Contemporary diagnosis and treatment of conduct disorder in youth

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Abstract:

Introduction: Conduct disorder (CD) is characterized by repetitive and persistent antisocial behaviors, being among the most frequently reported reasons of referral in youth. CD is a highly heterogeneous disorder, with possible specifiers defined according to age at onset, Limited Prosocial Emotions (LPE) otherwise known as Callous-Unemotional (CU) traits, Emotional Dysregulation (ED), and patterns of comorbidity, each with its own specific developmental trajectories.

Areas Covered: The authors review the evidence from published literature on the clinical presentations, diagnostic procedures, psychotherapeutic and psychoeducational approaches, and pharmacological interventions from RCT and naturalistic studies in youth. Evidence from studies including youths with LPE/CU traits, ED and aggression are also reviewed, as response moderators.

Expert opinion: Due to its clinical heterogeneity, relevant subtypes of CD should be carefully characterized to gain reliable information on prognosis and treatments. Thus, disentangling this broad category in subtypes is crucial as a first step in diagnosis. Psychosocial interventions are the first option, possibly improving LPE/CU traits and ED, especially if implemented early during development. Instead, limited information, based on low-quality studies, supports pharmacological options. Second-generation antipsychotics, mood stabilizers, and stimulants are first-line medications, according to different target symptoms, such as aggression and emotional reactivity. Developmental pathways including ADHD suggest a specific role of psychostimulants.

Key Words: Conduct Disorder, Callous-Unemotional traits, Emotional Dysregulation, Attention-Deficit/Hyperactivity Disorder, Second Generation Antipsychotics, Mood Stabilizers, Psychostimulants.

Article Highlights Box

- Conduct disorder is a highly heterogeneous condition characterized by antisocial behaviors and one of the most frequently reported reasons of referral in youth.

- Relevant subtypes of CD, based on the presence of callous-unemotional traits, emotional dysregulation and patterns of comorbidity should be carefully characterized.

- Several clinical measures are available for screening purposes and may be used to identify youth with behavioral problems at risk for developing CD and related issues.

- Psychosocial interventions are the first option, possibly improving callous-unemotional traits and emotional dysregulation, especially if implemented early during development.

- Limited information based on low-quality studies supports the use of pharmacological agents including antipsychotics, mood stabilizers and stimulants, according to different target symptoms.

1. Clinical Features of Conduct Disorder

1.1. Epidemiological Overview and Clinical Picture

Conduct disorder (CD) is featured by persistent and repetitive behaviors that defy societal norms and infringe upon the rights and rules of others [1]. Typically, it emerges during a child's school years or early adolescence and is one of the most frequently cited reasons for referral in young individuals. Globally, CD affects approximately 1.5% of the population [2], with a notable gender disparity, as it is twice as prevalent in boys (3 – 4%) compared to girls (0.5 – 1%) [3]. This condition places a substantial socio-economic burden on public health [4]. Notably, retrospective assessments of lifetime prevalence and prospective studies on cumulative prevalence suggest that approximately 10% of youths experience CD at some point during their childhood and adolescence [5,6]. Furthermore, the prevalence of CD has shifted over time and has notably increased in the last three decades [7]. While some of this increase may be attributed to heightened clinical awareness and diagnosis efforts, it remains a topic of debate, with varying trends observed worldwide, particularly between high-income and low- or middle-income countries. Despite these trends, the socio-economic burden of CD continues to rise, particularly in high-income regions like North America, East and South Asia, with males experiencing the most significant increase [7]. Importantly, the global impact of CD extends beyond the realm of psychiatry, as youths with CD also exhibit a higher prevalence of neurological, gastrointestinal, and other physical health issues [8]. Additionally, they face an elevated risk of premature mortality, stemming not only from suicidal behaviors and substance abuse but also from other risky behaviors later in life [9,10].

In the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) [1]. CD is categorized under the "Disruptive, Impulse-Control, and Conduct Disorders" chapter of the manual. It shares this category with the Oppositional-Defiant Disorder (ODD), the Intermittent Explosive Disorder (IED), and the Antisocial Personality Disorder (AsPD), as well as other specified and unspecified conditions. CD is characterized by symptoms falling into four main categories: aggression towards people and animals, property destruction, deceitfulness or theft, and serious violations of rules. Subtypes are further defined based on the age at which symptoms onset occurs, either before (childhood-onset) or after (adolescent-onset) the age of 10. The International Classification of Diseases (ICD-11) [11] also outlines criteria and subtypes for "Conduct-Dissocial Disorder".

The clinical presentation of CD evolves over time, with new symptom patterns

emerging as individuals age [12]. While aggressive behaviors tend to decrease in frequency with age, non-aggressive transgressions become more prevalent in adolescents [13,14]. Regarding gender differences, boys with CD often exhibit more physical aggression, theft, and property damage, while girls with CD are more inclined to engage in serious rule violations such as lying and truancy. Girls also tend to display relational aggression more frequently than physical aggression compared to boys [15]. Additionally, CD in boys tends to manifest with more severe symptoms and an earlier onset, while in girls, onset is delayed and associated with greater school-related difficulties [15]. Gender-specific psychiatric comorbidity profiles have also been identified, with females reporting more emotional disturbances and early adverse experiences than males [15,16].

A major challenge in diagnosing CD is its high heterogeneity, as it encompasses a wide range of symptom profiles and clusters, each with its unique developmental trajectory and underlying causes [17–19]. Childhood-onset CD, as opposed to late-onset, is more strongly associated with developmental vulnerability, neurobiological correlates, greater symptom severity, and more detrimental psychosocial outcomes later in life, including increased risk of substance abuse, criminality, and homelessness [20]. Various symptom specifiers, such as the Limited Prosocial Emotions specifier in DSM-5-TR and ICD-11 criteria, have been identified and studied to reduce this heterogeneity.

In clinical practice, CD often presents with different comorbidities, contributing to its heterogeneity. Like many other psychiatric conditions, CD frequently co-occurs with other emotional and behavioral disturbances, notably the Oppositional-Defiant Disorder (ODD), with youths with CD having a 15-fold higher risk of meeting ODD criteria than their peers [21]. Remarkably, CD often emerges after ODD, even before school age, highlighting the importance of early intervention to alter its developmental trajectory. Attention-Deficit/Hyperactivity Disorder (ADHD) is another common comorbidity, especially in boys, who have a 10-fold higher risk of CD compared to their peers without CD [22]. CD with comorbid ADHD tends to onset earlier, exhibit more severe symptoms, and follow a more persistent course [23]. Substance abuse, particularly tobacco, alcohol, and cannabis, is a frequent comorbidity in adolescence, and early and maladaptive substance use is considered a potential diagnostic criterion for CD itself [24]. Notably, substance use disorders later in life are especially prevalent in individuals with both CD and ADHD [25,26]. Treatment-seeking patients with SUD and ADHD present earlier onset of CD, earlier age of first substance use and higher symptom loads [27]. Finally, behavioral addictions, including gaming and internet use, as well as DSM-5-based Internet Gaming Disorder, are common in individuals with

comorbid CD and ADHD [28–31].

An intriguing bidirectional association exists between CD and Bipolar Disorders (BD), consistently observed in clinical, epidemiological, and research studies [32]. Comorbidity rates can be as high as 40% [33], characterized by higher rates of impulsive, reactive, non-predatory and disorganized aggression [34], as well as increased impulsive, reactive, non-predatory, and disorganized aggression, higher substance use, and cigarette smoking [35]. This association often overlaps with the simultaneous presence of ADHD [36] – among boys with ADHD, 55% of those with CD also had BD and 71% of the boys with BD also had CD [37] – forming the CD-BD-ADHD triad, which poses a significant risk for subsequent substance abuse and more severe clinical outcomes [38,39]. Additionally, CD frequently co-occurs with internalizing disorders, such as Major Depression and Anxiety Disorders, particularly in girls who have experienced early trauma or adverse events, though the temporal sequence of this association remains unclear [15,16]. Importantly, a substantial proportion of CD adolescents with high levels of anxiety and depressive symptoms also engage in non-suicidal self-injury (NSSI) and have an elevated risk of suicide [40–42], with NSSI being a predictive factor for suicidal behaviors, even when controlling for emotional symptoms [43].

