

Medication Strategies in Childhood Aggression: A Review

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Objective: To review studies of psychopharmacological management of aggression in common childhood psychiatric disorders.

Method: Using OVID software, we searched Medline for studies that were undertaken in the last 30 years. Controlled and uncontrolled data are summarized for each condition.

Results: A paucity of evidence-based information currently exists. Even so, specific indications from the existing literature can be suggested for several classes of psychotropics, particularly in conduct disorder (CD), attention-deficit hyperactivity disorder (ADHD), mood disorders, and other conditions.

Conclusions: Clinicians can use findings from reviewed controlled and, where necessary, uncontrolled studies to inform pharmacologic practice. This review offers suggestions for future research directions that will aid clinical practice.

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Clinical Implications

- Controlled trials exist for individuals with attention-deficit hyperactivity disorder (ADHD), conduct disorder (CD), psychotic disorders, mental retardation, and autism.
- Many open trials in most conditions have found some evidence for efficacy of many psychotropic classes of medications in diagnostic-specific conditions.
- More and larger controlled trials are needed.

Limitations

- The child psychopharmacological literature in general is rather sparse but growing.
- Many children present with comorbidity, and these complex cases are underrepresented in clinical trials.
- Aggression itself has not often been a specific focus of intervention in psychopharmacological trials.

Key Words: *psychopharmacology, aggression, child psychiatric disorder, evidence-based practice*

Aggression is defined as outward destructive behaviour that results from the confluence of longer-term factors (for example, biological, psychological, personality, family, peer, school, and community), short-term influences (for example, internal states of anger, boredom, or intoxication), and situational variables (that is, conflict, opportunity, and blockage of goals or needs) (1). Violence is overt and intentional aggression that includes hitting, choking, kicking, throwing objects, using a weapon, forcing sex, verbally threatening, and destroying property. This behaviour

impoverishes children's relationships in various spheres of their lives.

Aggressive behaviour in children is very common in referred samples. Aggressive and other antisocial behaviours typically account for up to 50% of all child and adolescent psychiatric referrals (2). Such children usually have a myriad of psychiatric, psychological, educational, legal, peer, and familial difficulties and impairments. Several effective psychosocial interventions are emerging (3). Consistently effective and

safe psychotropic medications for childhood aggression have yet to be established.

Owing to our incomplete understanding of the underlying pathophysiology of aggression, past medical treatments have been largely nonspecific. Aggression has been previously targeted for intervention as a symptom, with less attention to underlying cause or diagnosis. This has resulted in the use of many and varied agents, increasing the possibility of poor treatment outcomes and treatment-emergent side effects.

One approach that has been used to circumvent this lack of specificity is diagnostic assessment to carefully identify primary and comorbid psychiatric or neuropsychiatric disorders. The most common diagnosis that clinicians tend to give to aggressive children is conduct disorder (CD). However, considering other diagnoses is imperative, because these are often overlooked, are less obvious, and are potentially more responsive to medical or psychotherapeutic intervention. Common diagnoses include attention-deficit hyperactivity disorder (ADHD), mood disorders, thought or psychotic disorders, and brain injury. Other diagnostic possibilities with childhood aggression include seizure disorder, posttraumatic stress disorder (PTSD), mental retardation, and autism spectrum disorders (4).

Conduct Disorder

CD is by far the most common diagnosis in children and adolescents who are referred for aggression (5). The Ontario Child Health Study found that 5.5% of all children suffered from this condition (6). The DSM-IV definition for CD is “a disruptive behavioural disorder that can feature fighting, bullying, cruelty, robbery, sexual coercion, firesetting, conning, truancy, and other legal or societal violations” (7). There can be substantial psychiatric comorbidity with CD (that is, ADHD, affective disorders, and thought disorder), most of which is detailed elsewhere in this review. Treatment of such concordant conditions will likely reduce morbidity.

Psychotropic treatment alone, unfortunately, has not helped in CD. These youths have many needs that involve multiple modes of treatment, various professionals, and numerous systems of care and monitoring. Even so, a justifiable goal of medication is to reduce irritability, explosiveness, and impulsivity to facilitate response to psychosocial therapies.

