# Recommendations for Pharmacological Management of Inpatient Aggression in Children and Adolescents

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#### **ABSTRACT**

**Objective.** While there has been a great deal of speculation by clinical researchers over the last three decades on effective and safe methods for the pharmacological management of aggression in children and adolescents, it is only in the last decade that there have been welldesigned studies available to address this issue. Medication is commonly used to control aggression in children and adolescents in inpatient units. Also, there exists a need for evidencebased guidelines for the use of these different pharmacological agents for managing pediatric aggression on inpatient units. The aims of this article are to provide a systemic review and to provide treatment guidelines based on these limited but currently available studies.

Methods. The articles reviewed in this study were obtained through a PubMed search using the key words 'children,' 'adolescents,' 'aggression,' 'inpatient,' 'ziprasidone,' 'lithium,' and 'risperidone.' A total of 499 studies were generated. Only studies focusing on pharmacological management of inpatient pediatric aggression with mean duration less than six weeks and



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**KEY WORDS:** children, adolescents, aggression, inpatient, ziprasidone, behavioral, psychiatric, antipsychotics, management

published during January 1980 to August 2009 were included. Only English articles were considered. A total of 13 studies met these criteria, which were included in the review without any further statistical analysis. Recommendations are made on this available evidenced-based literature.

Results. There is some evidence for the standing use of oral lithium, haloperidol, olanzapine, and risperidone for aggression related to specific psychiatric diagnoses. Intramuscular ziprasidone and olanzapine administered as needed were found to be effective for the rapid management of moderate to severe aggression. Oral or intramuscular diphenhydramine administered as needed was found to be useful for managing mild aggression due to a placebo effect.

Conclusions. Studies are available on managing aggression in children and adolescents in inpatient treatment settings but are limited. Further studies on the use of various psychotropic medications are needed in order to develop comprehensive guidelines for the safe and effective pharmacological management of child and adolescent inpatient aggression.

### **INTRODUCTION**

Although there are many studies on the use of psychotropic medications to treat pathological aggression in children and adolescents,¹ research is limited and often conflicting on the use of medications to treat aggression in hospitalized pediatric patients. Medications prescribed on an asneeded basis (PRN) are frequently used<sup>2,3</sup> to manage aggression or disruptive behavior on inpatient units, but the studies supporting the use of this method with children and adolescents are mixed. In contrast. adult studies on the use of PRN medications for agitation suggest effectiveness.4 Furthermore, atypical antipsychotics administered on a regular basis have been found to reduce the use of seclusion and restraints on adult psychiatric patients.5-7 However, the effectiveness of scheduled atypical antipsychotic medications with child and adolescent

inpatients is still not as clearly established.

A study investigating aggressive incidents and the use of restraints on inpatient units reported that PRN medications were used in 38 percent of incidences before restraints and in 22 percent of incidences during restraints.8 Despite their frequent use, the evidence is limited to support the effectiveness of PRN medications for inpatient aggressive pediatric patients. A study on PRN medication for 49 children on an inpatient unit found that PRN medications were effective in only one-third (32%) of the total incidences.3 The purpose of this review article is to explore the recent but limited evidence for the use of

standing use of medications were considered. A total of 13 studies met these criteria. As these studies were lacking consistency in their methods, all of these 13 studies were considered for review without any further statistical analysis. Recommendations were made mainly based on the data from these studies.

#### RESULTS

The following studies examine the usefulness of psychotropic medications for managing inpatient child and adolescent aggression.

**Antihistaminics.** Antihistamines, particularly first generation (older) antihistamines, are known to have effects on the central nervous system

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medication for inpatient pediatric aggression in order to provide practical clinical guidelines based on the available studies.

#### **METHODS**

We conducted the PubMed electronic database search using words 'children,' 'adolescents,' 'aggression,' 'inpatient,' 'ziprasidone,' 'lithium,' and 'risperidone.' The different combinations of these words were used as follows: 1) 'children+adolescents+inpatient+ aggression; 2) 'ziprasidone+children', 3) 'ziprasidone+adolescents;' 4) 'lithium+children+adolescents+ aggression;' and 5) 'risperidone+ adolescents+aggression. A total of 499 related studies were generated using these combinations. Out of these, we only included the studies focusing on the pharmacological management of aggression in hospitalized children and adolescents. Only studies in the date range January 1980 to August 2009 were included. Studies more than six weeks of mean duration were excluded. Only studies in English were considered. Studies on both PRN and

by causing rapid sedation and slowing down psychomotor performance and cognitive function.<sup>9,10</sup> Antihistamines are the most frequently prescribed medication for hospitalized pediatric patients for inducing sleep<sup>11</sup> and may be considered to be appropriate for usage in medically ill children with behavioral instability. Diphenhydramine (an antihistamine) can be administered by oral, intramuscular (IM), and intravenous (IV) route and is generally well tolerated.<sup>10</sup> The potential for serious side effects exists. If the patient experiences airway or cardiac problems, then vigilant monitoring is required.<sup>10</sup> Despite the common use of antihistamines for aggression and agitation, there is only one published, controlled study for an antihistamine (diphenhydramine) on managing child and adolescent aggression on psychiatric inpatient units on acute

