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## **Pharmacological Treatment of Aggression in Children with Attention Deficit Hyperactivity Disorder (ADHD)**

### **Clinical Question**

P (population/problem)	Among children with ADHD and aggression
I (intervention)	is the pharmacological treatment of ADHD
C (comparison)	versus no pharmacological treatment of ADHD
O (outcome)	effective in reducing aggressive behavior?

**Target Population:** Children and adolescents up to 20 years of age with ADHD and signs of aggression

- Bipolar disease has been ruled out
- Treatment in an outpatient setting

**Recommendations** (See Table of Recommendation Strength following references)

1. It is strongly recommended that appropriate pharmacological treatment for ADHD be first-line pharmacotherapy for aggression in children and adolescents with ADHD (*Connor 2002 [1a], Ipser 2007 [1b], Connor 2006 [1b], Pappadopulos 2006 [1b], Crenshaw 1997 Dissertation [1b], Pappadopulos 2003 [5a], Kutcher 2004 [5b], Steiner 2003 [5b]*).  
**Note 1:** Appropriate pharmacological treatment includes a trial of ADHD medication in terms of length and dosing that is sufficient for symptom response (*Pappadopulos 2003 [5a], Steiner 2003 [5b]*). See the evidence-based CCHMC Clinical Practice Guideline titled "[Outpatient Evaluation and Management of Attention Deficit/Hyperactivity Disorder](#)" for detailed information regarding the pharmacological treatment of ADHD (*Cincinnati Children's Hospital Medical Center 2004 [5a]*).  
**Note 2:** Children with ADHD often meet *DSM-IV*<sup>1</sup> criteria for oppositional defiant disorder (ODD) or conduct disorder (CD). The choice of pharmacological treatment is often influenced by the nature of comorbid disorders and which disorder is currently the most impairing of major life activities (*Pliszka 2007 [5a]*). The recommendation above applies when the primary disorder is ADHD. The treatment of ODD or CD as the primary disorder contributing to a patient's inattention or hyperactivity/impulsivity is outside the scope of this Best Evidence Statement.
2. It is recommended that children and adolescents be advised to seek psychotherapy in addition to the pharmacological treatment of ADHD and aggression (*Fossum 2008 [1b], Sukhodolsky 2004 [1b], MTA Cooperative Group 1999 [2a], Pliszka 2007 [5a], Pappadopulos 2003 [5a], Steiner 2007 [5b], Kutcher 2004 [5b], Local Consensus [5b]*).
3. It is recommended that when psychosocial interventions and ADHD medications are effective in the control of core ADHD symptoms but fail to reduce aggression, risperidone be added to current treatment (*Aman 2002 [2b], Snyder 2002 [2b], Aman 2004 [4b], Pappadopulos 2003 [5a]*). See Table 1 for a suggested dosing strategy.

<sup>1</sup> *DSM-IV*: Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition.

**Note 1:** Risperidone has been studied in randomized controlled trials for the treatment of aggression in pediatric patients. Other atypical antipsychotics have not been studied under controlled conditions for pediatric aggression (*Connor 2006 [1b]*).

**Table 1 Dosing strategy for risperidone**

Atypical Antipsychotic	Starting Daily Dose	Titration Dose ↑ every 3 to 4 days (Minimum days to therapeutic dose)	Post-titration Daily Dose Range	
			Child	Adolescent
Risperidone (Risperdal®)	0.25 mg for children 0.50 mg for adolescents	0.5 to 1 mg (18 to 20 days)	0.25 to 2 mg	2 to 3 mg