1.2. Conduct Disorder specifiers: Limited Prosocial Emotions and Emotional Dysregulation

Starting from its fifth edition, the Diagnostic and Statistical Manual of Mental Disorders (DSM) [44] attempted to address the diagnostic challenges arising from the diversity within Conduct Disorder (CD) [45]. It aimed to assist clinicians in identifying a profile that maps the developmental trajectory leading to adult Antisocial Personality Disorder (ASPD), known as "with limited prosocial emotions" (LPE) [for recent lines of research [46]]. To meet this specifier, two or more additional criteria must be present for at least 12 months, observed in different relationships and settings. These criteria include: 1) absence of remorse or guilt; 2) callousness and lack of empathy; 3) disregard for performance; 4) superficial or deficient emotional expression. The main difference between the definitions of LPE in the two major classification systems, DSM-5 and ICD-11, is that ICD-11 includes an extra symptom related to indifference to punishment and permits this specifier to be applied to children who meet criteria for Oppositional-Defiant Disorder (ODD) as well. Moreover, there is growing interest in extending the LPE specifier to children and adolescents who do not fully meet CD criteria but exhibit a severe and persistent pattern of behavioral problems [47,48]. Additionally, research since Karpman's study on early precursors of psychopathy has suggested a distinction

between “primary” and “secondary” variants of CU traits, although these distinctions are still not recognized in current diagnostic systems; its clinical relevance will be discussed later on.

The presence of LPE and callous unemotional (CU) traits in early life is a significant risk factor for aggressive and antisocial behaviors, CD, adult ASPD, and psychopathy [49]. This holds true for both clinical and non-clinical populations [50,51], as well as in samples of incarcerated young individuals [52,53]. In a large study involving young children, those with LPE exhibited more symptoms of Oppositional-Defiant Disorder (ODD) and Attention-Deficit/Hyperactivity Disorder (ADHD) and had a higher risk of developing CD symptoms and comorbid issues in adolescence [47,54]. Another longitudinal study emphasized that the LPE specifier identifies children with a particularly severe pattern of behavioral disturbances, a notable prevalence of comorbidities, and high levels of antisocial behaviors later in life [55]. Importantly, these traits tend to persist from childhood through adolescence and into adulthood [56] and are associated with a poor prognosis and overall adverse outcomes throughout one's lifespan [55,57,58]. Furthermore, children and adolescents with LPE have traditionally been considered to respond less favorably to treatments than those with CD but without CU traits [59]. Nevertheless, recent research, as summarized in a meta-analysis by Perlstein and colleagues, clarified that antisocial youth with CU traits begin and end treatment with more severe conduct problems [60].

Precursors of CU traits have been identified in preschoolers [61], and even earlier in infants [62], with reciprocal relationships found with parental practices [63,64]. In preschool-age children, these precursors are associated with specific temperamental traits, including fearlessness, low levels of anxiety [65], and limited emotional expression [66,67]. Fearlessness is particularly linked to impaired sensitivity to parenting and environmental cues, such as rules, social norms, and punishment. This restricted ability to learn about the consequences of harmful behavior increases the risk of antisocial behaviors [48]. Children with a fearless temperament may experience dysfunctional family interactions, including low warmth, minimal positive affect, harsh parenting, emotional detachment, neglect, and maltreatment. Consequently, they may struggle to develop affective empathy, prosocial values, and moral reasoning [64,68]. The exploration of developmental precursors of CU traits has extended to early infancy, including the reduced preference for tracking a face with direct gaze during caregiver interactions. These findings offer promising potential for parent-mediated interventions for at-risk children.

Deficiencies in empathic skills from early childhood significantly influence the development of antisocial behaviors, including aggression, bullying, sexual offenses, and

serious violent crimes [69]. Adolescents with elevated empathic skills tend to exhibit more altruistic and prosocial behavior, while those with reduced levels are more prone to aggression [69,70]. Studies have shown that individuals with LPE, especially young children, often exhibit deficits in the cognitive aspect of empathy [68,71]. However, research focusing on adults with psychopathy and youths displaying Callous-Unemotional (CU) traits has more clearly revealed deficits in affective empathy [72,73]. In alignment with this, young individuals with CU traits often demonstrate reduced attention to, recognition of, and responsiveness to emotional stimuli, particularly when it comes to distress cues. Recent findings have suggested potential disruptions in the processing of animacy information [74]. Additionally, a diminished emotional response, as observed through various measures like behavior, physiology, and self-report, appears consistent, with no signs of heightened responsiveness to attachment-related stimuli [75]. Nevertheless, the profile of empathy deficits typically found in CD patients with CU traits remains a subject of debate, as more recent research indicates that prosocial behavior and sympathy, rather than affective empathy, are predictive of callous-unemotional traits in youth [76].

The disruptive and antisocial behavior exhibited by youths with Conduct Disorder (CD) is, in part, attributed to difficulties in processing affective information and regulating emotions. In these individuals, poor management of impulsive actions and distressing emotions is linked to the misinterpretation of social cues in a negatively skewed and stereotypical manner. Additionally, they may lack effective strategies for coping with anger and exhibit deficits in behavioral control and response inhibition [77]. Emotion recognition deficiencies, especially for negative emotions, have also been identified in CD patients [66,67,78,79], although these poor emotion recognition skills and emotion regulation challenges are more prominent in a specific subgroup of CD patients [80]. Consequently, altered responses in the amygdala and dysfunction in other regions associated with empathic responses and social learning have been consistently observed in fMRI studies in response to emotional stimuli [refer to a meta-analysis on the subject [81]].

Clinically, Emotional Dysregulation (ED) in youth with CD manifests as severe irritability, characterized by aggressive outbursts, temper tantrums, a low tolerance for frustration, and a heightened reactivity threshold [82,83]. Reactive aggression in such individuals is linked to physiological overarousal and poor emotion regulation [84], and elevated aggression levels are associated with increased emotional responses, particularly anger [85]. Clinical assessments of ED are correlated with both internalizing and externalizing issues, including social difficulties, anxiety, depression, attention problems, and disruptive

behaviors [86]. In cases of comorbid ADHD, there may also be negative emotional lability with intense emotional reactions [87].

Previous investigations have linked atypical, dysfunctional, or delayed development of emotion regulation strategies in youths exhibiting severe aggressive and antisocial behaviors to early traumatic experiences [88–90]. This association is especially prominent in girls with CD, who tend to present with more pronounced internalizing symptoms and difficulties regulating emotions than boys. Consequently, clinicians, influenced by previous scholars like Karpman, have advocated for distinguishing a "symptomatic" or "secondary" type that encompasses emotional symptoms and adverse environmental factors such as maltreatment, neglect, sexual abuse, and exposure to violence [91,92]. More recent robust research supports the existence of this secondary variant (for further details please see [93]), which becomes even more pertinent when considering CU traits as precursors of psychopathy. While this "secondary" type may not differ significantly in terms of aggression, norm violations, callousness, or lack of empathy, these individuals often exhibit heightened emotional reactivity, predominantly characterized by negative affectivity, including anxiety, depression, irritability, and hypersensitivity [94]. Some scholars propose categorizing them as "Callous-Emotional" [79], emphasizing that this variant likely has specific developmental risks, particularly in relation to suicidal tendencies, and distinct treatment needs [95]. Nonetheless, it's essential to consider complex developmental combinations of psychological features; indeed, interactions between levels of irritability and callousness have been linked not only to clinical measures of aggression and functional impairments [96] but also to neurofunctional aspects of reward processing [97,98].