Diphenhydramine (Benadryl). In this double-blind, placebo-controlled, pilot study of an antihistamine for 21 male patients (aged 5–13 years old), PRN diphenhydramine was not

basis.2

superior to placebo in reducing aggression, as there was a significant placebo effect. Interestingly, the most effective route of administration for reducing aggression was IM, regardless of whether the injection contained diphenhydramine or placebo.<sup>2</sup>

**Mood stabilizers.** Divalproex was found to be effective in reducing aggressive episodes in outpatient pediatric population after a random placebo-controlled clinical trial of six weeks. <sup>12</sup> However, after doing a literature search, we conclude that lithium carbonate and carbamazepines are the only scheduled mood stabilizers studied for treating child and adolescent inpatient aggression.

Lithium carbonate (Eskalith).

Malone et al13 in 2000 conducted a double-blind, placebo-controlled study of 40 hospitalized aggressive children and adolescents with conduct disorder (CD). Lithium was superior compared to place in terms of decreasing inpatient aggression as measured by the Overt Aggression Scale (OAS) over four weeks of inpatient treatment. However, as compared to placebo, patients on lithium did experience side effects other than weight gain, such as increase in urinary frequency and gastrointestinal side effects (e.g., vomiting and nausea).13 In an older study, 61 inpatient children (from 5.2–12.9 years) with diagnoses of conduct disorder, aggressive type and resistant to treatment were treated with haloperidol and oral lithium carbonate over a four-week period. This was also a double-blind, controlled study with the use of placebo versus haloperidol or lithium. Lithium carbonate and haloperidol were both found to be superior to placebo in reducing aggressive behavior. Regarding safety, lithium was less frequently associated with unwanted side effects. The most common unwanted side effects associated with haloperidol were drowsiness, followed by acute dystonia. The most common unwanted side effects associated with lithium were stomachache and headache.14

Another double-blind, placebocontrolled study of lithium carbonate with 33 inpatients (aged 12–17 years) with CD showed no improvement in aggression based on OAS ratings after two weeks of treatment.<sup>15</sup> This may suggest that lithium carbonate should be continued for at least four weeks in order to observe improvement in child and adolescent inpatient aggression. This time course of efficacy may not be practical for most inpatient units with short hospital stays but may be more appropriate for child and adolescent residential units or state hospitals. Drugs having more rapid onset that can be used as PRN and that have a minimal side effect profile would be the best choice for controlling aggression on inpatient child psychiatry units. Giving lithium and monitoring the levels for weeks on inpatient units may not be a practical approach.

Carbamazepine (Tegretol). Ten hospitalized patients aged 5 to 10 years with CD showed improvement in inpatient aggression after three weeks of treatment with carbamazepine. However, this was an open pilot study.16 In a double-blind, placebocontrolled study, Cueva et al<sup>17</sup> in 1996 studied the effect of carbamazepine in children with treatment-resistant aggression.<sup>22</sup> Inpatient children with CD (age range 5-12 years) were randomized to receive carbamazepine or placebo for six weeks. Surprisingly, the study concluded that both carbamazepine and the placebo had similar clinical outcomes.<sup>17</sup> Therefore, we need to evaluate a different category of medication other than mood stabilizers that would be rapidly effective for inpatient pathologic pediatric aggression.

Atypical antipsychotics. The use of atypical antipsychotics has expanded to treat a broad range of psychiatric diagnoses for children and adolescents despite the limited empirical evidence supporting their efficacy. For acute treatment of aggression on child and adolescent inpatient units, ziprasidone is the most extensively studied atypical antipsychotic medication. The usefulness of other antipsychotics is also discussed.