*Pappadopulos(2003 [5a], Local Consensus [5b])*

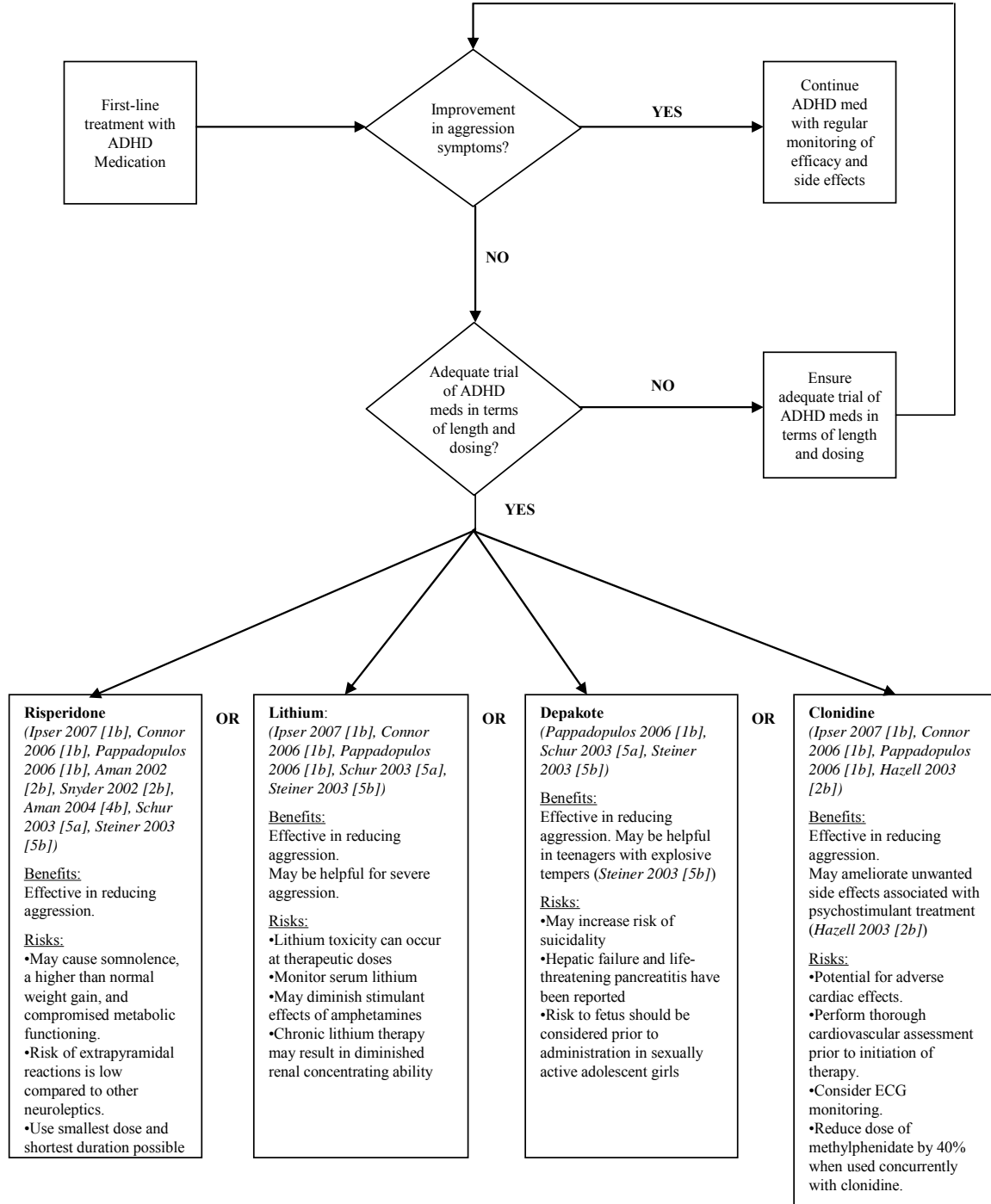
**Note 2:** Atypical antipsychotics are preferred over typical antipsychotics for the treatment of aggression because they have a lower risk for tardive dyskinesia, neuroleptic malignant syndrome, cognitive impairment, and extrapyramidal symptoms (*Pappadopulos 2003 [5a]*).

**Note 3:** The quality of evidence for risperidone in the target population of children and adolescents with ADHD and pathological aggression is low to moderate. Further research is likely to have an impact on our confidence in this recommendation and may even change the recommendation statement. Clinicians may also want to consider alternative pharmacological therapy that has been effective in the treatment of aggression within the context of ADHD (*Connor 2006 [1b], Local Consensus [5b]*). See Figure 1 for details.

4. It is recommended that the efficacy of pharmacological treatment for aggression be assessed at each follow-up visit (*Pappadopulos 2003 [5a], Greenhill 2002 [5a], Kutcher 2004 [5b]*). See Figure 1 for the pharmacological treatment of aggression in children and adolescents with ADHD.

**Note:** An assessment tool such as the modified overt aggression scale (MOAS) provides a standard method for evaluating treatment efficacy (*Local Consensus [5b]*).

