REVIEW AGGRESSIVE BEHAVIOR

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Aggressive Behavior in Children and Adolescents With Bipolar Spectrum Disorder: A Systematic Review of the Prevalence, Associated Factors, and Treatment

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Objective: Bipolar disorder (BD) in childhood and adolescence is associated with aggressive behaviors, which might be common and in turn associated with poor clinical outcomes. This is the first systematic review to provide a comprehensive view of the current status of the knowledge about aggressive behaviors in youth with BD.

Method: We conducted a PRISMA–compliant systematic review of studies investigating aggressive behaviors in children and adolescents with BD (PROSPERO: CRD42023431674). A systematic multi-step literature search was performed on PubMed and the Web of Science. Literature search and data extraction were carried out independently. We provided a systematic synthesis of the findings from the included studies We assessed risk of bias using a modified version of the Newcastle-Ottawa Scale for cross-sectional and cohort studies.

Results: Of the 2,277 identified records 35 were included; mean age was 12.4 years, and 57.1% were male individuals. 7 studies reported on the prevalence of aggressive behavior among BD children and adolescent population, with 5 of them reporting a prevalence of over 69.0%. Aggressive behaviors were more common in children and adolescents with BD than in those with ADHD or depression. Aggressive behaviors were associated with borderline personality disorder features and poor family functioning. Valproic acid received empirical support for its efficacy in reducing aggressive behavior in BD.

Conclusion: Aggressive behaviors are prevalent among youth with BD and warrant clinical attention and specific evidence-based management. Further research on prognostic factors and psychosocial interventions evaluated prospectively is required.

Plain language summary: In a systematic review including 35 articles, aggressive behaviors were found to be prevalent among young people with bipolar disorder. Aggressive behaviors among children and adolescents are more common in youth with bipolar disorder than youth with major depressive and attentional disorders and are associated with borderline personality disorder features and poor family functioning. More research is needed on prognostic factors and treatments for these highly impacting behaviors.

Diversity & Inclusion Statement: One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented racial and/or ethnic groups in science. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented sexual and/or gender groups in science. One or more of the authors of this paper self-identifies as living with a disability. We actively worked to promote sex and gender balance in our author group. We actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our author group.

Key words: aggressive behavior; BD; adolescents; systematic review

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Bipolar disorder (BD) is a chronic condition with a lifetime prevalence around 1% that frequently has its onset before the age of 18 years.[1] Different categorizations include bipolar disorder I (BD-I), bipolar disorder II (BD-II), and bipolar disorder not otherwise specified (BD-NOS).[1] BD-I is distinguished by the presence of at least 1 manic episode, often accompanied by 1 or more depressive episodes, whereas individuals with BD-II experience episodes of depression and hypomania.[2] BD-NOS is diagnosed when a person's symptoms for either BD-I or BD-II are present but lack sufficient duration or severity of manic symptoms.[2,3]

One of the significant challenges associated with BD in children and adolescents is the appearance among this population of aggressive behavior, which is broadly defined as intentional behavior aimed at causing harm to individuals or property.[4] Aggressive behaviors not also impose significant challenges on individuals, families, and society,[5] but also pave the way for adverse outcomes in adulthood, encompassing mental and physical illnesses, unemployment, socioeconomic

disadvantage, and forensic issues.[6] Within the youth BD population, aggressive behavior has shown to be a common comorbidity,[7] which seems to be associated with poor clinical outcomes, such as increased rates of psychiatric hospitalizations.[8]

Unlike other disorders such as attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder,[9] for which aggressive behavior has been extensively studied, the research on aggressive behavior in BD remains scant. Despite the notable impact of such behavior on individuals or their communities, there is limited evidence regarding the factors associated to this behavior, and whether it exhibits differential traits, clinical, and neurobiological correlates compared to the aggression present in the aforementioned disorders. Furthermore, there is limited advice on the management of aggressive behavior in young BD population, and whether specific interventions are needed for it or whether effective treatment for the underlying BD is sufficient. Clinical guidelines, such as National Institute of Health and Care Excellence (NICE) guidelines recommend a combination of psychotherapeutic and pharmacological approaches for the management of BD in youth.[10] Nonetheless, no systematic review has evaluated aggressive behaviors in BD.

Based on the above, the aim of this study was to provide a comprehensive review of the current status and advances in the prevalence, associated factors, and treatment of aggressive behaviors among children and adolescents with bipolar disorder.

METHOD

This study protocol was registered on PROSPERO (registration number: CRD42023431674). The study was conducted in accordance with PRISMA,[11] following EQUATOR Reporting Guidelines[12] (PRISMA checklists are outlined in Table S1 and Table S2, available online).

Search Strategy and Selection Criteria

A systematic multi-step literature search was performed by 2 independent researchers (EB, SR) using the following keywords: ("child*" OR "adolesc*" OR "paediatric" OR "pediatric" OR "teen" OR "early-onset") AND ("mania" OR "bipolar disorder" OR "bipolar" OR "bipolar prodrom*" OR "cyclothymic" OR "bipolar at risk" OR "hypersensitive temperament" OR "mood swings" OR "bipolar disorder-not otherwise specified" OR "BD-NOS" OR "MD-NOS") AND ("attack*" OR "fight*" or "aggress*" OR "violen*" or "hostil*" OR "agg* externalizing behav* "or "externalizing problem*").

First, PubMed and the Web of Science database (Clarivate Analytics) were searched, incorporating the Web of Science Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index, from inception until May 1, 2023, without language restriction. Second, data were searched for in relevant trial registries (clinicaltrials.gov). Third, the search was completed by manually reviewing the references of systematic reviews or meta-analyses retrieved during the literature search.

Articles identified were screened as abstracts, and after excluding those that did not meet the inclusion criteria, the full texts of the remaining articles were assessed for eligibility and inclusion. Decisions regarding their final inclusion in the systematic review were made by consensus or tie-break by a third reviewer (GSP).