Ziprasidone (Geodon). Ziprasidone was the first atypical

antipsychotic available in IM form<sup>19</sup> and this might be the reason that it was observed as the most extensively studied antipsychotic for managing aggression in inpatient children and adolescents. Ziprasidone has been found to be beneficial in treating aggression in child and adolescent inpatients<sup>20–24</sup> as well as adolescents in the emergency room.47 A case report of three youths treated with IM ziprasidone reported an immediate beneficial effect on controlling the aggressive episode on the inpatient child psychiatry unit.<sup>22</sup> A retrospective study comparing the efficacy of IM ziprasidone and IM olanzapine PRN in 100 juvenile (younger than 18 years) psychiatric inpatients found that these medications were similar in terms of their ability to address inpatient aggression.<sup>20</sup> However, patients taking IM ziprasidone received significantly more doses of IM ziprasidone, as well as other potentially calming medications, such as antihistamines or lorazepam. Somnolence was the most common side effect noted during this study for either IM ziprasidone or IM olanzapine. Neither medication had any documented significant effect on QTc interval, blood pressure, or heart rate.<sup>20</sup> At this time, it is not possible to put together definitive conclusions for the safety of using IM ziprasidone and IM olanzapine with children, given the possibility that adverse events have been inadequately charted in this retrospective study.<sup>20</sup>

In another retrospective study, treatment with IM ziprasidone was compared to IM haloperidol with lorazepam for severe aggressive episodes in adolescents (12–17 year olds) in psychiatric emergency rooms.<sup>24</sup> Both treatment groups had similar outcomes in regards to restraint time and use of rescue medications. Behavior Activity Rating Scale (BARS) scores were available only for 7 out of 28 adolescents that received IM ziprasidone. The BARS scores in these seven subjects started decreasing immediately after the IM ziprasidone injection and had a significant decrease after one half hour and continued to decrease up to two hours. Although no severe side effects, such as profound

TABLE 1. Available pharmacological studies on management of inpatient pediatric aggression

STUDY	MEDICATION	ROUTE	TYPE OF STUDY	DIAGNOSES	AGE GROUP	DOSE
Khan et al (2006) <sup>20</sup>	Ziprasidone (Geodon*)	IM	Retrospective chart review	Bipolar with psychotic features; MDD with psychotic features; psychosis NOS; MDD NOS; substance use/dependence; TSD	Mean age 14.6±2.1 yrs. (included children as well as adolescents)	20mg (15.66±4.35) for children; 20mg (19.45±2.13) for adolescents
Barzman et al (2007) <sup>21</sup>	Ziprasidone (Geodon*)	IM	Retrospective chart review	Bipolar; MDD; MDD NOS; psychotic disorder; disruptive disorder; ADHD; impulse control disorder	12–19 years	20mg (81% received)
Hazarey et al. (2004) <sup>22</sup>	Ziprasidone (Geodon*)	IM	Case report	CD; ADHD; explosive outburst; GAD; oppositional defiant disorder; bipolar NOS	12–13 years	10mg
Stellar et al (2004) <sup>23</sup>	Ziprasidone (Geodon*)	IM	Retrospective chart review	Not available	8–16 yrs	20mg (87% received)
Khan et al (2006) <sup>20</sup>	Olanzapine (Zyprexa*)	IM	Retrospective chart review	Bipolar with psychotic features; MDD with psychotic features; psychosis NOS; MDD NOS; substance use/dependence; PTSD	13.7±2.4 (included children as well as adolescents)	5mg (5.92±2.18) for children, 10mg (9.17±1.77) for adolescents
Krishnamoorthy et al (1998) <sup>25</sup>	Olanzapine (Zyprexa*)	PO	Open label	Bipolar, psychosis NOS, schizophrenia, ADHD	6–11 years	7.5mg (22mg/kg)
Campbell et al (1984) <sup>14</sup>	Haloperidol (Haldol*)	PO	Double blind, placebo controlled	CD aggressive type	5.2–12.9 years	1 to 6mg (0.04–0.21mg/kg/day)
Buitelaar JK et al (2001) <sup>28</sup>	Risperidone (Risperdal*)	P0	Double blind, randomized (parallel group design)	Disruptive disorder	adolescents	2.9mg (1.5–4mg)
Campbell et al (1984) <sup>14</sup>	Lithium Carbonate (Eskalith*)	P0	Double blind, placebo controlled	CD aggressive type	5.2–12.9 years	500–2000mg (Serum lithium level 0.32–1.51mEq/liter)
Rifkin et al (1997) <sup>15</sup>	Lithium Carbonate (Eskalith*)	PO	Double blind, placebo controlled	CD (IQ >70)	12–17 years	Variable dose to maintain blood lithium level of 0.6 to 1mmol/litre
Malone et al (2000) <sup>13</sup>	Lithium Carbonate (Eskalith*)	PO	Double-blind placebo controlled	CD	Median age 12.7 years	300–2100mg to maintain the level of 0.8–1Mmol/litre
Vitiello et al (1991) <sup>2</sup>	Diphenhydramine (Benadryl*)	PO/IM	Double-blind placebo controlled	CD, ADHD, MDD	5–13 years	25–50mg
Jangro et al (2009) <sup>47</sup>	Ziprasidone (Geodon*) vs haloperidol and lorazepam	IM	Retrospective chart review	Substance use/dependence, psychotic disorders, adjustment disorders, impulse control disorder	12–17 years	20mg (82% received) 10mg (18% received)