2. Clinical Assessment of Conduct Disorders and Related Psychopathological Dimensions

Clinical screening for CD is pivotal in recognizing adolescents with severe behavioral issues, especially in early development when interventions are most effective. Typically, parents or teachers utilize clinical rating scales to appraise conduct issues that may escalate to CD, determining if these behaviors deviate from age-appropriate norms. Various validated assessment tools are now accessible for both clinical and non-clinical applications. A commonly used measure is the Child Behavior Checklist for ages 1.5 to 5 years (CBCL – 1.5/5) and for ages 6 to 18 years (CBCL – 6/18) [99], a 99- and 118-item scale, respectively, providing a range of syndromes and symptom scales, including Aggressive and Rule-Breaking

Behaviors, and yielding scores for Internalizing, Externalizing, and Total Problems. As children grow, self-reported conduct problems become crucial, with the Youth Self Report (YSR) [99], a self-rated version of the Achenbach System of Empirically Based Assessment (ASEBA), catering to this need.

Other tools assess conduct problems and related issues in youth, such as the Strengths and Difficulties Questionnaire (SDQ) [100] includes a 5-item Conduct Problems parent-rated scale with normative data available across multiple countries and languages. The Teacher Observation of Childhood Adaptation – revised version (TOCA-R) [101] is a 16-item teacher-rated questionnaires that explores overt aggression, oppositional behaviors, covert antisocial conducts and authority acceptance. The Eyberg Child Behavior Inventory (ECBI) and the Sutter-Eyberg Student Behavior Inventory – revised (SESBI-R) [102] are available for a more comprehensive screening of conduct problems at home and school, respectively. The Behavior Assessment System for Children (BASC) [103] is a multidimensional system used to evaluate behavioral and emotional problems and self-perceptions of children, adolescents, and young adults aged 2 to 25 years with two rating scales (parent- and teacher-rated) and a self-report scale (for children older than 6 years), as well as a structured developmental history form; these tools are helpful to comprehensively assess youths' behavioral issues in different settings. Two further recently developed scales can be also considered: the Conduct and Oppositional Defiant Disorder Scales (CODDS) [104] and the Diagnostic Interview Schedule for Children Adolescents and Parents (DISCAP) [105].

For children at risk, diagnosis of CD is typically based on standardized criteria from classification systems like DSM-5 and ICD-11. Trained psychiatrists often confirm the diagnosis through semi-structured interviews, such as the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL) [106]. This diagnostic interview is the most widely used instrument to assess current and past symptoms of disruptive behavior disorders in children aged 6 – 18 years old. The K-SADS-PL diagnostic interview reviews the most severe current and lifetime symptoms of disorders grouped into modules, by means of probes and scoring criteria for each symptom presented. The interview also helps clinicians in ruling out differential diagnoses and/or clinical comorbidities whose presence should be carefully investigated, not only due to their frequent occurrence but also because of the substantial impact on both clinical outcomes and treatment strategies.

Evaluating CU traits can be achieved by directly examining associated symptoms and characteristics [107]. Various measures are available, including self-reports, parent reports, and

teacher reports. However, obtaining perspectives from multiple informants is generally the most reliable way to assess CU traits in young individuals, as each type of report has its limitations [108]. Several clinical tools have been developed and validated for specific populations, catering to various age groups and cultural backgrounds. For a comprehensive overview of available measures in clinical settings, please refer to please refer to [109]. Among the commonly used surveys, the Antisocial Process Screening Device (APSD) [110] stands out. It's a clinician-administered rating scale designed for adolescents aged 11 to 18, applicable to parents and teachers. It comprises 20 items grouped into three primary factors: Narcissism, Impulsivity, and Callous-Unemotional. It exhibits a good fit in both clinical and community samples. Similarly, the Inventory of Callous Unemotional Traits (ICU) [111] is widely utilized. It includes self-reports for individuals aged 11 to 17, as well as parent and teacher versions. This measure is comprehensive and has been used from preschool age to young adulthood [112]. The youth version contains twelve positively and twelve negatively worded items, with an internal structure comprising three factors: Callous, Uncaring, and Unemotional. These factors load onto a general CU/LPE factor and have shown good convergent validity, high internal consistency, and reliability in clinical, forensic, and community samples. Notably, a preschool version of the ICU has also been developed [113].

Nevertheless, recent evidence suggests that assessing dimensions beyond just CU traits in young individuals, such as Interpersonal (grandiose/manipulative), Lifestyle (daring/impulsive), and Antisocial domains, is highly predictive of persistent and severe conduct problems in childhood [114,115]. Indeed, a multidimensional structure, extensively overlapping that reported for adult psychopathy, has also been detected in children and adolescents [116]. Various tools have been developed to assess all dimensions of psychopathy in youth, including the Youth Version of the Psychopathy Checklist (PCL:YV) [117]. However, this is a semi-structured clinical interview for adolescents aged 12 to 18, and it can be time-consuming, making it less suitable for clinical and large-scale community studies.

Alternatively, the 50-item self-report Youth Psychopathic Traits Inventory (YPI) [118] is available for adolescents aged 12 to 20. It features ten factors that load onto the three primary dimensions of psychopathy: Interpersonal, Affective, and Lifestyle. A shorter 18-item version is also available for clinical settings. Other instruments for evaluating psychopathy in youth include the Child Problematic Traits Inventory (CPTI) [119] and the Childhood Psychopathy Scale (CPS) [120], both of which exhibit good psychometric properties [further details on these two measures are available in [46,109]].

Nonetheless, these latter scales do not specifically take into account the antisocial dimension of youth psychopathy and the presence of CD symptoms. In order to overcome this limitation, as well as to address the antisocial dimension of youth psychopathy and the presence of Conduct Disorder symptoms, the Proposed Specifiers for Conduct Disorder (PSCD) [121] was developed by Salekin and Hare [122]. These specifiers assess all components of youth psychopathy, including grandiose-manipulative traits, CU traits, daring/impulsive behavior, and ODD/CD symptoms, through parent and self-reports. A further validation of the scores on the PSCD was recently conducted in an Italian sample of adolescents aged 11 – 14 years old [115] that confirmed the reliability and usefulness of this tool in clinical settings; other translations are now available [123–126], as well as a short version of the questionnaire [127], though the measure is still understudied relative to the previously mentioned tools. Finally, other instruments for the evaluation of CU traits and psychopathy in young people, that have been the subject of less empirical study as compared to APSD and ICU, include the Clinical Assessment of Prosocial Emotions (CAPE), the Triarchic Psychopathy Measure (TriPM) [128] and the University of New South Wale (UNSW) system [109].

Given the link between empathic skills and CU traits, it is essential for clinicians to evaluate empathy competences and related constructs in these patients [109]. Various techniques have traditionally been used to measure empathic abilities in young individuals, including story-based methods, facial affect and gestural reactions, and experimental induction procedures [129]. However, clinical questionnaires and interviews involving multiple informants are more practical in clinical settings [130]. Notable measures for assessing empathy in children and adolescents include the Basic Empathy Scale (BES) [69] and the Interpersonal Reactivity Index (IRI) [131], which are among the most widely used measures for a multidimensional assessment of empathy in youths; Other clinical measures of empathy include, for instance, the recently developed Measure of Empathy in Early Childhood (MEEC) [76], a novel multidimensional parent-rated scale for 4 to 7-year-old children with scores showing good psychometric properties.

As for the assessment of ED in this clinical population, several measures are now available for everyday practice [132]. The Child Behavior Checklist (CBCL) [99] has been widely used to identify children with ED features. The Dysregulation Profile (CBCL - DP) is an indirect index of ED, computed based on t-scores from the Anxious/Depressed, Attention Problems, and Aggressive Behaviors scales. Interestingly, higher scores in ODD children are associated with a greater risk for later ADHD and mood disorder in adolescence [86]. Similarly, the Strength and Difficulties Questionnaire (SDQ) also provides a

Dysregulation Profile (SDQ-DP) [133] based on a 5-item operationalization, equivalent in clinical implications to the CBCL-DP [134]. Scores on this measure have been validated in a clinical population of ADHD children [135], though the use of a novel 15-item profile is recommended [136]; the profile is also now available based on teacher report [137].