Eligibility Criteria

We included studies investigating aggressive behaviors in children and adolescents with BD (definitions of aggressive behavior are detailed in Supplement 1, available online). Inclusion criteria comprised the following: (1) individual studies with original data, (2) conducted in children and adolescents (<18 years of age); (3) diagnosed with BD, according to *DSM* criteria (any version) or *International Classification of Diseases* (*ICD*) criteria (any version); (4) evaluating the presence, associated factors, neuroimaging correlates, or treatment of aggressive behaviors; (5) written in any language; (6) with no restriction on the topics being covered as long as they evaluated our population (1 and 2 above) and outcome. Exclusion criteria consisted of (1) reviews, editorials, conference proceedings, or clinical cases; (2) studies focusing on self-harm or suicidal behavior only; and (3) studies reporting on other mental health conditions or focusing on adults only.

Data Extraction

Two researchers (EB, SR) independently extracted data from all included studies. Any discrepancies were resolved through consensus, consulting a third party (GSP) when necessary. A summary of selected variables included the following information: author and year of publication, country in which the study was conducted, study design (cross-sectional, cohort, prospective, retrospective, or clinical trial), study quality (see below), primary diagnosis of BD, definition of aggressive behavior, psychometric instrument used to assess aggressive behaviors and BD, sample size, mean age and range, percentage of male individuals, ethnicity, and key findings.

Risk of Bias (Quality) Assessment

Risk of bias was assessed using a modified version of the Newcastle–Ottawa Scale for cross-sectional and cohort studies, which has been used frequently in the field[13] (Table S3, available online).

Strategy for Data Synthesis and Statistics

A systematic synthesis of the findings from the included studies was provided. The available evidence was structured into the prevalence of aggressive behaviors among children and adolescents with BD, their diagnostic factors (general diagnostic and epidemiologic factors, comorbidity, risk factors, and neuroimaging factors), and therapeutic factors (response to interventions).

RESULTS

Study Selection

A total of 2,277 studies were identified across different sources. After de-duplication, 1,774 studies were screened for eligibility. Of these, 1,635 were excluded at the title/abstract level, and 139 articles were assessed in full text according to the predetermined criteria (Figure 1). Altogether, 35 studies were included in this systematic review (Table 1[14–47]).

Study Characteristics

Of the 35 studies included, 7 studies[3,16,19,26,32,40,47] examined the prevalence of aggressive behaviors among children and adolescents BD, 16 studies[16,17,19–21,23–25,28,30,34,37,41,44,46,47] examined general diagnostic and epidemiologic factors, 9 studies[14,18,22,27,29,35–37,47] examined response to treatment, 4 studies[23,26,31,43] examined demographic factors associated with aggressive behavior in BD, 3 studies[15,38,42] examined neuroimaging associations, 2 studies[23,39] examined the association with comorbid diagnoses, 1 study[45] examined risk factors, and 1 study[33] examined functioning. A total of 26 studies[3,14,16,17,19,20,23–28,30–34,38–46] (74.3%) adopted a cross-sectional design; 6 (17.1%)[15,18,22,29,36,47] were clinical trials, and 3 (8.6%)[21,35,37] were retrospective cohort studies. The overall database comprised 2,747 individuals; the mean age of the sample was 12.4 years (range, 2-18 years), and 57.1% were male. The majority of studies (80.0%) were carried out in the United States, and the mean duration of follow-up in the longitudinal cohort studies was 37.4 weeks.

Prevalence of Aggressive Behaviors Among Children and Adolescents With BD

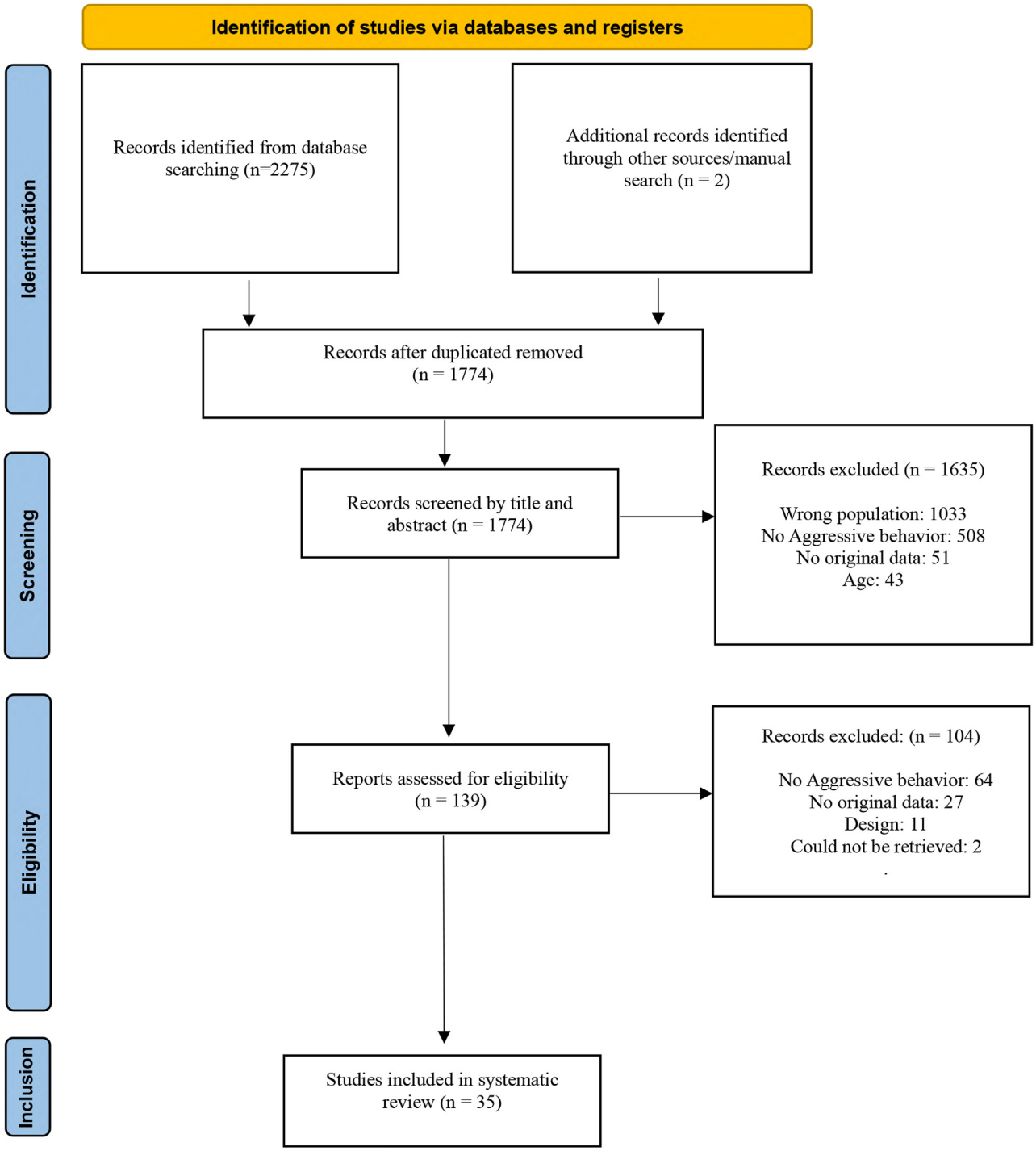
The prevalence of aggressive behaviors among young individuals with BD was reported in 7 studies,[3,16,19,26,32,40,47] including a total sample of 340 participants. Prevalence varied significantly among studies, with reported rates ranging from 21.0%[47] to 98.4%.[40] However, 5[3,16,26,32,40] of the 7 studies, including 302 patients, reported a prevalence of aggressive behaviors of over 69.0%. Although all of the articles were consistent in the use of *DSM* [2] to establish a BD diagnosis, a significant heterogeneity was found in the psychometric instruments used to assess aggressive behavior. This included clinical assessments by senior clinicians,[26] general psychopathology and bipolar symptom scales and interviews,[3,16,19,40] and specific aggressive behavior scales[32,47] (Table S4, available online).