Several medications have been found useful in controlled studies of primary CD, and neuroleptics are most commonly used. The use of risperidone (up to 3.0 mg daily) was well tolerated and was superior to placebo in reducing aggression in 10 youths (8). Extrapyramidal side effects have not been a problem in this study or in past open studies (9), with the main difficulties appearing to have been weight gain and sedation.

Haloperidol has been the most rigorously studied, despite associated neurological side effects (10).

Several controlled studies have found lithium equivalent in efficacy to typical neuroleptics, with 1 study as the first known to produce positive results on an aggression rating scale (Overt Aggression Scale) (11). Dosages in the literature have ranged from 500 mg to 2100 mg daily, resulting in serum levels of 0.32 mEq/L to 1.79 mEq/L. Many subjects have experienced nausea, vomiting, enuresis, cognitive dulling, fatigue, and ataxia. Despite these effects, most authors generally considered lithium use as safe (10,11). However, there have been 2 negative studies published, one involving adolescent inpatients and the other outpatients (12,13).

Clinicians have tried other mood stabilizers in treating CD. An open trial of carbamazepine was found to be effective in a small ($n = 10$) study of preadolescents with CD and explosive aggression (14). In this study, the average dosage was 630 mg daily, achieving a mean blood level of 6.2 $\mu\text{g/mL}$. Unfortunately, a later controlled study found that carbamazepine was not superior to placebo (15). Use of valproic acid in 12 of 15 children with oppositional defiant disorder (ODD) or CD did prove to decrease explosiveness and mood lability in a double-blind controlled study (16).

Two controlled studies have found that methylphenidate decreases aggression without the presence of ADHD (17,18). In Klein's study, the dosage range was up to 60 mg daily, and Gadow's paper found that 0.3 mg/kg was an effective dose. Yet, other studies have reported mixed findings (19).

Other medications that were tried in open studies include clonidine, benzodiazepines, and trazodone. An open trial of clonidine in 17 aggressive children found a decrease in aggression with treatment, possibly correlated with plasma gamma-aminobutyric acid (GABA) levels (20). A randomized controlled trial found some effect on aggression with chlordiazepoxide, but concerns were raised about dependence and disinhibition in children (21). Trazodone in an open trial of 22 hospitalized children helped to reduce impulsivity and aggression, and this effect seemed to persist on follow-up several months later (22).

To summarize, clinicians should attempt psychosocial interventions first or in conjunction with psychopharmacological strategies (23). If no obvious comorbidity exists, then the literature does, in a limited way, support the use of various agents. These include efficacy in controlled studies of risperidone, haloperidol, lithium, valproate, and methylphenidate. Efficacy has also been found in open trials of clonidine, trazodone, and carbamazepine. Some suggest that aggression associated with explosiveness or impulsivity may respond better to medication than would instrumental (premeditated) aggression or more covert behaviours (for

example, conduct symptoms of lying, stealing, cheating, and rule violations). However, more controlled research and larger clinical trials would help.

Attention-Deficit Hyperactivity Disorder

ADHD is second only to CD in frequency of diagnosis in aggressive children (24). ADHD occurs concomitantly with CD in 30% to 50% of cases (25). Despite extensive comorbidity, clinicians advise some caution in attributing inattention, hyperkinetic states, and impulsivity to ADHD only. These can also occur in bipolar disorder (BD) or dissociative disorders.

Clearly, psychostimulants—predominantly methylphenidate—have proven efficacy in the core symptoms of ADHD. Over 70% of children have collectively responded in over 150 controlled studies (26). There have been several controlled studies in the literature that evaluated the effect of methylphenidate on aggression in children with ADHD. The largest study was conducted by Klein (18), wherein two-thirds of the 84 children met criteria for CD and ADHD. These children responded to up to 60 mg of methylphenidate for the 5-week trial, and ADHD did not necessarily need to be present for therapeutic effect.