Several other self or parent-report measures are available to assess ED in youths [138]. Among the formers, the Emotion Regulation Questionnaire (ERQ) [139,140] is a self-rated instrument for youths aged 10 to 18 years old composed of ten items specifically focusing on self-regulation strategies, namely Cognitive Reappraisal and Expressive Suppression, which is widely used in clinical settings and shows strong psychometric properties. The Difficulties in Emotion Regulation Scale (DERS) [141], with its three-factor structure based on cognitively conceptualized components of ER (Accept, Impulse and Goals), is commonly used to assess difficulties in recognizing and managing negative affects in adolescents aged 11 to 18 years old. The Cognitive Emotion Regulation Questionnaire (CERQ) [142] for children aged 9 to 11 years old shows a similar multifaceted internal structure including 36 items and nine factors based on cognitive strategies of emotion regulation (e.g., Rumination, Positive reappraisal). Parent-report measures, instead, may be used in even wider clinical populations also including young children and youths with disabilities. The Emotion Regulation Checklist (ERC) [143] is a parent-rated tool to assess children abilities to regulate emotional experiences, composed of 24 items divided into two scales related to Emotion Regulation and Emotional Lability/Negativity. The Multidimensional Emotion Questionnaire (MEQ) [144] assesses four basic emotions (namely Fear, Sadness, Anger and Positive Emotions) in relationship to children ability to regulate them (Self-regulation and Help to others). On the other hand, the Affective Reactivity Index (ARI) [145] is a dimensional measure of irritability and emotional impulsivity in mental health settings that has been developed to be rated by both youths and parents, composed of only six items, plus a seventh one to evaluate the clinical severity.

More recently, a novel instrument has been developed to comprehensively assess the different dimensions of ED, given its multifaceted dimensional concept of ED, known as Reactivity, Intensity, Polarity and Stability (RIPoSt) scale [146]. Originally developed for the adult population [147], the questionnaire has been adapted for youth aged 11 to 18 years old [148,149] based on 31 items along three subscales (Affective Instability, Emotional Reactivity, Interpersonal Sensitivity). Good-to-excellent internal consistency and adequate construct as well as concurrent and convergent validity have been confirmed; cut-off scores are also available to identify at-risk individuals. Finally, other tools can be also used to explore ED in the context of a more general evaluation of executive dysfunctioning. The Behavior Rating

Inventory of Executive Function (BRIEF) [150], in its several versions including the parent, teacher and self (11 to 18 years old) reports, is largely used in clinical practice and provides a thorough assessment of Emotional and Behavioral Regulation Indexes and related subscales (Inhibit/Self-Monitor and Emotional Control/Shift, respectively). Similarly, the Conners' Rating Scales Revised [151] with its Impulsivity/Emotional Lability Scale, Conners' Global Index with its Emotional Lability Scale, and the Barkley Emotional Dysregulation Scale [152].

3. Non-Pharmacological Treatments

The nonpharmacological treatments for children and adolescents with conduct problems aim to address the main symptoms of these conditions, implementing emotion awareness and regulation, improving problem-solving and social skills, and fostering moral development. Among the most evaluated psychosocial treatments for youths' conduct problems, three approaches can be reported, including parent-focused, child-focused, and multimodal programs, the latter integrating the first two types of interventions [153]. Parent-focused programs (i.e., behavioral parent training) are considered the first-line approach for younger children. Instead, a combination of behavioral parent training and child-focused programs, usually based on cognitive-behavioral techniques, is more beneficial for older youths than for younger patients, who usually exhibit less developed metacognitive skills for engaging in CBT sessions [94,153]. Multimodal interventions are considered valid options for both children and adolescents and are particularly recommended for severe conduct problems [94,153,154].

As regards the efficacy of nonpharmacological treatments for conduct problems, previous studies have reported small-to-moderate effect sizes [154–157], with parent-focused programs reporting larger effect sizes than child-focused ones [157]. However, available findings are rather inconsistent. Indeed, in a systematic review and meta-analysis, Bakker and colleagues analyzed 17 studies describing 19 nonpharmacological interventions for children and adolescents with clinical conduct problems and CD, and found that effect sizes varied prevalently according to the rater [158]. Specifically, effect sizes were significant but small for parent- and teacher-reported outcomes (respectively 0.36 and 0.26) and blinded observer (0.26) outcomes; however, they were not significant if the children themselves completed the outcome measures. The authors proposed several possible explanations that might account for these discrepancies, including parents' expectations about the treatment, slower generalization of the acquired skills to the school setting, and youths' tendency not to report on their externalizing

behavior. Methodological differences among studies (e.g., sample composition, measures employed) might also have influenced the results.

3.1.Parent Training Interventions for Children and Adolescents with Conduct Problems

Parent training interventions based on operant and social learning theory, which targets the quality of parenting and educational strategies, are considered the most cost-effective interventions for conduct problems, especially during early and middle childhood [94,159,160]. Currently, several manualized parent training programs have shown to be effective in reducing youths' conduct problems. Despite some differences between the activities proposed in these programs, they share most of their aims, including: a) implementing warmth and positive parenting (e.g., use of rewards and praise); b) improving parents' ability to provide effective instructions and rules; c) reducing harsh, aggressive (e.g., time-out, ignoring minor behavior) and inconsistent discipline.

A meta-analysis by Leijten and colleagues revealed that, at the treatment level, parenting programs have a moderate effect on disruptive behavior (d = -0.69). More interestingly, they found that, among several techniques, those associated with greater effects were positive reinforcement and non-aggressive disciplines, such as praise and natural/logical consequences, and these effects could be increased with additional techniques, such as fostering parents' self-management abilities [161].

In this context, worthy of mention is the Incredible Years® (IY) program [162], a series of evidence-based sessions for parents, teachers, and children initially developed for children aged 3 to 8 years with or at risk for conduct problems. The IY parenting program adopts a collaborative group-based model. Parents are encouraged to recognize their skills and identify strategies to reach their goals. Methods applied in the IY include problem-solving, brainstorming, role-plays, and homework. A meta-analytic review [163] confirmed the effectiveness of the IY parenting program, reporting a mean effect size of d = 0.27 for disruptive behavior across informants and, more specifically, of d = 0.50 for parent-reported outcomes.

Finally, robust evidence is also available for the Parent Child Interaction Therapy (PCIT), another BPT program that has demonstrated very large effect sizes according to a recent meta-analysis by Thomas and colleagues [164]. This approach includes an intensive coaching component involving both parents and children in treatment, and two phases focusing on relationship enhancement and standard behavior modification skills. Notably, this type of

intervention is particularly relevant for the aims of the present review since the PCIT has been adapted and validated also for children with CU traits [165–167].

3.2. Child-Focused and Multimodal Programs for Conduct Problems

Children might benefit from being directly involved in the treatment as their age increases. Child-focused interventions usually involve cognitive behavioral skills trainings, which target children' self-regulation abilities, problem-solving skills, and social-cognitive processes. The Problem-Solving Skills Training (PSST) [155] is one of the most evaluated child-focused programs for conduct problems. The PSST involves 25 group sessions once a week, during which children (aged 7 – 13 years) can practice their problem-solving and social skills with peers. This program has been shown to be effective in reducing children' aggressive and defiant behavior at home and school and increasing their prosocial behavior.

Despite the effectiveness of child-focused programs, better results can be obtained when implemented along with parent training interventions [94,168]. For this reason, multimodal programs, which include child and parent components, are particularly recommended during late childhood and adolescence or in severe cases of conduct problems [94,169]. One of the most implemented multimodal interventions for children and adolescents with conduct problems is the Coping Power Program (CPP) [170]. The CPP is a group-delivered intervention based on cognitive behavioral principles and practices for children aged 8 – 12 years at risk for aggressive and conduct problems. The program provides children with cognitive behavioral therapy and their parents with a parent training intervention. The CPP has yielded positive effects across multiple randomized controlled trials, and a recent meta-analysis highlighted that its efficacy is supported by rigorous research and that the CPP effectively reduces maladaptive behavior, including externalizing problems, delinquency, and aggressive behavior [170–174].