General Diagnostic and Epidemiologic Factors

No differences were found among BD diagnoses, including BD-I, BD-II, and BD-NOS.[3,46] Five studies[16,20,24,28,41] revealed statistically significantly greater levels of aggressive behavior among children and adolescents with BD compared to healthy controls as measured with the Child Behavior Checklist (CBCL) and the Aggression Questionnaire (AQ). Furthermore, 5 studies[16,24,25,30,44] revealed a greater prevalence of aggressive behavior among youth with BD compared to youth with ADHD, as measured with the CBCL. One of these studies revealed that individuals with BD exhibited greater levels of verbal and reactive aggressive behavior than individuals with ADHD ($t = 2.4$; $p < .05$), but not proactive aggressive behavior.[25] Three studies revealed statistically significantly greater prevalence of aggressive behavior among individuals with BD than among individuals with depression[19,46] or depressive/anxiety features[24] ($p < .01$), as measured with the CBCL aggressive behavior scale. A greater prevalence of aggressive behavior among youth with BD compared with the offspring of parents with BD ($d = 0.41$; $p = .03$) was also reported in 1 study.[41]

Three studies[23,31,43] examined the association between age and aggressive behavior in BD, and 1 study[26] explored how aggressive behavior scores as reported by parents differed between the sexes. One study found that, among individuals who received a bipolar disorder diagnosis later in life (age 5-17 years), parent-reported aggressive behavior was prevalent among 10% of individuals before the age of 3 years, and this increased to 52% by the age of 7 to 12 years.[31] In addition, another study revealed that BD individuals aged 9 to 10 years exhibit the highest levels of aggressive behavior ($p = .018$)[23] within a sample of individuals aged 4 to 17 years. However, another study found that prevalence of aggressive behavior was significantly greater among younger girls aged 3 to 11 years than among older girls aged 12 to 17 years ($\chi^2 = 5.2$; $p < .05$).[43] Results from 1 study indicated that, overall, aggressive behavior did not differ between boys and girls.[26]

FIGURE 1 PRISMA Flow Diagram of Study Selection Process



Comorbidity

Research has produced mixed findings regarding aggressive behavior in youth with BD and comorbid conditions. Two studies revealed greater aggressive behavior among children and adolescents with comorbid ADHD and BD (ADHD+BD) compared with ADHD alone,[34] and comorbid conduct disorder and BD (CD+BD) compared with CD alone.[36] Conversely, other studies found no difference in aggressive behavior between young people with ADHD+BD compared to those with ADHD alone,[21] and comorbid