**Figure 1: Pharmacologic treatment of aggression in children and adolescents up to 20 years of age with ADHD**



**Discussion/summary of evidence**

The pharmacological treatment of ADHD may control the aggressive behavior associated with ADHD. Several meta-analyses report the effectiveness of stimulants in the treatment of aggression for children and adolescents with ADHD (Connor 2002 [1a], Pappadopulos 2006 [1b], Crenshaw 1997 Dissertation [1b]). Mean

effect sizes<sup>2</sup> across stimulant categories ranged from 0.6 to 0.84 (medium to large). The largest effect size (mean = 0.9) reported was for methylphenidate (MPH). A meta-analysis of Atomoxetine (ATX) trials showed a small effect size (mean = 0.18) for ATX on pediatric aggression at a weighted mean dose of 1.3 mg/kg/day (Pappadopulos 2006 [1b]). Given a desired effect size of  $\geq 0.4$  for clinical significance, the authors suggest ATX may not be an optimal psychotropic agent for treating pediatric aggression in patients with a primary diagnosis of ADHD. However, in a post hoc analysis of a double-blind randomized controlled trial,  $n = 293$ , Newcorn et al. (2005 [4b]) suggest a possible dose-response relationship between ATX and pediatric aggression. Patients with ADHD and ODD showed a greater response to ATX at 1.8 mg/kg/day versus 1.2 mg/kg/day. Additional research is needed to evaluate the efficacy of ATX and other ADHD medications on pediatric aggression. In a meta-analysis of psychotropic agents for treating aggression, low to medium effect sizes (range = 0.3 to 0.5) were reported for  $\alpha$ -2 agonists and antidepressants (Pappadopulos 2006 [1b]).

The implementation of appropriate psychosocial interventions is another consideration when determining adequate first-line therapy. Psychosocial interventions have been shown to be effective in the treatment of aggression in youth (Fossum 2008 [1b], Sukhodolsky 2004 [1b], Schur 2003 [5a]). Behavior therapy combined with pharmacotherapy for ADHD may lower the ADHD medication dosage required to achieve general ADHD symptom control (MTA Cooperative Group 1999 [2a], Pappadopulos 2003 [5a]). Further research is needed, however, regarding the use of behavior therapy in the treatment of aggression within the specific population of youth with ADHD. Much of the current literature has examined aggression across diagnostic categories. There is uncertainty as to whether medication combined with behavioral treatment is more effective than medication alone in children and adolescents with ADHD and aggression (MTA Cooperative Group 1999 [2a]).

For children who have exhausted first-line pharmacotherapy and psychosocial treatment for ADHD and aggression and for those whose ADHD symptoms are adequately controlled but who continue to have problems with aggressive behavior, additional pharmacotherapy specifically targeting aggression may be the next step (Barzman 2008 [5b]). Risperidone is the best studied atypical antipsychotic for reducing aggression (Connor 2006 [1b]). The safety and efficacy of risperidone has been demonstrated in two controlled trials of aggressive children age 5 to 12 years with subaverage IQ (Aman 2002 [2b], Snyder 2002 [2b]). In a post hoc analysis of data from these two trials, risperidone-treated children with comorbid ADHD showed an average symptom reduction (measured on subscales of the Nisonger Child Behavior Rating Form and the Aberrant Behavior Checklist) of 45.7% from baseline to endpoint at 6 weeks, regardless of whether stimulants were taken (Aman 2004 [4b]). Given the weaknesses of the post hoc design and notable attrition rates in the original trials, the body of evidence for the efficacy of risperidone in children with ADHD and pathological aggression is low to moderate and further research is likely to have an important impact on choice of second-line therapy. Lithium and depakote are alternatives to risperidone that have been effective in the treatment of aggression within the context of ADHD (Ipser 2007 [1b], Connor 2006 [1b], Pappadopulos 2006 [1b], Schur 2003 [5a], Steiner 2003 [5b]). The efficacy of clonidine in combination with psychostimulant medication to reduce conduct symptoms associated with ADHD has also been examined. Significantly more clonidine-treated children compared with placebo were responders on the conduct subscale of the parent-report Conners Behavior Checklist in a sample of 67 children age 6 to 14 years with ADHD and comorbid oppositional defiant disorder (ODD) or conduct disorder (CD) (Hazell 2003 [2b]). Caution is advised when combining clonidine with additional medications in children with cardiac or cardiovascular disease (Turgay 2009 [5b]).

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<sup>2</sup> Effect size: Typically used to conduct a meta-analysis, a Cohen's *d* effect size (ES) is the difference between the experimental and control group means divided by a pooled standard deviation. An ES less than 0.2 is considered a small effect; 0.21 to 0.5 is a medium effect; and greater than 0.8 is a large effect. In clinical practice, effect sizes  $\geq 0.4$  are desirable because they are associated with observable changes in patients (Pappadopulos 2006 [1b]).