The CPP has also been adapted as a treatment model for children and adolescents with ODD and CD, and studies have provided evidence of its short- and long-term efficacy. Overall, when applied in clinical settings, the CPP yields a reduction of children' externalizing problems, aggressive behavior, and substance use risk and an improvement in prosocial behavior and global functioning [171,175,176].

3.3. Virtual Reality (VR) Based Interventions

Researchers have recently claimed that the effectiveness of evidence-based cognitive behavioral therapies for children with CD and aggressive behaviors may be enhanced by Virtual Reality (VR) techniques and technology-based interventions. VR-based interventions have been repeatedly shown to be effective for treating ADHD [177] and improving executive dysfunctions [178], as well as in the rehabilitation programs for other psychiatric conditions [179,180]. Unfortunately, evidence for the use of VR-based treatment specifically addressing youth with CD is still missing, although preliminary evidence is available for other impulse control disorders [181]. Nonetheless, findings from a recent study supported its feasibility for children with aggressive behaviors [182], whereas another empirical study [183] demonstrated that a specific VR-based intervention program was effective in improving disruptive behavior problems in a sample of adolescents from secure residential youth care facilities and secondary special education schools. A recent multicenter randomized controlled trial [184] compared the effectiveness of three intervention programs, namely VR-based CBT, CBT with roleplays, or care-as-usual, in children with aggressive behavioral problems. The authors found that CBT with virtual reality more likely reduced aggressive behaviors compared to the other treatments, and more likely enhanced emotional engagement, practice immersion, and treatment appreciation of children. Interestingly, according to the preliminary findings of an ongoing clinical trial on youth with DBD [NCT03927612], VR-based interventions may also be effective to improve perspective taking and social skills, thus being a potentially useful approach to children with CU traits.

3.4.New Challenges in the Treatment of Conduct Problems: Callous-Unemotional Traits and Emotion Dysregulation

Children and adolescents with conduct problems show very different clinical profiles, with significant implications on treatment outcomes. Therefore, it is imperative to take into account the youths' characteristics when planning a course of treatment. In the context of childhood conduct problems, CU traits and ED represent two of the main challenges clinicians have to face.

CU traits are generally associated with poorer response to traditional treatment models. Despite some manualized multimodal programs shown to be able to reduce CU traits [171,172,185], there is a need for more tailored interventions able to address the peculiar impairments of youths with CU traits. In particular, treatment efforts could be strengthened by adding activities focused on emotion processing and emotional engagement [186,187], as also

pointed out by a recent RCT [165]. The authors tested the efficacy of an evidence-based parent training intervention adapted to address the emotion processing deficits of youths with conduct problems and CU traits with promising results. Another promising intervention specifically developed for children with CU traits has been proposed by White and colleagues [188]. The model addresses the impaired sensitivity for emotional distress using a computerized automated feedback and incentive system.

Regarding emotion dysregulation, behavior management training, and cognitive behavioral and metacognitive therapy can yield positive results [82]. For instance, Trillingsgaard and colleagues reported that parent training had significant effects on children' ED and, notably, these effects were maintained across six months in a sample of preschoolers with ADHD and ODD [189]. Similar results were reported by Graziano and Hart in a sample of children (mean age 5.16 years) with externalizing problems [190]. Cognitive behavioral and metacognitive therapies, instead, can help children self-regulate by focusing on the influence of thoughts and emotions on one's behavior and promising results have been highlighted by some previous studies. For instance, Tamm and colleagues tested the efficacy of a play-based metacognitive executive functioning training for children aged 3-7 years old and found that it also significantly improved participants' emotion regulation skills [191]

Finally, mindfulness-based interventions can provide children and adolescents with effective tools to better regulate their emotions and behavior. A recent systematic review concluded that, despite some inconsistent results, mindfulness-based interventions could be effective in improving youths' emotion dysregulation and that better results are obtained when home practice is recommended [192].

4. Pharmacological Treatments

Within a multimodal intervention encompassing both pharmacological and psychosocial treatments, many subjects may require adjunctive pharmacotherapy for the control of specific symptoms [154,193]. Pharmacological options should be considered after treatment non-response although further research is needed. Despite the increasing use of medications for the treatment of CD, especially of the associated aggression, no drug is currently licensed for the treatment of this disorder in youth, except for Risperidone which is indicated for the short-term treatment of persistent aggression in Disruptive Behavior Disorders (DBD) from the age of 5 years in youths with Intellectual Disability (ID). The most influential guidelines tend to recommend the pharmacologic option (mainly stimulant medications) for

the treatment of oppositional behavior, conduct problems and aggression only in case of comorbid ADHD, or suggest adding Risperidone in the short-term for controlling severe aggression or explosive anger, after comorbid ADHD is treated [154,194].

Even though the evidence supporting the clinical practice is still limited and the effectiveness of medications remain relatively underexplored, a growing literature shows that several drugs can be at least somewhat effective in the treatment of aggression in DBD, with more limited evidence on the specific diagnostic category of CD. Prior systematic reviews have concluded that more evidence is needed to confirm the efficacy and safety of medications in CD. The high heterogeneity of the disorder, both from a clinical and from a neuropsychological point of view, and the high inconsistency and variability in the clinical trials outcome measures, prevent to draw firm conclusions [195]. Here we provide an update to the most recent systematic reviews on the topic and review the most important findings about the pharmacological options mostly used for the treatment of CD, including psychostimulants, D_2-blockers, mood stabilizers, α_2-agonists, and β-blockers.

4.1.Second Generation Antipsychotics

D_2-receptor antagonists, both as First (FGA) and Second (SGA) Generation Antipsychotics, appear to be efficacious for the management of aggression in children and adolescents [196,197], albeit the troublesome safety profile can limit their use [198]. The meta-analysis by van Schalkwyk and colleagues [199], including 14 RCTs, confirmed that antipsychotics are *effective* in reducing aggression and irritability in children with a moderate to high effect size (SMD = 0.74, 95% confidence interval [CI] 0.57 – 0.92, $p < 0.0001$). In particular, Risperidone and Aripiprazole resulted significantly superior to placebo in controlling aggression and irritability with no specific differences according to diagnostic indication including CD. A recent systematic review and network meta-analysis [200] confirmed SGA as the most efficacious pharmacological treatments for the management of DBD in youth with a comparable SMD of 0.668 (95% CI 0.537 – 0.800).

4.1.1. Risperidone

Risperidone is the most extensively studied medication for the treatment of aggression in children, however only a few RCTs investigated its efficacy in the CD population. Most of Risperidone trials have included mixed population, generally under the category of DBD or ADHD associated with aggression as a primary diagnosis, with high heterogeneity of the

samples in terms of age, gender distribution, comorbidities (including ID), and different proportions of CD subjects, usually representing less than 40% of the total sample [201]. An updated and critical review [193] aimed to summarize the literature findings on the antipsychotics use for the management of DBD in children and adolescents, by reviewing previously published systematic reviews (from 2012 to 2017) as well as the most recent clinical trials on antipsychotics in this population. The three systematic reviews included in this work [197,202,203] investigated 8 trials on Risperidone, and concluded that Risperidone is superior to placebo in reducing ODD symptoms and aggression in the short term, regardless the comorbidity of ADHD or ID, although not as effective in reducing ADHD or CD symptoms. The authors also agree that adverse events reporting is generally inconsistent and of low quality across trials, and that data on efficacy in the mid and long term are poor as they are generally limited to 4 to 10 weeks. The more recent review by Balia and colleagues [201] confirms these data, highlighting that whilst the Cochrane review [197] found limited evidence of efficacy for Risperidone in reducing aggression and conduct problems in children and youths with DBD in the short term, this was not overwhelming and was dependent on the small number of studies characterized by high methods heterogeneity and several limitations.