TABLE 1 Characteristics of Included Studies

Author (year), reference	Country	Study design (NOS RoB score)	BD sample size	Age, y, mean ± SD (range)	Male individuals, %	Ethnicity, %	BD diagnosis, %	Key findings
Barzman *et al.* (2014)[14]	US	Cross-sectional (Medium)	10	15 ± 1 (12-17)	50	n.a.	BD-I	Aggressive behavior is inversely correlated with activation in the following regions: left subgenual anterior cingulate gyrus (ES n.a.; $p = .024$), right amygdala (ES n.a.; $p = .025$), left Brodmann area 10 (ES n.a.; $p = .029$), and the right thalamus ($p = .039$).
Barzman *et al.* (2016)[15]	US	Clinical trial (low)	33	15.3 ± 1.5 (12-18)	36	African American (18), White (76), other (6)	BD-I	After 28 days, divalproex (unstandardized $d = 7.3$; $p < .001$) and quetiapine (unstandardized $d = 8.0$; $p < .001$) reduced aggressive behavior.
Biederman *et al.* (1995)[16]	US	Cross-sectional (Low)	31	8.1 ± 2.8 (0-12)	86	n.a.	BD-I	Prevalence of aggressive behavior of 82.5%. Aggressive behavior was more prevalent in bipolar individuals compared to those with ADHD and healthy controls (OR = 20.3; $p < .01$).
Carlson and Dyson (2012)[17]	US	Cross-sectional (Medium)	102	12 ± 3.6 (5-18)	73.5	White (83), other (17)	BD-I	There was a non-significant trend whereby rates of bipolar seemed higher in children with both teacher- and parent-reported aggressive behavior (ES n.a.; $p = .061$) compared to those with aggressive behaviors only reported by 1 of the informants.
Chang *et al.* (2006)[18]	US	Clinical trial (Low)	19	15.8 ± 1.7 (12-17)	35	African American (5), Hispanic (5), White (90)	BD-I (35), BD-II (30), BD-NOS (35)	Lamotrigine resulted in significant reductions in aggressive behavior after 8 wk ($t = 2.6$, $df = 18$, $p = .02$).
Connor *et al.* (2017)[19]	US	Cross-sectional (Low)	49	15.8 ± 1.7 (12-17)	44	CaucasianAmerican (72), non-Caucasian American (28)	BD-I	Prevalence of aggressive behavior 39.0%. Aggressive behavior was more common in adolescents with BD than in adolescents with depression ($\chi^2 = 7.44$; $p = .006$).
Cordeiro et al (2020)[20]	Brazil	Cross-sectional (Medium)	75	8.9 ± 1.3 (n.a)	76.1	n.a.	BD-I	Children with BD and BD+ADHD had greater levels of aggressive behavior that healthy controls (CBCL *T* score 79 vs 78 vs 58; $p < .001$). Aggressive behavior in BD and BD+ADHD was not significantly different (ES n.a.; $p > .05$).
Danielyan *et al.* (2007)[21]	US	Retrospective cohort (Medium)	25	n.a.	73.1	African American (3.8), Caucasian (92.3)	BD-I (26) BD-NOS (61.5)	Children with BD and BD+ADHD did not differ in levels of aggressive behavior (ES n.a.; $p > .05$)
DelBello *et al.* (2004)[22]	US	Clinical trial (Low)	30	14.5 ± 2 (12-18)	53	Caucasian (83), other (17)	BD-I	Divalproex resulted in a significant reduction in aggressive behavior after 6 wk (YMRS aggression mean change ± SD, −0.9 ± 2.0, $p = .05$). Aggressive behavior reduced in 73% adolescents with BD.

(*continued*)

TABLE 1 Continued

Author (year), reference	Country	Study design (NOS RoB score)	BD sample size	Age, y, mean ± SD (range)	Male individuals, %	Ethnicity, %	BD diagnosis, %	Key findings
Demeter *et al.* (2013)[23]	US	Cross-sectional (Low)	535	10.5 ± 3.5 (4-17)	63	African American (13), Caucasian (78), Hispanic (2), other (7)	BD-I/II (54.2), BD-NOS/ cyclothymic disorder (45.8)	Within a sample of individuals aged 4 to 17 y, those aged 9 to 10 y in the BD group exhibited the highest aggressive behavior (ES n.a.; $p = .018$). ADHD comorbidity was associated with significantly higher aggressive behavior (ES n.a.; $p = 0.04$).
Dienes *et al.* (2002)[24]	US	Cross-sectional (Low)	16	11.0 ± 2.9 (6-18)	60	n.a.	BD-I	Youth with BD exhibited greater levels of aggressive behavior than the depressed/anxious group (CBCL score 75.6 ± 13.9 vs 60.1 ± 7.8; $p < .01$), the ADHD group (65.7 ± 7.4; $p = .03$), and the no diagnosis group (57.9 ± 11.0; $p < .01$).
Doerfler *et al.* (2011)[25]	US	Cross-sectional (Medium)	27	12 ± 3.5 (n.a.)	66.7	African American (2), Asian American, or other (2), Caucasian (92), Latino (4)	BD-I	Parents reported that children with BD reported greater levels of verbal and reactive aggressive behavior than youth with ADHD ($t = 2.4$; $p < .05$). The groups did not differ on proactive aggressive behavior (ES n.a.; $p > .05$).
Faedda *et al.* (2004)[26]	US	Cross-sectional (Medium)	82	10.6 ± 3.6 (3-17)	65.9	n.a.	BD-I	Prevalence of aggressive behavior of 90.2%. Aggressive behavior was present in 90.2% of subjects. Prevalence of aggressive behavior did not differ between sexes (ES n.a.; $p > .05$).
Frazier *et al.* (1999)[27]	US	Cross-sectional (Medium)	28	10.4 ± 3.8 (4-17)	96.4	n.a.	BD-I	Risperidone treatment resulted in a significant reduction in aggressive behavior (CGI severity score 5.1 ± 1.2 at baseline and 3.0 ± 1.2 at follow-up; $p < .01$). Aggressive behavior scores improved for 82% of the sample.
Giles *et al.* (2007)[28]	US	Cross-sectional (Low)	28	14.2 ± .4 (10-18)	57	White (89), other (11)	BD-I	The BD group scored significantly higher than in aggressive behavior than in healthy controls (CBCL score 70.0 vs 51.0; $p < .001$).
Hafeman *et al.* (2020)[29]	US	Clinical trial (Low)	413	12.6 ± 3.3 (7- 17.11)	53.5	Caucasian (82.1), other (17.9)	BD-I (59.1), BD-II (6.8), BD-NOS (34.1)	Lithium compared to other, non-lithium mood stabilizers was associated with less parent-reported aggressive behavior ($\beta = -1.1$; $p < .001$) in BD
Hazel *et al.* (1999)[30]	Australia	Cross-sectional (Medium)	25	n.a. (9-13)	100	n.a.	BD-I	The BD+ADHD group had significantly higher aggressive behavior scores than the ADHD-only group ($F = 26.5$; $p < .01$).
Hernandez *et al.* (2017)[31]	US	Cross-sectional (Medium)	83	9.4 ± 3.8 (5-17)	60	n.a.	BD-I (28.9), BD-II disorder (1.1), BD-NOS (61.5)	Parent-reported aggressive behavior was reported in more than 10% of patients before the age of 3 y. By age 7 to 12 y, 52% of individuals had parent-reported aggressive behavior.