Some negative findings, however, have been reported (27,28). In the first, Hinshaw found no significant effects of 0.3 mg/kg of methylphenidate on anger and verbal or physical aggression in children with ADHD. In the second, Matier noted no changes in impulsivity in aggressive or in nonaggressive children with ADHD.

Dextroamphetamine has also been used in small trials. Winsberg used dextroamphetamine (20 mg twice daily) and also reported effect in aggressive and hyperactive children (29). Amery used 15 mg to 30 mg daily and reported decreased aggressive behaviours (30).

Other medications have also been studied in aggressive ADHD. Previous controlled studies of clonidine use in ADHD found positive effects (31). Connor conducted one of the few studies on clonidine in 24 ADHD children who were also aggressive (32). This group found that clonidine, in doses up to 0.3 mg daily, was effective with or without concurrent methylphenidate use. Yet, because of the small statistical power, a direct comparison between clonidine and methylphenidate could not be done. Side effects involving fine motor control were noted with clonidine. Guanfacine acts similarly but more selectively on alpha 2A receptors. It has a longer half-life and is less sedating. Hunt found that, in 13 children, guanfacine reduced hyperactive and immature behaviours in children with CD and ADHD (33).

With respect to antidepressants, bupropion has been reported in a controlled study to reduce disruptive behaviour and

aggression in 30 prepubertal children with ADHD (34). Tricyclic antidepressants, particularly desipramine, have been useful in ADHD generally, but not specifically in aggressive children with the disorder (35). Fluoxetine or sertraline, in combination with methylphenidate, has been found to reduce irritability and conduct behaviours in ADHD that is comorbid with depression (36). In fact, an open trial found efficacy for fluoxetine alone in ADHD (37). Aggressive CD, however, has not been studied specifically in this respect. Likewise, venlafaxine has not specifically been used in aggressive ADHD, but a low dosage (mean 60 mg daily) was useful in some children to reduce behavioural but not cognitive ADHD symptoms (38).

Controlled studies of neuroleptics have found that aggression in children with ADHD responded to thioridazine, chlorpromazine, and haloperidol. Stimulants, however, have been found to be more effective with fewer side effects. Interestingly, case reports suggest that neuroleptics have combined successfully with psychostimulants in ADHD cases with atypical psychosis (39).

Hence, more controlled studies exist for ADHD than for CD. These suggest efficacy in aggressive ADHD for methylphenidate, clonidine, bupropion, and some neuroleptics (for example, thioridazine, chlorpromazine, and haloperidol). Yet, mixed results (with methylphenidate) and concerns about side effects (with neuroleptics) do complicate clinical practice. With respect to open studies, guanfacine and dextroamphetamine have been useful in children with ADHD and aggressive behaviour. With comorbid depression, sertraline or fluoxetine with methylphenidate may benefit, but this combination is understudied. Venlafaxine and desipramine may have general ADHD effects but have not yet shown specific antiaggressive effects. However, the small numbers of studies, the number of patients in trials, and the largely uncontrolled nature of the research require some caution in interpretation.

Mood and Anxiety Disorders

BDs in childhood and adolescence have an estimated prevalence of about 1% (40). Of relevance, nearly 6% of this sample had experienced a distinct period of abnormally and persistently elevated, expansive, or irritable mood without fulfilling full BD criteria. Childhood BD can closely resemble disruptive behaviour disorders (that is, ADHD, CD, and ODD) and therefore can be easily overlooked (41). Irritability, explosiveness, mixed states, rapid cycling, suicidality, academic underachievement, substance use, illegal activities, aggression, and family psychiatric history typically characterize the clinical presentation, although this has been an area of some controversy.