## Health Benefits/Side Effects/ Risks

The clinician and family must decide which agents are best for the initial treatment of patients with ADHD and aggression. Stimulants are most effective for aggression and long-acting formulations offer greater convenience for the patient and family in addition to enhancing confidentiality for school-age patients (Pliszka 2007 [5a]). The lowest possible therapeutic dose of any medication is preferred to avoid adverse events, and preference is given to monotherapy medication approaches in order to assess treatment response. Monotherapy may also improve patient and family treatment adherence by decreasing the complexity of the treatment regimen (Pappadopulos 2003 [5a]).

Some clinicians have questioned whether aggression reflects underlying psychopathology or if it is a treatment-emergent adverse drug reaction to ADHD medication, particularly atomoxetine. Polzer (2007 [1b]) examined the incidence of hostility events in atomoxetine trials in patients with ADHD. The results of this meta-analysis showed more aggression/hostility-related events in patients treated with atomoxetine versus placebo, but the difference was not statistically significant. In addition, the risk of aggression was similar in patients treated with atomoxetine or methylphenidate. Atomoxetine may be preferred for patients who experience severe side effects to stimulants. However, increased risk of suicidal ideation and rare but serious adverse effects on the liver and heart have been reported with atomoxetine (Turgay 2009 [5b]).

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Note: Full tables of evidence grading system available in separate document:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (abbreviated table below)

**Table of Evidence Levels** (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

**Table of Recommendation Strength** (see note above)

<b>Strength</b>	<b>Definition</b>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

**Dimensions:** In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (*direct benefit*)
4. Burden to patient of adherence to recommendation (*cost, hassle, discomfort, pain, motivation, ability to adhere, time*)
5. Cost-effectiveness to healthcare system (*balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis*)
6. Directness (*the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]*)
7. Impact on morbidity/mortality or quality of life

## Supporting information

### Introductory/background information

Aggression is a nonspecific sign associated with a wide variety of psychiatric disorders. Pharmacological approaches to treatment are either disorder-oriented or target symptom-oriented (Connor 2006 [1b]). The disorder-oriented approach is preferred and seeks to treat the underlying psychiatric disorder of which aggression is one associated sign. Therefore, the accurate identification and treatment of a medication-responsive primary diagnosis is important (ADHD, depression, bipolar disorder, and anxiety disorders) (Connor 2006 [1b]). Oppositional defiant disorder (ODD) and conduct disorder (CD) are generally not considered robustly medication responsive and are included in a target-symptom approach initiated after the context in which they occur is fully appreciated (Connor 2006 [1b]). Within the context of ADHD, pharmacological treatment of aggression then first focuses on the use of ADHD medications. If lack of response to ADHD medications is observed, the primary underlying condition may be inaccurately identified (Steiner 2003 [5b]). When ADHD medications are effective in the control of core ADHD symptoms (inattention, hyperactivity, and impulsivity) but fail to fully control signs of aggression, additional pharmacological approaches may be necessary.

### Group/team members

#### Division of Psychiatry

Drew Barzman, MD

Michael Sorter, MD

#### Clinical Effectiveness Support

Betsy List, MPH, RN, Methodologist

Danette Stanko-Lopp, MA, MPH, Epidemiologist

Carla Williams, MSA, Outcomes manager

### Search strategy

1. Database: Ovid MEDLINE(R) <1996 to May Week 5 2009>

Search Strategy:

1 exp Aggression/ (9234)

2 (guideline or meta analysis or practice guidelines or systematic review).pt. or "the cochrane library".jn. or "cochrane database of systematic reviews".jn. (32039)

- 3 1 and 2 (63)
- 4 limit 3 to english language (62)
- 5 limit 4 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") (31)
- 6 from 5 keep 1-31 (31)

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2. Database: PsychInfo – similar search to MEDLINE

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3. Database: National Guideline Clearinghouse – aggression, limited to children

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4. Additional articles identified from reference lists of retrieved articles (RCTs limited to those with n >100) and from clinician experts

### Applicability issues

Two process measures and one outcome measure will be monitored in relation to these recommendations.

#### Process Measures:

1. Appropriate Medication - Percentage of patients with ADHD and aggression who are receiving ADHD medications
2. Psychotherapy - Percentage of patients with ADHD and aggression who receive a referral for psychotherapy

#### Outcome Measure:

Symptom Improvement - Percentage of patients with ADHD and aggression who report improvement in severity status from baseline to most recent assessment using the modified overt aggression scale (MOAS)

Complete operational definitions are on file.

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Copies of this Best Evidence Statement (BESt) are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm>

Examples of approved uses of the BESt include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the BESt may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
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### Note

**This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.**

**Reviewed by** Clinical Effectiveness