(*continued*)

TABLE 1 Continued

Author (year), reference	Country	Study design (NOS RoB score)	BD sample size	Age, y, mean ± SD (range)	Male individuals, %	Ethnicity, %	BD diagnosis, %	Key findings
Jerrel and Prewette (2008)[32]	US	Cross-sectional (Medium)	82	n.a. (6-17)	48	White (80), other (20)	BD-I	Aggressive behavior was present in 69% of BD children and adolescents.
Keenan-Miller *et al.* (2012)[33]	US	Cross-sectional (Low)	115	15 ± 1.4 (12-18)	46	African American (7.0), Asian/Pacific Islander (2.6), Caucasian (85), Hispanic (9.6), Native American (1.7), other/biracial (3.5)	BD-I (59), BD-II (41)	Aggressive behavior was significantly associated with reductions in child-reported ($\beta = 0.21$; $p = .02$) and parent-reported ($\beta = 0.50$; $p < .001$) family functioning.
Lus and Mukaddes (2009)[34]	Turkey	Cross-sectional (Medium)	10	10.2 ± 2.5 (7-14)	80	n.a.	BD-I	The ADHD+BD group had significantly higher aggressive behavior than the ADHD group (ES n.a.; $p = .001$).
Macmilan *et al.* (2006)[35]	US	Retrospective cohort (Medium)	31	11.5 ± n.a. (n.a)	87.1	n.a.	BD-I	Oxcarbazepine was associated with increases in aggressive behavior at 4 mo (divalproex discontinuation 0%; oxcarbazepine discontinuation 27.3%; $p = .037$). In the patients who discontinued oxcarbazepine, aggressive behavior improved.
Masi *et al.* (2008)[36]	Italy	Clinical trial (Low)	201	8.8 ± 5.2 (n.a.)	61.4	n.a.	BD-I	Aggressive behavior is more prevalent in children with comorbid CD+BD than CD alone ($\chi^2 = 35.2$; $p = .003$). Greater reductions in aggressive behavior compared to that in the BD+CD group after 6 to 9 mo of exposure to psychopharmacological interventions ($\chi^2 = 15.1$; $p < .002$). Psychosocial interventions did not reduce aggressive behavior ($F = 3.4$; $p = .182$).
Masi *et al.* (2011)[37]	Italy	Retrospective Cohort (Low)	51	14.2 ± 3.1 (6-18)	58.8	Italian (92.2), non-Italian (7.8%)	BD-I	Non-responders to treatment result in greater aggressive behavior scores toward objects ($F = -2.2$; $p = .03$) and others ($F = -2.1$; $p = .04$) compared to responders following exposure to interventions (psychosocial, psychopharmacological, psychoeducational, and psychotherapeutic).
Salazar de Pablo *et al.* (2020)[3]	US	Cross-sectional (Low)	76	15.6 ± 1.4 (12-18)	40.8	White (51.4), other (48.6)	BD-I (24), BD-NOS (29), MD-NOS (23)	Aggressive behavior was prevalent in 69.9% of participants.

(*continued*)

TABLE 1 Continued

Author (year), reference	Country	Study design (NOS RoB score)	BD sample size	Age, y, mean ± SD (range)	Male individuals, %	Ethnicity, %	BD diagnosis, %	Key findings
Saxena *et al.* (2012)[38]	US	Cross-sectional (Medium)	10	13.9 ± 3.6 (7-17)	40	n.a.	BD-I	Results demonstrated a negative correlation between history of aggressive behavior and connectivity values in the anterior commissure ($r = -0.66$; $p = .04$)
Saxena *et al.* (2018)[39]	US	Cross-sectional (Low)	30	12.9 ± 3.1 (7-17)	53.3	Black/African (13.3), White (83.3), other (3.3)	BD-I (66.6), BD-II (10), BD-NOS (23.3)	There was a significant association between borderline personality disorder features and aggressive behavior symptoms ($r = 0.75$; $p = .001$) in young individuals with BD.
Scheffer and Niskala Apps (2004)[40]	US	Cross-sectional (Medium)	31	n.a.	67.7	African American (9.7), Caucasian (87), Hispanic (3.3)	BD-I	Prevalence of aggressive behavior of 98.4%.
Simonetti *et al.* (2021)[41]	US	Cross-sectional (Low)	42	13.4 ± 2.9 (7-17)	41.9	African American (20.9), Caucasian (67.4), more than 1 (11.7)	BD-I	Individuals with BD showed higher levels of aggressive behavior compared with healthy controls ($d = 0.41$; $p < .05$) and offspring of parents with bipolar disorder ($d = 0.41$; $p < .03$).
Simonetti *et al.* (2021)[42]	US	Cross-sectional (Low)	23	12.3 ± 3.2 (7-17)	34.8	African American (8.7), Caucasian (91.3)	BD-I	Individuals with BD displayed higher levels of aggressive behavior and cortical thinning in the frontoparietal network and cingulo-opercular network than healthy controls (ES n.a.; $p < .001$).
Staton *et al.* (2008)[43]	US	Cross-sectional (Medium)	130	11.6 (3-17)	n.a.	n.a.	BD-I	The prevalence of aggressive behavior was significantly higher among younger female individuals (3-11 y) than among older female individuals (12-17 y) ($\chi^2 = 4.97$; $p < .05$).
Tramontina *et al.* (2003)[44]	Brazil	Cross-sectional (Low)	36	9.6 ± 3.5 (<15)	69.4	n.a.	BD-I	Children with BD had significantly higher rates of aggressive behavior than those with ADHD (CBCL score 67.0 vs 47.0; $p < .05$).
Turan *et al.* (2022)[45]	Turkey	Cross-sectional (Low)	145	14.4 ± 2.4 (n.a.)	33.8	n.a.	BD-I	Aggressive behavior was higher in BD adolescents that present irritability and psychomotor agitation ($\chi^2 = 5.2$; $p = .021$).
Van Meter *et al.* (2016)[46]	US	Cross-sectional (Low)	58	n.a.	n.a.	n.a.	BD-I (31), BD-II (22.4), BD-NOS (46.6)	Children and adolescents with BSD had significantly greater levels of aggressive behavior than individuals with depression (CBCL subscale 11.1 ± 4.9 vs 6.7 ± 4.9; $p < .05$). Results indicated no difference in aggressive behavior scores among the 3 bipolar groups (ES n.a.; $p > .05$).