Table 1 Approach to pharmacologic treatment of children's aggression

Comorbid condition	Higher-level evidence (1 controlled study)	Lower-level evidence (open trial)
Conduct disorder	Risperidone	Carbamazepine
	Haloperidol	Clonidine
	Lithium	Trazodone
	Valproic Acid	
	Methylphenidate	
Attention-deficit hyperactivity disorder	Methylphenidate	Dextroamphetamine
	Clonidine	Guanfacine
	Bupropion	Fluoxetine
	Thioridazine	Sertraline
	Chlorpromazine	
Bipolar disorder	Lithium	Valproate
		Risperidone
Depression		Fluoxetine
		Sertraline
		Trazodone
Anxiety		Buspirone
Traumatic brain injury		Propranolol
Autism	Haloperidol	Trifluoperazine
	Clomipramine	Fluphenazine
		Thiothixene
		Molindone
		Clonidine
		Fluoxetine
		Buspirone
		Propranolol
		Nadolol
		Propranolol
Posttraumatic stress disorder		Propranolol
		Nadolol
		Lithium
		Carbamazepine
		Buspirone
Mental retardation	Chlorpromazine	Propranolol
	Thioridazine	Nadolol
	Haloperidol	Lithium
	Methylphenidate	Carbamazepine
	Risperidone	Buspirone

aggression in 36 hospitalized adolescents with various diagnoses, principally BD (45). Another small, uncontrolled study that included 11 adolescents found that valproate had a positive effect on aggression in adolescent mania (46). Typical initial target dosages found useful for acute adolescent mania are in the range of 1000 mg to 2500 mg (44). In addition, 20 mg/kg daily has also been suggested as a guideline (47); this should ideally yield a serum level of 50 µg/mL to 100 µg/mL. Adverse effects in children may include nausea, weight gain, hepatotoxicity, and thrombocytopenia.

Risperidone has been of some interest, but controlled trials, particularly in childhood aggressive BD, are lacking. In fact, one chart review found a positive effect on aggression in 28 youths with BD with largely mixed states. Of these, 82% improved in their manic and aggressive symptoms and 69% in their psychotic features, but only 8% showed a significant decline in ADHD symptoms (48). The mean (SD) dosage was 1.7 (1.3) mg daily. Another open study did find risperidone useful in comorbid mood disorder and aggression (49).

Epidemiologic studies have found that depressive or dysthymic symptoms are comorbid with CD or ODD in 21% to 83% of clinical and community samples; depression coexisting with ADHD has been found in up to 57% of children (50). Children who suffered from depression had greater cognitive difficulties in controlling their anger. Male children, in particular, had core symptoms of irritability and aggression that were congruent with depressive disorders (51). Aggressive boys with ADHD had more symptoms of depression than did boys with ADHD and no aggression. As a result, these boys reported more depression than did control subjects (52). Aside from the previously mentioned study of fluoxetine and sertraline use in children with ADHD and depression, studies of selective serotonin reuptake inhibitors (SSRIs) in aggressive children with depression are lacking. One open trial with psychiatric adolescent inpatients found no benefit from SSRIs on aggression (53). Trazodone, however, has

In one of the few well-controlled studies, Geller studied 25 adolescents with BD and comorbid substance abuse. Aggression, however, was not specifically studied. She found that 6 weeks of lithium treatment yielded clinically significant functional improvement and reduction in substance abuse (42). Lithium has generally been used in a dosage range of 600 mg to 2100 mg in 2 or 3 divided doses daily to yield a serum level of 0.6 mEq/L to 1.4 mEq/L. A dosage of 30 mg/kg daily, at least in preadolescents, has also been suggested as a guideline (43). Possible adverse effects in children have included nausea, diarrhea, vomiting, polyuria, headache, sedation, tremor, weight gain, and hypothyroidism (44).

Similarly, controlled studies about the use of other mood stabilizers in aggressive children with BD are severely lacking. Of these, an open study found that valproate decreased

reduced aggressivity and impulsivity in inpatient psychiatric children with disruptive behaviours (54).

Buspirone has been used for generalized anxiety. One open study of 19 hospitalized children with aggression and anxiety found decreased aggression and need for restraint. Conversely, 4 individuals exhibited increased aggression (55).

Hence, an increasing armamentarium of psychotropics is showing evidence of effect in child and adolescent mood and anxiety conditions, although largely in open trials and small studies. Studies that look at the construct of aggression in this context are lacking but, hopefully, will be a focus of future research.