The five clinical trials, published in the last 5 years, and synthesized by Rajkumar in his review [193], are all focused on the efficacy of Risperidone. Three placebo-controlled trials examined the efficacy of Risperidone as an adjunctive treatment [204–206], one was a RCT with Risperidone *versus* Clozapine [207], while the last one was a naturalistic trial comparing Risperidone and Methylphenidate [208]. None of these trials included subjects with ID, while the comorbidity with ADHD was almost the rule (4 over 5 trials). The comparison of 20 ADHD/ODD males treated with MPH (mean age 8.95 ± 1.67 years) to 20 ADHD/ODD males treated with Risperidone (mean age 9.35 ± 2.72 years) and followed up for 6 months in a naturalistic study, showed that both drugs were similarly effective in managing symptoms of ODD, however Methylphenidate was superior to Risperidone in reducing core symptoms of ADHD [208]. Finally, one doble-blind randomized trial compared the efficacy of Clozapine *versus* Risperidone for the treatment of aggression in CD in children and adolescents aged 6 to 16 years for 16 weeks: both medications resulted similarly effective in controlling overt aggression, however Clozapine was superior to Risperidone in improving conduct externalization factors, delinquency trait, and global functioning [207].

Although MPH, when adequately modulated, have been proved to be efficacious in controlling emotional dysregulation in monotherapy in about 63% of subjects [206], a combined therapy with stimulants and antipsychotic is recommended in highly aggressive

patients presenting a comorbidity with ADHD. In the two placebo-controlled studies including DBD subjects with comorbid ADHD and treated with MPH at standard dose, adjunctive Risperidone resulted superior to placebo in the management of oppositional symptoms [205] and aggression [206]. In this last trial, Risperidone resulted even superior to the other comparator Divalproex [206].

The TOSCA study [209,210] confirmed that the addition of Risperidone to stimulant treatment can represent a good approach at reducing severity of parent-rated peer aggression (p = 0.02, Cohen's d = 0.32), improving social competencies and reducing impulsive aggression (ES = 0.29). In the single continuation trial of prior responders to adjunctive Risperidone, subjects belonging to the Augmented group (Parent training [PT] + stimulant + Risperidone) did not significantly differ from the Basic subjects (PT + stimulant + placebo) on primary outcome measures, however they showed more improvements than those receiving placebo on the Nisonger NCBRF Positive Social subscale (p = 0.005, d = 0.44), the Antisocial Behavior Scale Reactive Aggression subscale (p = 0.03, d = 0.36), and marginally on the Disruptive Behavior Total subscale (p = 0.058, d = 0.29), the primary outcome [204].

4.1.2. Other Second Generation Antipsychotics

Although Aripiprazole is licensed for the treatment of aggression in ASD subjects, as for our knowledge no RCT has been conducted so far on its efficacy in the CD population. Evidence of effectiveness in treating aggression in CD and its good tolerability are reported in several open label studies [211,212], nevertheless any firm conclusion is limited by the very small sample sizes and the short term of each trial (from 15 days to 8 weeks).

Similarly, no randomized clinical trials have been performed on Olanzapine in CD population. Olanzapine was shown to be effective in reducing ADHD symptoms and overt aggression when combined with Atomoxetine in a 10-week open label trial [213]. Olanzapine also appeared to be associated with a significant improvement in the Modified Overt Aggression Scale (MOAS) and the Children Global Assessment Scale (C-GAS) within a retrospective study including 23 severe CD adolescents who had had a scarce response to non-pharmacological intervention or mood stabilizers (Lithium and/or Valproate) [214].

One double-blind RCT examined the effect of Quetiapine in 19 adolescents with CD within a 7-week study confirming the efficacy of Quetiapine on the primary outcome (CGI severity scores) in nine individuals randomized to quetiapine compared to 10 subjects receiving placebo; no differences were found on the parent overt aggression scale (OAS), and the conduct problems subscale of the Conners' Parent Rating Scale (CPRS-CP) [215]. Quetiapine (mean

dose 150 mg/day) was also proven to be safe, well tolerated, and efficacious in managing aggression in CD children in two open label trials both when used in monotherapy or in addition in methylphenidate treatment-resistant adolescents with comorbid ADHD, CD/ODD, and aggression [216,217].

A recent study [218] examined the antimanic effects of selected antipsychotics (Risperidone, Olanzapine, Quetiapine, Ziprasidone, and Aripiprazole) in youth with Bipolar Disorder with and without comorbid CD. By a secondary analysis of six prospective 8-week open-label trials, the authors evidenced no significant difference in the two populations, highlighting possible secondary benefits of these medications in mitigating the morbidity associated with CD. Another interesting recent 12-week double-blind trial made a head-to-head comparison of Clozapine, Olanzapine, and Haloperidol in the treatment of aggressive schizophrenia subjects with and without conduct disorder [219]. Patients with a diagnosis of CD before the age of 15 years had more frequent and severe assaults than those without conduct disorder. In this trial, Clozapine was superior to haloperidol and olanzapine, and olanzapine was superior to haloperidol in reducing violent episodes. Clozapine showed the greater anti-aggressive efficacy over haloperidol and its effectiveness was even more evident in patients with conduct disorder [219].

4.2.Stimulant Medications

Stimulant medications enhance the impact of dopamine (DA) and norepinephrine (NE) neurotransmission, by blocking their reuptake, and increasing their release from synaptic vesicles in case of Amphetamines [220]. Stimulant medications are among the most efficacious treatments in psychiatry as well as in general medicine [221], with moderate to high effect sizes, ranging around 0.7 – 1.0, for the management of the core ADHD symptoms. They are also helpful in improving global functioning preventing negative outcomes and in the managing comorbid symptoms, including aggression and irritability [222].

Possible efficacy of a timely implementation of MPH in preventing subsequent negative outcome, in terms of CD, AsPD end substance use disorder (SUD), is strongly supported by a large longitudinal study [223], including 176 ADHD children (mean age 6.12 years) followed up to late adolescence (18 years) and adulthood (25 years), with a significant positive relationship between earlier age at treatment initiation of MPH and substance use disorder, with AsPD explaining this relationship. Even when controlling for SUD, age of MPH initiation was positively related to the later development of AsPD. Using Swedish national registers,

Lichtenstein and coauthors [224] explored the risk of criminal behavior in 25,656 patients with ADHD, comparing those receiving and not ADHD medications. In patients receiving ADHD medication, there was a significant reduction in the criminality rate for men and even more for women, strongly suggesting that ADHD medication may decrease the risk of criminality among patients with ADHD.

Several systematic reviews and meta-analyses confirmed that stimulants can be helpful in reducing pediatric aggression in ADHD when comorbid with ODD and/or CD [202,225]. The meta-analysis by Connor and colleagues [226] included 28 RCT (twenty-one on MPH, five on Amphetamine [AMP] and two on Pemoline [PEM]) examining 683 children with a diagnosis of ADHD plus comorbid ODD/CD (75% of subjects). The overall weighted mean effect size was estimated at 0.84 for overt aggression and at 0.69 for covert aggression, effect sizes were similar for MPH (d = 0.80) and AMP (d = 0.83) studies, with no correlation with dosage. Interestingly, overt aggression was less responsive to stimulants in ADHD subjects with a comorbid CD diagnosis. Four years later, the review by Pappadopulos and colleagues [225] including 18 RCTs (sixteen on MPH, one a combination of MPH and Amphetamine mixed salts, and one on a combination of MPH, Dextroamphetamine and Pemoline) in 1057 subjects (mean age 9,1 y), confirmed a similar, although slightly lower, effect of stimulants on pediatric aggression (effect size = 0.78). Authors explained this slightly difference in effect size by the possible statistical influence of studies published after 2002. Pringsheim and collaborators in 2015 [202] substantially updated the review by Connor and included 12 studies: eleven on MPH (both immediate release and long-acting formulation), and one on Lisdexamfetamine (LDX), with a total of 1681 participants and a percentage of ODD/CD comorbidity ranging between 44% and 93%. As in Pappadopulos' review, measures of conduct problems and aggression were included as secondary outcome confirming an effect size of stimulants vs placebo of 0.84 on teachers' measures and 0.55 on parent-rated oppositional, behavior, conduct problems, and aggression.