Abbreviations: Pts—patients; IM—intramuscular, PO—per oral; MDD—major depressive disorder; NOS—not otherwise specified; yrs—years; PRN—as needed; QTc—QT interval on EKG, BP—blood pressure; H—heart rate; ADHD—attention deficit hyperactivity disorder; CD—conduct disorder; GAD—generalized anxiety disorder; PTSD—posttraumatic stress disorder; GI—gastrointestinal; EKG—electrocardiogram. \*Trade name

**TABLE 1, continued.** Available pharmacological studies on management of inpatient pediatric aggression

	FREQUENCY AND DURATION	CLINICAL OUTCOME	SIDE EFFECTS	NO. PATIENTS
Khan et al (2006) <sup>20</sup>	PRN	Effective for decreasing aggression	Somnolence, no EKG changes ( QTc)	50
Barzman et al (2007) <sup>21</sup>	PRN	"Much to very much improved" (81%) "minimally improved" (16%) "no change" (1.3 %) "minimally worse" (1.3%) "much worse" (1.3 %)	Somnolence (60%)	59
Hazarey et al. (2004) <sup>22</sup>	PRN	Immediate calming down effect and going to sleep	Syncope—reported only in one patient	3
Stellar et al (2004) <sup>23</sup>	PRN	Effecitve in management of acute behavioral discontrol	None reported	49
Khan et al (2006) <sup>20</sup>	PRN	Effective for deacreasing aggression	Drowsiness, no EKG changes ( QTc)	50
Krishnamoorthy et al (1998) <sup>25</sup>	Daily for 32 days (Range 2–7 weeks)	Better control of aggression in three out of five patients	Sedation, weight gain (upto 16 lbs), akathasia	5
Campbell et al (1984) <sup>14</sup>	Daily for 6 weeks	Superior than placebo to control aggression (made child more manageable)	Drowsiness most common in frequency followed by acute dystonia	61
Buitelaar JK et al (2001) <sup>28</sup>	Daily for 6 weeks	Significant improvement in Overt Aggression Scale	Transient fatigue in more than half of the patients, GI symptoms—nausea, sialorrhea. No EKG changes, no effect on BP	38
Campbell et al (1984) <sup>14</sup>	Daily for 6 weeks	Superior than placebo to control aggression (reduce explosiveness)	Weight gain more than 30kg, stomachaches, headaches, hand tremors	61
Rifkin et al (1997) <sup>15</sup>	Daily for 2 weeks	No significant effects on decreasing the score in Overt Agression Scale	Side effects due to autonomic system malfunctioning	33
Malone et al (2000) <sup>13</sup>	Daily for 4 weeks	Rating on Overt Agression Scale decreased as compared to placebo	GI symptoms: nausea, vomiting and more than 50% patients experiencing increased frequency of urine	40
Vitiello et al (1991)²	PRN	IM more effective than PO	Sedation	21
Jangro et al (2009) <sup>47</sup>	PRN	There were no differences between the two treatment groups in the outcomes of restraint duration or use of rescue medications	Decreased pulse	52

Abbreviations: Pts—patients; IM—intramuscular, PO—per oral; MDD—major depressive disorder; NOS—not otherwise specified; yrs—years; PRN—as needed; QTc—QT interval on EKG, BP—blood pressure; H—heart rate; ADHD—attention deficit hyperactivity disorder; CD—conduct disorder; GAD—generalized anxiety disorder; PTSD—posttraumatic stress disorder; GI—gastrointestinal; EKG—electrocardiogram.