Other Conditions

Importantly, most children and adolescents with psychosis or who suffer from a psychotic disorder are not violent. However, the more violent youths are, the more likely they have psychotic, particularly paranoid, features (56). Unfortunately, controlled studies of medication interventions specifically for aggression in these populations have not been done, despite many studies on both typical and atypical neuroleptics in childhood-onset schizophrenia, far less related psychotic spectrum conditions. Interestingly, the adult literature is finding increasing evidence of beta blocker use (such as, nadolol), especially as an adjunct for reducing aggression in adults with psychotic disorders (57).

Similarly, children with organic brain syndromes, such as traumatic brain injury, may exhibit aggressiveness, explosiveness, and irritability. Propranolol in dosages up to 960 mg daily has been used in children and adolescents with prominent rage outbursts, some of whom met criteria for intermittent explosive disorder. Most received between 80 mg and 320 mg daily (58). Propranolol has also been found to help in an open trial of children with acute PTSD, who may be vulnerable to aggression, owing to hostility, irritability, impulsivity, and sympathetic overdrive (59). Controlled studies in subjects who suffer from mental retardation support the use of chlorpromazine, thioridazine, haloperidol, pimozide, methylphenidate, and more recently, risperidone for aggression (4,60). Open studies have found some effects from propranolol, nadolol, lithium, carbamazepine, buspirone, and fluoxetine in this population (4). Risperidone has also been useful in children with Tourette syndrome and aggression in an open, retrospective trial (61). For autism spectrum conditions, haloperidol has the most evidence of effect in controlled studies (62,63). In addition, a small controlled study supported use of clomipramine for anger attacks (64); other medications generally useful in this group include trifluoperazine, fluphenazine, thiothixene, molindone, clonidine, fluoxetine, buspirone, propranolol, and nadolol (4).

Summary

Aggressive behaviour is extremely common in the clinical child and adolescent population. Psychiatric evaluation should be part of a comprehensive multidisciplinary assessment that encompasses medical, neurological, psychological, psychosocial, familial, and academic domains. Accordingly,

clinicians should provide multimodal treatment to address the many vulnerabilities. The differential diagnosis of childhood aggression includes CD, ADHD, BD, depression, psychotic disorders, traumatic brain injury, intermittent explosive disorder, PTSD, mental retardation, autism spectrum disease, and dissociative disorders.

Such a diagnostic assessment can lead the clinician toward possible psychopharmacological approaches (Table 1). If the general child psychopharmacology literature is thought to be in its infancy, then the relevant literature on child aggression is most likely best characterized as "postnatal." Nevertheless, some evidence exists to guide psychotropic choice in certain conditions, but children and youths are complex beings with much comorbidity. Hence, there may at this point be more art than science in medical intervention, especially as polypharmacy is a current and likely future trend. More controlled studies, larger sample sizes, more diagnostic specificity, standardized measures of aggression, and longer follow-up studies are needed. Only then will we be more scientifically informed about evidence-based approaches in this complex and challenging area.

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Résumé : Stratégies de médication pour le comportement agressif des enfants : une revue

Objectif : Examiner les études sur le traitement psychopharmacologique du comportement agressif dans les troubles psychiatriques communs chez les enfants.

Méthode : À l'aide du logiciel OVID, une recherche des études entreprises dans les 30 dernières années a été effectuée dans Medline. Des données contrôlées et non contrôlées sont résumées pour chaque affection.

Résultats : Il existe présentement une rareté d'information fondée sur des données probantes. Toutefois, des indications spécifiques tirées de la documentation existante peuvent être suggérées pour plusieurs classes de psychotropes, en particulier dans le trouble des conduites, le trouble d'hyperactivité avec déficit de l'attention (THADA), les troubles de l'humeur et d'autres affections.

Conclusions : Les cliniciens peuvent se servir des résultats des études contrôlées revues et si nécessaire, des études non contrôlées pour éclairer leur pratique pharmacologique. Cette revue offre des suggestions pour de futures orientations de la recherche qui aideront la pratique clinique.