(*continued*)

TABLE 1 Continued

Author (year), reference	Country	Study design (NOS RoB score)	BD sample size	Age, y, mean ± SD (range)	Male individuals, %	Ethnicity, %	BD diagnosis, %	Key findings
West (2011)[47]	US	Clinical trial (Low)	65	10.9 ± 3.3 (8-18)	65	African American (17), Caucasian (71), Hispanic (2)	BD-I	Prevalence of aggressive behavior of 21.0%. No differences in aggressive behavior were found between BD+DBD and BD groups. Effects of divalproex/risperidone after 6 wk were attenuated by high baseline aggressive behavior levels (CAFAS score 11.0 ± 27.7 vs 25.3 ± 43.7) (p = .021).

Note: ADHD = attention-deficit/hyperactivity disorder; BD = bipolar disorder; BD-NOS = bipolar disorder not otherwise specified; CAFAS = Child and Adolescent Functional Assessment Scale; CBCL = Child Behavior Checklist; CD = conduct disorder; CGI = Clinical Global Impressions scale; DBD = disruptive behavior disorder; ES = effect size; n.a. = not available; Newcastle–Ottawa Scale; MD-NOS = mood disorder not otherwise specified; OR = odds ratio; RoB = risk of bias; YMRS = Young Mania Rating Scale.

disruptive behavior disorder (DBD) and BD (DBD+BD) compared to BD alone.[47] One study[23] found that comorbid ADHD was significantly associated with higher aggressive behavior scores. No studies were found in which the role of impulsivity as a trait (regardless of the primary diagnosis) and its impact on aggressive behavior could potentially clarify these contradictory outcomes. Another study[38] indicated a significant association between aggressive behavior and borderline personality disorder features among youth with BD.

Risk Factors

Two studies suggest potential risk factors related to the emergence of aggressive behaviors in youth with BD. One study[45] identified baseline irritability and psychomotor agitation as risk factors for later presenting aggressive behavior in youth with BD in the context of an inpatient unit (χ^2 = 5.2; p = .021). On the other hand, another study[33] highlighted diminished family functioning in the 3 months prior, as reported both by children (β = 0.21; p = .02) and by parents (β = 0.50; $p < .001$), as a risk factor for the emergence of aggressive behaviors at the time of assessment. However, as the authors note, given the cross-sectional design of the latter study and the disruptive effect of aggressive behavior on family functioning, establishing causality is challenging.

Neuroimaging Factors

Three studies reported on neuroimaging correlates of aggressive behavior in children and adolescents with BD. One of these studies[14] indicated an inverse correlation between aggressive behavior and activation in the following regions: right amygdala, left Brodmann area 10, the right thalamus and left subgenual anterior cingulate gyrus—all of them areas previously involved in the pathway to aggression, suggesting dysregulation at these levels. Another study[38] revealed a negative correlation between history of aggressive behavior and fractional anisotropy values in the anterior commissure (p = .04) among BD youth with aggressive behaviors. This might suggest disruption of interhemispheric communication, which may contribute to emotional deficits that contribute to aggression. Finally, 1 study[42] illustrated that youth with BD demonstrated greater levels of aggressive behavior and cortical thinning in the frontoparietal network and cingulo-opercular network compared with healthy controls. This might indicate the existence of altered affective processing and executive dysfunction, which facilitates aggressive responses to stimuli.

Response to Treatment

Three independent studies[15,22,35] found that divalproex successfully reduced aggressive behavior in children and adolescents with BD, with varying effect sizes. However,

none of them had a randomized controlled design, which constitutes a significant limitation (Table 1). In addition, 1 study[27] revealed the positive effect of risperidone in reducing aggressive behavior (Clinical Global Impressions [CGI] scale severity score 5.1 ± 1.2 at baseline and 3.0 ± 1.2 at follow-up; $p < .01$). Lamotrigine ($t = 2.6$; $p = .02$),[18] quetiapine ($d = 8.0$; $p < .001$),[15] and lithium also reduced aggressive behavior. Lithium, compared to other, non-lithium mood stabilizers, was associated with lower aggressive behavior ($\beta = -1.1$; $p = .001$).[29] Oxcarbazepine resulted in increased discontinuation because of aggressive behavior at 4-month follow-up compared to divalproex (divalproex discontinuation, 0%; oxcarbazepine discontinuation, 27.3%; $p = .037$).[35]

One study[36] showed a positive effect on aggressive behavior at follow-up subsequent to receiving psychosocial interventions (parent training, playground behavior programs, and periodic individual sessions) and psychopharmacological interventions (mood stabilizers) for children with BD compared to individuals with CD+BD; however, results did not survive the Bonferroni correction. Another study[37] comparing responders and non-responders to psychosocial, psychopharmacological, psychoeducational, and psychotherapeutic interventions revealed significant reductions in aggressive behavior for the responder group ($F = -2.2$; $p < .05$) (responders were categorized as patients who, at the end of hospitalization, had achieved a CGI Scale score of 1 (very much improved) or 2 (much improved).