The more recent meta-analysis by Balia and colleagues [201] identified 5 studies investigating the efficacy of MPH on aggression in CD and included 242 subjects (mean age = 10.66 years). A significant effect of stimulant medications compared to placebo was evidenced by both teachers' ($p = 0.01$) and parents' ratings of conduct problems ($p = 0.11$). The analysis of measures of aggression (IOWA aggression), performed in two studies, revealed only a trend towards efficacy of Methylphenidate. It is worth noting that, within the five selected studies, only two were conducted in subjects with a primary diagnosis of CD while the other were performed in ADHD subjects with comorbid CD. Optimized stimulant treatment was reported

to decrease both CU traits and proactive aggression in ADHD children with ODD/CD [227], however, the systematic review and meta-analysis [201] reports that not enough evidence is available to correlate the presence of CU traits with pharmacologic treatment effect.

Conduct disorder and ODD comorbidity is also frequently related with Emotional Dysregulation (ED) in ADHD. In a prospective longitudinal study [228] performed in 118 ADHD + ODD/CD patients (mean age of 9.0 ± 1.9 years) and treated with MPH for 1 year, symptoms of ADHD and ED were significantly improved after 1-year of MPH treatment ($p < 0.05$). The improvement in ED was independent from other clinical determinants and the authors therefore conclude that MPH can be considered a beneficial medication for ED in ODD/CD comorbid ADHD cases.

Although long term effects of stimulants, both as for efficacy and safety, are still a matter of debate, growing evidence confirm the safety of MPH [229] as well as its efficacy in preventing conduct disorder behaviors in the long term [230]. It is recommended to optimize stimulant dosing, and to switch to another stimulant class, prior to add or starting other medications [194].

4.3.Mood Stabilizers

Mood stabilizers, including Lithium and Divalproate have been shown to be helpful in reducing aggressive symptoms in the contest of CD with a moderate average weighted effect size (0.4) in RCTs [225].

4.3.1. Lithium

Lithium has been shown to be helpful in the management of adolescent aggression when complicating ADHD [225] or associated with DBD [231]. Several studies found that lithium was effective by reducing fighting, bullying, and temper outbursts in severely aggressive CD youth [196,232–235]. In studies including a hospitalized population, lithium treatment, in the short term, resulted efficacious in the management of severely aggressive and explosive patients [196], significantly superior to placebo [234], and similarly to haloperidol, helpful in decreasing aggressive and hostile behaviors [196]. However, a 2-week, double blind, placebo controlled clinical trial showed that lithium carbonate was not different from placebo for the treatment of CD in 33 subjects aged 12–17 [196].

In a retrospective 6- to 12-month naturalistic study [236], 48.3% of 60 CD subjects consecutively enrolled were considered responders to lithium monotherapy or lithium plus

atypical antipsychotics for aggression. Pringsheim and colleagues [202] in their meta-analysis reported an odds ratio of response or remission with lithium of 4.56 ($p < 0.001$), although the quality of the studies was considered low. Study samples are generally small making difficult to accurately assess its real efficacy.

4.3.2. Divalproate/Divalproex Sodium

Few randomized controlled trials examined Divalproate (DVPX) as a potentially effective medication for CD. In a 12-week 2-phase double blind, placebo controlled clinical crossover study including 20 outpatients, aged 10 – 18 years, with a diagnosis of CD or ODD, DVPX was superior to placebo ($p = 0.003$) [237]. DVPX resulted also effective in reducing aggression as an add-on treatment to stimulant medication in an 8 weeks controlled study including children (aged 6–13 years) diagnosed with ADHD and ODD/CD with stimulant-resistant chronic aggression [238], but children affected by CD represented only the 11% of the total sample. These results were later confirmed in a recent trial including 6 – 12-year-olds with ADHD, a disruptive disorder, significant aggressive behaviors, and prior stimulant treatment. The Adjunctive DVPX group showed a good response with greater reductions in aggression ratings than the placebo group although not as large as in the Risperidone adjunctive group [206].

4.4.Non-Stimulant Medications

4.4.1. Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor approved as a treatment for ADHD [239]. Research has indicated that it can reduce emotional lability [240] and that it can induce some benefit in the management of pediatric aggression and oppositional behaviors in youth with ADHD, with or without formal ODD or CD diagnosis [201], with low (0.18) [225] to moderate-high (0.61, 0.72) effect sizes [241].

4.4.2. α_2-Agonists and β-Blockers

Clonidine and Guanfacine are α_2-adrenergic agonists that can be indicated as second-line treatments for ADHD [239], however they also appear to be helpful in treating oppositional and aggressive behaviors in ADHD children and adolescents, with or without formal ODD or CD diagnosis, either in monotherapy, when stimulants are contraindicated, or as an add on treatment, when stimulant determine only partial effectiveness [201]. When CD occur in

patients with previous traumatic experiences or a Post-Traumatic Stress Disorder (PSTD), often associated with stable noradrenergic activation (e.g., increased arousal, impulsiveness, aggression, insomnia), α_2-adrenergic agonists may be helpful [242].

A meta-analysis supported efficacy of Clonidine in ameliorating impulsive aggression [243], and two later RCT [244,245] demonstrated its efficacy, in monotherapy or in add on to MPH, in reducing oppositional and conduct symptoms in children with ADHD and comorbid aggressive CD/ODD.

Guanfacine, better tolerated than Clonidine for its less sedating and hypotensive characteristics, may improve hyperactivity, low frustration tolerance, and irritability [246]. In its extended-release formulation, guanfacine has been shown to decrease both oppositional and ADHD symptoms in children [247].

Propranolol, a non-cardioselective β-blocker, mostly known for its antihypertensive effect and its use in cardiovascular diseases, is often prescribed off-label for the treatment of anxiety and PTSD as well as for the treatment of aggression and behavioral dysregulation in subjects with ASD, intermittent explosive disorder or brain injury [248,249]. Nonetheless, evidence is still limited and of poor quality, suggesting that randomized control trials are needed specifically in children and adolescent with CD to prove its efficacy in this population.

5. Expert Opinion

CD is a highly heterogeneous though very broad and overinclusive category, encompassing a wide range of disorders not only in terms of disease severity and clinical course but also in developmental aspects. These developmental aspects include the age at which symptoms first appear and the clinical presentation, which can vary across different dimensions for various subtypes. These variations are likely linked to distinct underlying neurobiological factors. To better understand and target pharmacological treatments, it is essential to meticulously characterize these developmental subtypes for both clinical and research purposes. Thus, the initial step in the diagnostic process involves disentangling this expansive category into clinical subtypes. For instance, distinguishing between childhood-onset and adolescent-onset CD has important implications for prognosis and treatment. Additionally, incorporating specifiers like Limited Prosocial Emotions and Emotional Dysregulation profiles can reduce the overall heterogeneity. Lastly, defining patterns of psychiatric comorbidity based on structured clinical interviews for patients and parents can aid in prognosis and treatment decisions.

The clinical assessment of individuals with CD starts with the confirmation of the presence of the disorder through standardized diagnostic criteria, medical history, and clinical observations conducted by trained psychiatrists. A comprehensive medical examination should ideally be performed to rule out signs of maltreatment, malnutrition, or untreated infections. Furthermore, patients should undergo screening for various conduct problems, considering factors such as the severity (mild, moderate, or severe) and type (reactive or proactive) of aggression, as well as the harm caused to peers and adults. These factors play a pivotal role in predicting long-term outcomes and determining the appropriate intensity of treatment and the therapeutic setting (hospital or community) to ensure the safety of others. Additionally, it is crucial to evaluate patients for various challenges in daily life, including legal and social issues, educational and occupational difficulties, and psychiatric comorbidities. Identifying differential diagnoses and clinical comorbidities is essential because they significantly influence clinical outcomes and treatment strategies. Thorough medical history exploration should delve into early socio-emotional and behavioral development stages, temperamental traits, and premorbid features. This assessment should also consider family history and parenting strategies.

