hawes DJ. Disruptive behaviour disorders and DSM-5. Asian J Psychiatr. 2014;11:102–5. https://doi.org/10.1016/j.ajp.2014.06.002.
55. Fanti KA. Understanding heterogeneity in conduct disorder: areview of psychophysiological studies. Neurosci Biobehav Rev. 2018;91:4–20. https://doi.org/10.1016/j.neubiorev.2016.09.022.
56. Urben S, Habersaat S, Pihet S, Suter M, de Ridder J, Stephan P. Specific contributions of age of onset, callous-unemotional traits and impulsivity to reactive and proactive aggression in youths with conduct disorders. Psychiatr Q. 2018;89(1):1–10. https://doi.org/10.1007/s11126-017-9506-y.
57. Sukhodolsky DG, Smith SD, McCauley SA, Ibrahim K, Piasecka JB. Behavioral interventions for anger, irritability, and aggression in children and adolescents. J Child Adolesc Psychopharmacol. 2016;26(1):58–64. https://doi.org/10.1089/cap.2015.0120.
58. Battagliese G, Caccetta M, Luppino OI, Baglioni C, Cardi V, Mancini F, et al. Cognitive-behavioral therapy for externalizing disorders: a meta-analysis of treatment effectiveness. Behav Res Ther. 2015;75:60–71. https://doi.org/10.1016/j.brat.2015.10.008.
59.•• Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry. 2015;60(2):52–61. https://doi.org/10.1177/070674371506000203. **This article provides a systematic review and meta-analysis for the management of aggression, conduct problems, and oppositional behaviors in youth with ADHD using antipsychotics and mood stabilizers.**
60.• Epstein RA, Fonnesbeck C, Potter S, Rizzone KH, McPheeters M. Psychosocial Interventions for child disruptive behaviors: a meta-analysis. Pediatrics. 2015;136(5):947–60. https://doi.org/10.1542/peds.2015-2577. **This systematic review showed that**

interventions including a parent component had the largest effect on the treatment of disruptive behavioral disorders.

61.• Bakker MJ, Greven CU, Buitelaar JK, Glennon JC. Practitioner review: pychological treatments for children and adolescents with conduct disorder problems - a systematic review and meta-analysis. J Child Psychol Psychiatry Allied Discip. 2017;58(1):4–18. https://doi.org/10.1111/jcpp.12590. **This meta-analysis showed that psychological treatments have a small effect on CD, but that there is not enough evidence to support one specific psychological treatment over another.**

62. Falkowitz SAN, Greenhill L. Attention deficit/hyperactivity disorder. In: FR MVM, editor. Clinical Manual of Child and Adolescent Psychopharmacology. Arlington: American Psychiatric Association Publishing; 2017.

63. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal treatment study of children with ADHD. Arch Gen Psychiatry. 1999;56(12):1073–86. https://doi.org/10.1001/archpsyc.56.12.1073.

64. Gadow KD, Arnold LE, Molina BS, Findling RL, Bukstein OG, Brown NV, et al. Risperidone added to parent training and stimulant medication: effects on attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, and peer aggression. J Am Acad Child Adolesc Psychiatry. 2014;53(9):948–59.e1. https://doi.org/10.1016/j.jaac.2014.05.008.

65.•• Balia C, Carucci S, Coghill D, Zuddas A. The pharmacological treatment of aggression in children and adolescents with conduct disorder. Do callous-unemotional traits modulate the efficacy of medication? Neurosci Biobehav Rev. 2018;91:218–38. https://doi.org/10.1016/j.neubiorev.2017.01.024. **This systematic review and meta-analysis shows methylphenidate and risperidone having the largest effects on aggression in CD, and discusses the limited evidence on the effects of CU traits on treatment.**

66. Li Y, Gao J, He S, Zhang Y, Wang Q. An evaluation on the efficacy and safety of treatments for attention deficit hyperactivity disorder in children and adolescents: a comparison of multiple treatments. Mol Neurobiol. 2017;54(9):6655–69. https://doi.org/10.1007/s12035-016-0179-6.

67.• Ruggiero S, Clavenna A, Reale L, Capuano A, Rossi F, Bonati M. Guanfacine for attention deficit and hyperactivity disorder in pediatrics: a systematic review and meta-analysis. Eur Neuropsychopharmacol : the journal of the European College of Neuropsychopharmacology. 2014;24(10):1578–90. https://doi.org/10.1016/j.euroneuro.2014.08.001. **This systematic review and meta-analysis showed that guanfacine is safe and effective for the treatment of youth ADHD.**

68.•• Chan E, Fogler JM, Hammerness PG. Treatment of attention-deficit/hyperactivity disorder in adolescents: a systematic review. JAMA. 2016;315(18):1997–2008. https://doi.org/10.1001/jama.2016.5453. **This systematic review shows that methylphenidate ER, amphetamine ER, atomoxetine, guanfacine ER in the treatment of adolescent ADHD.**

69. Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. J Am Acad Child Adolesc Psychiatry. 2003;42(8):886–94. https://doi.org/10.1097/01.CHI.0000046908.27264.00.

70.•• Schwartz S, Correll CU. Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: results from a comprehensive meta-analysis and metaregression. J Am Acad Child Adolesc Psychiatry. 2014;53(2):174–87. https://doi.org/10.1016/j.jaac.2013.11.005. **This meta-analysis and meta-regression shows that short-term use of atomoxetine is superior to placebo in ADHD.**

71. Shafiq S, Pringsheim T. Using antipsychotics for behavioral problems in children. Expert Opin Pharmacother. 2018;19(13):1475–88. https://doi.org/10.1080/14656566.2018.1509069.