Two studies reported on the adverse effects of the pharmacological treatments used for aggressive behavior in youth with BD, which did not substantially differ from those observed in other contexts and indications. MacMillan *et al.*[35] and Barzman[15] found that divalproex use elicited side effects of sedation, headaches, tremor, drooling, and nausea among part of their sample. Common side effects of risperidone use included weight gain, sedation, and drooling. The most common side effects for quetiapine were sedation, gastrointestinal upset, and headaches.[15] The studies exploring lamotrigine and lithium use did not present information on side effects.

One study[47] revealed that the efficacy of interventions is diminished in the presence of high baseline aggressive behavior. High baseline aggressive behavior resulted in suppressed improvements in global functioning after a 6-week course of risperidone or divalproex (CAFAS score 11.0 ± 27.7 vs 25.3 ± 43.7; $p = .021$, $p = .021$). However, the study reliability was limited by a small sample size and the lack of assessment of individual effects of each independent variable before examination.

Risk of Bias (Quality Assessment)

Thirteen cross-sectional studies (37.1%) showed medium overall risk of bias, and 13 (37.1%) showed low overall risk of bias (Table 1). The primary source of risk of bias was "measurement of selection." This domain returned a high-level risk of bias due to a lack of studies justifying that their sample size was satisfactory or providing a summary of non-respondent characteristics. Moreover, the quality assessment using the Newcastle–Ottawa Scale adjusted for cohort studies indicated a low risk of bias; 7 studies (20.0%) displayed low overall risk of bias, and 2 studies (5.7%) displayed medium risk of bias.

DISCUSSION

To the best of our knowledge, this is the first systematic review to provide a comprehensive view of the current status of the knowledge about aggressive behaviors in children and adolescents with BD, including evidence on their prevalence, associated and therapeutic factors. This study reveals a high prevalence of aggressive behaviors among young individuals with BD and a wide range of factors that are associated with aggressive behaviors. From a diagnostic perspective, this review identifies general diagnostic and epidemiologic factors that increase the likelihood of children and adolescents with BD eliciting aggressive behaviors or increasing their severity. From a therapeutic perspective, this review provides valuable information on the response to interventions.

Several findings arise from this study. Aggressive behaviors are highly prevalent among children and adolescents with BD, which highlights a substantial disparity in aggressive behavior levels compared with the evidence base examining adult BD populations, which present a lower prevalence of aggressive behavior (10.6%-11.9%).[48,49] Furthermore, this stresses the greater vulnerability BD individuals with BD to distress, functional impairment, forensic problems, and other poor outcomes, as a result of higher levels of aggressive behavior.[6,7] It should be noted that only 7 studies presented data on the prevalence of aggressive behavior in pediatric BD, highlighting the limited research in this domain. More research is required to better understand the correlates of aggressive behavior in BD in childhood and adolescence.

Although findings suggest that aggressive behaviors across BD I, BD II, and BD-NOS are similarly frequent,[3,20] this study also reveals a greater prevalence of aggressive behavior in individuals with BD compared to other child and adolescent populations, including samples of healthy controls, individuals with ADHD, depression, or

depression/anxiety, and the offspring of parents with BD.[16,19,20,24,25,28,30,42,44,46] This evidence supports the notion that aggressive behavior is an often-present and significant characteristic of BD in childhood and adolescence.[7] Results also suggested that the detection of aggressive behaviors in BD children and adolescents may be facilitated by obtaining collateral information from different informants (eg, parents and teachers[17]), highlighting the importance for clinical practice of ensuring that a comprehensive assessment takes place that considers information from multiple perspectives. The results should encourage clinicians working with children and adolescents diagnosed with BD to be vigilant in screening for and assessing aggressive behaviors as a key aspect of symptomatology. Furthermore, the results underscore the importance of conducting a comprehensive assessment that considers information from multiple perspectives, including both teachers and parents, to gain a thorough understanding of aggressive behaviors in BD.

Another important finding of the current study is that there is an association between aggressive behavior and several diagnostic and epidemiologic factors. Although our results suggest that aggressive behavior in BD increases from early to late childhood, the evidence illustrating levels of aggressive behavior in adolescence is limited.[23,43] Furthermore, this review indicates that the research examining the influence of sex/gender on aggressive behavior in BD individuals is conflicting.[26,43] It may be that there is an interaction between sex/gender and age in regard to aggressive behaviors. Our findings should encourage further investigation into the influence of demographic factors on aggressive behavior in youth with BD.

Another diagnostic factor examined in this review is comorbid diagnoses. Findings presented in the available studies are limited and inconsistent, with the evidence exploring the influence of aggressive behavior on the relationship between BD and comorbidity with ADHD and other diagnoses being highly variable.[21,23,34] Considering the different demographics examined in each study provides a potential explanation for these conflicting results. The characteristics of said aggressive behavior also appear to differentiate according to the patient's disorder. Some authors propose that the manic component of young patients with BD precipitates acute and explosive outburst of aggressive behavior, which goes beyond the impulsivity–aggression sequence that is usually present in ADHD and conduct disorder (CD).[34] Investigating the link between impulsivity as a trait in youth with BD, regardless of the underlying comorbid disorder, could help clarify whether impulsive behaviors are essentially responsible for the elevated rates of aggression among youth with BD, or whether, on the other hand, it is substantially different from the aggressive behaviors seen in other disorders. Similarly, regarding the phenomenology of aggression in young people with mental disorders, it has been suggested to be more frequently non-predatory and disorganized in BD, and more purposeful, predatory, and organized in conduct disorder.[23] Future research should aim to directly compare the association and characteristics of aggressive behavior in BD and the development of ADHD, CD, or other comorbidities at different ages, as well as co-occurring factors such as alcohol and substance abuse disorders, which are frequent comorbidities across these 3 entities.