In clinical settings, structured clinical measures are frequently employed to assess the presence of Callous-Unemotional (CU) and Limited Prosocial Emotions (LPE) traits, including tools like the Antisocial Process Screening Device (APSD) [110] and the Inventory of Callous Unemotional traits (ICU) [111]. Additionally, the Proposed Specifiers for Conduct Disorder (PSCD) may be administered to specifically explore the antisocial dimension of CD with CU. For a more comprehensive evaluation of CD patients, the Youth Version of the Psychopathy Checklist (PCL:YV) may be considered, although it is a more time-consuming process. Assessing empathic skills is recommended, utilizing questionnaires such as the Interpersonal Reactivity Index (IRI) and the Basic Empathy Scale (BES). Regarding Emotional Dysregulation (ED), the Dysregulation Profile of the Child Behavior Checklist (CBCL – DP) indirectly indicates its presence, while the Strength and Difficulties Questionnaire (SDQ) provides a Dysregulation Profile (SDQ-DP) for screening purposes in clinical practice.

After completing the initial steps of the diagnostic process, it becomes imperative to implement treatment strategies. Primary options for patients with CD include psychotherapeutic and psychosocial interventions. These treatments not only address behavioral and emotional symptoms but can also target CU/LPE traits and the core features of ED, especially when administered early in development. Given that CD may precede the development of Antisocial Personality Disorder (AsPD) later in life, particularly in cases of

early-onset CD (before 10 years of age), which often carries a poorer prognosis, and considering that CU traits increase the risk of developing AsPD, it is crucial to provide intensive multimodal treatment to high-risk patients, especially young children with LPE. This treatment approach combines pharmacotherapy with specific psychotherapeutic and psychosocial interventions, aiming to improve not only behavioral issues but also CU traits. While the diagnostic process may be relatively straightforward to implement in clinical practice, especially in collaboration with other settings like schools, the treatment aspect poses challenges in terms of the specialized skills required by psychiatrists, psychologists, and therapists, as well as the organization of services and associated costs. Focusing on high-risk patient groups, such as group treatments, may enhance the feasibility of these interventions.

In situations where psychotherapies and psychosocial treatments are either impractical or difficult to implement due to resource constraints, poor patient compliance, or ineffectiveness, pharmacotherapy should be considered as an alternative. To determine an appropriate pharmacological approach, it is crucial to define specific target dimensions, including irritability, aggression, impulsivity, mood instability, reactivity, and anxiety. Meta-analyses and empirical studies suggest the potential use of Second Generation Antipsychotics (SGAs), such as Risperidone, Lithium salts, antiepileptic drugs, and psychostimulants as viable treatment strategies. The selection of these strategies should take into account clinical phenotypes, particularly the specific symptoms and comorbidities like Attention Deficit Hyperactivity Disorder (ADHD), as well as the tolerability of the medications. It is important to note that data regarding the efficacy of these medications on specific dimensions of CD, rather than categorical diagnoses, are still limited.

SGAs are currently the most commonly prescribed medications and are considered first-line options when severe aggression and violent behaviors are prominent features of the clinical presentation. Their efficacy should be assessed within the first three months, with continued treatment only for responders, and consideration of tentative discontinuation after one year to minimize the risk of side effects, particularly metabolic effects. Risperidone provides the most substantial empirical support, but other SGAs like Olanzapine, Aripiprazole, and Quetiapine may be considered as potential alternatives. Clozapine may be considered for patients who do not respond to at least two SGAs, a pattern similar to its use in schizophrenia. In cases where patients do not respond to SGAs or experience significant side effects like substantial weight gain and metabolic alterations, First Generation Antipsychotics can be considered, although extrapyramidal side effects, especially in long-term use, must be closely monitored.

Lithium salts and antiepileptic drugs may be the preferred choice when ED and irritability, rather than explosive aggression, are the primary features of the disorder. Lithium salts are particularly indicated when impulsivity, emotional reactivity, and excitation are prominent. Furthermore, Lithium should be considered, either as a monotherapy or in combination with other medications, when there are concerns about suicidality, which is often underestimated in individuals with CD and ED. Suicidal tendencies may not be obvious, as they are frequently masked by risky behaviors that appear to be performed without awareness, such as overdoses and reckless driving. Valproate, on the other hand, may be an option when aggressive outbursts are triggered by anxious reactivity to salient stimuli, leading to secondary impulsivity. Valproate offers the advantage of faster dosage titration, especially when acute anxious and impulsive behaviors are prominent.

Since the developmental path to CD, especially when it occurs early in life, often includes ADHD as a precursor or comorbid condition, psychostimulants play a crucial role. Timely pharmacological intervention with ADHD medications, either as a monotherapy or in combination with other drugs, may have a preventive effect on the later development of AsPD and Substance Use Disorder (SUD). Additionally, current treatment with psychostimulants may help prevent criminal behaviors in adult patients with ADHD. Stimulants can enhance impulse control and reduce proactive aggression in ADHD patients with CD by improving their ability to anticipate consequences of their actions, delay gratification, and redirect their behavior away from high-intensity, high-reward, risky situations. Importantly, co-occurring SUD should not be considered a clinical contraindication, given the availability of extended-release formulations of stimulants with a lower risk of misuse, as well as non-stimulant medications. However, it is essential to note that co-occurring SUD remains a negative predictor of treatment outcomes and responses. In cases where CD occurs in individuals with a history of early traumatic experiences or full-blown PTSD, often characterized by stable noradrenergic activation leading to symptoms like increased arousal, impulsiveness, aggression, and insomnia, alpha-2 inhibitors such as Clonidine or Guanfacine, as well as beta-blockers, may be considered as primary or adjunct medications.

There is potential for exploring novel treatments aimed at improving prosocial behaviors and empathy, such as oxytocin, in selected populations through future research. Additionally, further investigation into the gender-related specificity of interventions is warranted, as females with CD may possess unique biological, psychological, and social characteristics that are not yet fully understood. Future studies focusing on psychophysiological, cognitive, neurofunctional, and neuroanatomical correlates of CU/LPE

traits may aid in identifying specific subgroups of CD patients with distinct clinical outcomes and treatment requirements. More sophisticated studies should be conducted using specific samples (e.g., youths vs. adults), targeting specific dimensions of interest, and providing better definitions of primary outcomes. While many studies have focused on aggressive behaviors, less attention has been given to global and social functioning, and even less to the long-term effects of interventions (e.g., reconviction rates). Moreover, it is crucial to address specific personality traits, particularly CU/LPE traits characterized by a lack of empathy, remorse, and guilt, along with a disregard for prosocial norms and difficulties in forming intimate relationships. Early psychosocial interventions that aim to impact these fundamental aspects of individual functioning, beyond addressing aggression and impulsivity, should be systematically tested in clinical samples.

Further exploration of developmental trajectories and predictors of therapeutic response is necessary, with a particular focus on differentiating between patients with CU and harmful traits but higher social competencies and few psychiatric symptoms, and those with psychopathic traits characterized by extensive comorbid psychopathology and emotional instability. However, in the clinical management of these patients, especially during adolescence, there is a latent risk of rigidly categorizing them into emotionally "hot" and "cold" domains, with the former seen as within the psychiatric realm and the latter often deemed refractory to conventional psychological or pharmacological treatments and falling under the jurisdiction of the legal system. Instead, the identification of CU and psychopathic traits should not be viewed as a criterion for admitting or excluding patients from psychiatric treatment, but instead as a specifier leading to more timely, intensive, and specifically oriented programs, more expensive in the short-term, but cost-effective in the long-term.

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* [108] – comprehensive review of the clinical measures for assessing CU traits
* [46] – comprehensive review of epidemiology, diagnosis and treatment of DBD
** [93] – highly referential review for Conduct Disorder
** [109] – one of the most widely used measures for the assessment of CU traits (APSD)
** [110] – one of the most widely used measures for the assessment of CU traits (ICU)
** [157] – practitioner review with meta-analysis of psychosocial treatment for CD
** [189] – systematic review of psychopharmacological treatment strategies for CD and CU