72.•• Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 1: psychostimulants, alpha-2 agonists, and atomoxetine. Can J Psychiatry. 2015;60(2):42–51. https://doi.org/10.1177/070674371506000202. **This article provides a systematic review and meta-analysis for the management of aggression, conduct problems, and oppositional behaviors in youth with ADHD using psychostimulants, alpha-2 agonists, and atomoxetine.**

73. Craddock KDC, Driver DI, Gogtay N, Rapoport JL. Early-onset schizophrenia and psychotic illnesses. In: McVoy MFR, editor. Clinical manual of child and adolescent psychopharmacology. Arlington: American Psychiatric Association Publishing; 2017.

74.• Aman MG, Bukstein OG, Gadow KD, Arnold LE, Molina BS, McNamara NK, et al. What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/hyperactivity disorder? J Am Acad Child Adolesc Psychiatry. 2014;53(1):47–60 e1. https://doi.org/10.1016/j.jaac.2013.09.022. **This is the original TOSCA study, showing that augmented treatment with risperidone showed better improvement in aggression than stimulant and parent training alone when studying youth with ADHD with either ODD or CD.**

75. Findling RL, Townsend L, Brown NV, Arnold LE, Gadow KD, Kolko DJ, et al. The treatment of severe childhood aggression study: 12 weeks of extended, blinded treatment in clinical responders. J Child Adolesc Psychopharmacol. 2017;27(1):52–65. https://doi.org/10.1089/cap.2016.0081.

76.•• Bruno A, Celebre L, Torre G, Pandolfo G, Mento C, Cedro C, et al. Focus on disruptive mood dysregulation disorder: a review of the literature. Psychiatry Res. 2019. https://doi.org/10.1016/j.psychres.2019.05.043. **This article review the background, comorbidity, risks, consequences, and treatment options for DMDD**.

77. Tourian L, LeBoeuf A, Breton JJ, Cohen D, Gignac M, Labelle R, et al. Treatment options for the cardinal symptoms of disruptive mood dysregulation disorder. J Can Acad Child Adolesc Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent. 2015;24(1):41–54.

78. Blader JC, Pliszka SR, Kafantaris V, Sauder C, Posner J, Foley CA, et al. Prevalence and treatment outcomes of persistent negative mood among children with attention-deficit/hyperactivity disorder and aggressive behavior. J Child Adolesc Psychopharmacol. 2016;26(2):164–73. https://doi.org/10.1089/cap.2015.0112.

79.•• Wang Z, Whiteside SPH, Sim L, Farah W, Morrow AS, Alsawas M, et al. Comparative effectiveness and safety of cognitive behavioral therapy and pharmacotherapy for childhood anxiety disorders: a systematic review and meta-analysis. JAMA Pediatr. 2017;171(11):1049–56. https://doi.org/10.1001/jamapediatrics.2017.3036. **This systematic review and meta-analysis showed that CBT and SSRIs (and also SNRIs, but with less consistent evidence) are effective for youth anxiety.**

80. Smokowski PR, Cotter KL, Robertson CI, Guo S. Anxiety and aggression in rural youth: baseline results from the rural adaptation project. Child Psychiatry Hum Dev. 2013;44(4):479–92. https://doi.org/10.1007/s10578-012-0342-x.

81.• Bilgic A, Tufan AE, Yilmaz S, Ozcan O, Ozmen S, Oztop D, et al. Association of reactive-proactive aggression and anxiety sensitivity with internalizing and externalizing symptoms in children with attention-deficit/hyperactivity disorder. Child Psychiatry Hum Dev. 2017;48(2):283–97. https://doi.org/10.1007/s10578-016-0640-9. **This study examines youth with ADHD and the effect/type of aggression in the context of anxiety, depression, and anxiety sensitivity.**

82. Granic I. The role of anxiety in the development, maintenance, and treatment of childhood aggression. Dev Psychopathol. 2014;26(4 Pt 2):1515–30. https://doi.org/10.1017/S0954579414001175.
83.• Arnold LE, Gadow KD, Farmer CA, Findling RL, Bukstein O, Molina BSG, et al. Comorbid anxiety and social avoidance in treatment of severe childhood aggression: response to adding risperidone to stimulant and parent training; mediation of disruptive symptom response. J Child Adolesc Psychopharmacol. 2015;25(3):203–12. https://doi.org/10.1089/cap.2014.0104. **This study showed that improvement in disruptive behavior disorders in the augmented TOSCA group was mediated by improvement in anxiety.**
84. Strawn JR, Welge JA, Wehry AM, Keeshin B, Rynn MA. Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. Depress Anxiety. 2015;32(3):149–57. https://doi.org/10.1002/da.22329.
85. Wehry AM, Beesdo-Baum K, Hennelly MM, Connolly SD, Strawn JR. Assessment and treatment of anxiety disorders in children and adolescents. Curr Psychiatry Rep. 2015;17(7):52. https://doi.org/10.1007/s11920-015-0591-z.
86. Kang T, Louden JE, Ricks EP, Jones RL. Aggression, substance use disorder, and presence of a prior suicide attempt among juvenile offenders with subclinical depression. Law Hum Behav. 2015;39(6):593–601. https://doi.org/10.1037/lhb0000145.
87. Jacobs RH, Becker-Weidman EG, Reinecke MA, Jordan N, Silva SG, Rohde P, et al. Treating depression and oppositional behavior in adolescents. J Clin Child Adolesc Psychol. 2010;39(4):559–67. https://doi.org/10.1080/15374416.2010.486318.