Findings also indicate there is a link between psychomotor agitation, family functioning, and multiple neurobiological regions and increased aggressive behavior in BD.[14,33,38,41,45] Findings exploring psychomotor agitation revealed a small effect size,[45] and findings exploring family functioning indicated small-to-medium effect sizes.[33] It is important to note, however, that cross-sectional studies fail to establish directionality of the reported associations. Aggressive behavior is highly disturbing and can notably contribute to more distressed relationships. Future studies should aim at longitudinal designs that better allow for identifying causal risk factors. As for the neuroimaging results illustrated in this review, they show parallels with those in the existing literature conveying the association between activation of the amygdala and ventromedial prefrontal cortex in typical children and adolescents displaying aggressive behavior, which signal toward defective emotional processing and executive dysfunction. Interestingly, these findings have also been observed in children and adolescents with CD and high levels of aggressivity, which could indicate a transdiagnostic, neurobiological substrate for these behaviors.[50]

Some evidence was found as well for different treatments with the potential to reduce aggressive behavior in young individuals with BD. Results indicated that pharmacological treatments including divalproex, risperidone, lamotrigine, quetiapine, and lithium have the potential to reduce aggressive behavior.[15,18,22,27,29,35] Findings suggest that valproic acid (divalproex) has received notable empirical support for its efficacy in reducing aggressive behavior in BD in both childhood and adolescence, with findings replicated across samples. However, it is important to note that this evidence is still at its preliminary stages, and randomized controlled trials should be designed to better assess the effect of these compounds on aggressive behavior among youth with BD. Furthermore, 2 studies found that valproic acid use elicited side effects of sedation, headaches, tremor, drooling, and nausea among part of their sample.[15,35] Therefore, acceptance and tolerance need to be further

studied and balanced. It was also found that high levels of aggressive behavior attenuate the effect of interventions on reducing aggressive behavior in children and adolescents with BD.[47] Such findings mirror the existing literature outlining the impact of high levels of aggressive behavior on poor clinical outcomes in BD.[51]

At the moment, NICE recommendations reference the unlicensed use of risperidone, quetiapine, lamotrigine, and lithium for BD; however, these examples are considered an unlicenced recommendation and may not be the first-line approach.[10] Furthermore, NICE guidelines do not provide explicit directives regarding the management of aggressive behavior in BD. In any case, response and acceptance/tolerability of the pharmacological approaches discussed need to be evaluated. In addition, close monitoring is recommended.

The data presented suggest that the evidence for non-pharmacological interventions is insufficient.36,37 Although the findings of this review indicate significant reductions in aggressive behavior subsequent to receiving psychoeducational and psychotherapeutic interventions in BD young individuals, it should be considered that the data do not distinguish between the impact of these interventions. So far, the existing research indicates the efficacy of psychotherapeutic interventions, notably family-focused therapy, in improving affective stability and reducing BD symptoms in children and adolescents[52]; thus, further emphasis on the importance of future research investigating the efficacy of both pharmacological and non-pharmacological interventions on reducing aggressive behavior in BD is needed. For instance, online psychosocial interventions are being explored, but further data are required to establish their efficacy[10]; future research should assess the impact of such interventions on aggressive behavior. We hope that our research will encourage the development of effective and safe interventions that give adequate consideration to increased levels of aggressive behavior in BD and will help decrease their impact on young people and their families. On the basis of the available evidence, it yet remains unanswered whether aggressive behavior requires specific treatment in the context of young people with BD, or whether, on the other hand, effective treatment of the underlying BD will be enough.

The results of this study should be viewed in the light of some limitations. First, the current database may not be globally representative, as 80% of the studies were conducted in the United States. Future studies would benefit from investigating aggressive behavior in BD in alternative cultural contexts. Second, there was high heterogeneity. For instance, this review is categorized by our multifarious definition of aggressive behavior and evaluation procedures included in the reviewed evidence. Although this pragmatic approach was used to enable a comprehensive review of a wide range of studies and to facilitate treatment guidance, it comes with challenges. Various types of aggression, such as verbal and physical, reactive and proactive aggression, are described in the literature, with different instruments reporting on different aspects of aggression. Moreover, the severity of aggression, which has a significant impact on presentation among other factors, is not always uniformly reported in clinical trials. These nuanced aspects of aggressive behavior were often not detailed in the studies we reviewed, further highlighting a limitation of our review. The broad approach taken, therefore, encouraged the inclusion of numerous studies that share varying definitions, thresholds, and methods of measuring aggressive behavior, consequently increasing the possibility of including heterogeneous populations. Third, the 7 studies reporting the prevalence estimates of aggressive behavior were cross-sectional and did not make correlations with polarity or other factors to avoid confounding of bipolar symptoms with ADHD symptoms, potentially leading to an overestimation of the association between aggressive behavior and BD. Finally, the available research on prognostic factors was very limited, and 74.3% of studies were cross-sectional. Again, longitudinal data are essential for understanding the development and trajectory of aggressive behavior in children and adolescents with BD over time.

Aggressive behaviors are prevalent among children and adolescents with BD, and its clinical, comorbidity, and neuroimaging correlates seem to link them to impulsivity, altered affective processing, and executive disfunction. Although available evidence favors the use of divalproex to address these behaviors, advancement in clinical practice is limited by a lack of rigorous research exploring pharmacological and non-pharmacological interventions. Future research should focus on conducting longitudinal cohort studies to clarify and understand the risk factors and development trajectories of aggressive behavior among this population, as well as randomized controlled trials to assess their response to therapeutic interventions.

CRediT authorship contribution statement

Clàudia Aymerich: Writing – review & editing, Writing – original draft, Methodology. **Edward Bullock:** Writing – original draft, Investigation. **Savannah M.B. Rowe:** Writing – review & editing, Investigation. **Ana Catalan:** Writing – review & editing, Supervision. **Gonzalo Salazar**

de Pablo: Writing – review & editing, Supervision, Software, Methodology, Conceptualization.

This article is part of a special series devoted to addressing aggressive behavior as a focus of psychiatric attention and how its manifestations and treatment needs may vary across psychiatric disorders. The series is edited by Guest Editor Joseph Blader, PhD, Deputy Editor Robert Findling, MD, MBA, and Editor Manpreet K. Singh, MD, MS.

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