\*Trade name

somnolence, were found, side effects may not have been monitored or documented carefully.24 Nonetheless, the authors conclude that IM ziprasidone should be considered since it leads to a similar clinical outcome while avoiding potential severe adverse events associated with typical antipsychotic medications such as haloperidol.<sup>24</sup>

Olanzapine (Zyprexa). A study of five inpatients (aged 6–11 years) treated with open-label, oral olanzapine for 2 to 7 weeks found improvement in aggression in three of the children, but treatment was discontinued for all five of the patients due to unfavorable side effects or being short of therapeutic response. Side effects included significant weight gain, akathisia, and sedation.25

Risperidone (Risperdal). Risperidone is considered the most effective and safe in the treatment of aggression in children as per most of the available studies. Risperidone was also found to be useful in reducing aggression in children with autism.26 However, risperidone was only "modestly" effective in managing the treatment-resistant aggression in a short-term outpatient study of 25 children with attention deficit hyperactivity disorder (ADHD).<sup>27</sup> In this double-blind study, risperidone was added to the psychostimulant treatment.27

Most of the risperidone studies were conducted in outpatient settings and are targeted to treat chronic aggression rather than acute inpatient aggression. As per our search, only one study has attempted to observe the effects of risperidone in treating the aggression in an inpatient unit. In this study, 38 aggressive adolescent inpatients with CD and other oppositional problems were randomly assigned to risperidone or placebo treatment for six weeks in a doubleblind, placebo-controlled, randomized clinical trial. Risperidone was superior to placebo in reducing aggression. The most common side effect was drowsiness.28

Quetiepine (seroquel). As per our search, short-term studies on assessing the effectiveness quetiepine for

inpatient pediatric aggression are not available at this time. However, in one short-term (eight week), open-label, outpatient study (including 6-12 year old children with CD), quetiepine was found to be helpful and well tolerated when targeting aggression.29

Aripiprazole (Abilify). Although the inpatient studies on aripiprazole for pediatric aggression are also lacking, one open-label study of 15day duration suggests that it is effective and safe in reducing aggression in children and adolescents with CD.30

Summary. Overall, PRN use of IM ziprasidone and IM olanzapine and standing use of risperidone may have a positive effect for inpatient aggression on child and adolescent psychiatry units. PRN use of IM ziprasidone and IM olanzapine has a rapid onset of action but safety data is limited. Considering the effectiveness of quetiepine and aripirazole after short-term use, these medications may also be considered for this purpose.

#### Typical antipsychotics.

According to our literature review search results, the standardized studies of typical antipsychotic medications in reducing aggression in inpatient pediatric patients are limited. Since acute dystonia is notably associated with a younger age, it limits the utility of typical antipsychotics for the management of agitation in pediatric patients.31

Haloperidol (Haldol). Our search showed that the controlled trials for efficacy and safety profile for haloperidol PRN use in treating hospitalized pediatric patients are lacking. As mentioned previously, four weeks of haloperidol treatment has been found to be effective in reducing aggression in hospitalized children and adolescents with CD.<sup>14</sup>

Special safety issues with antispychotic medications. A few rare but acute serious side effects, such as acute dystonia (in the form of torticollis),32 akathisia,33 and neuroleptic malignant syndrome (NMS),<sup>34</sup> are reported in children and adolescents. It is necessary to consider these underestimated side

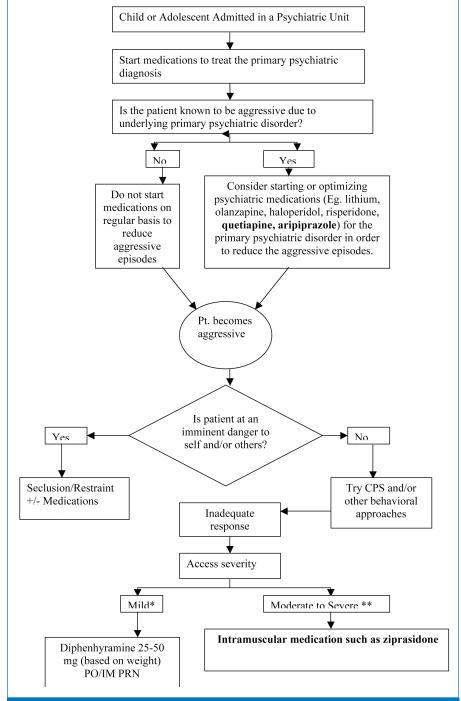
effects before starting antipsychotic medication in children and adolescents (Table 1).

**Benzodiazepines.** It is found that the use of benzodiazepines in children and adolescents can be associated with a paradoxical reaction including agitation and other adverse side effects.35 Abuse, dependence, and withdrawal symptoms are further clinical issues with these medications in adults<sup>36</sup> and similar risk of withdrawal exists in children.<sup>37</sup> A case report also suggested that benzodiazepines in children could induce psychotic symptoms in a physically abused child.<sup>38</sup> Despite these risks, benzodiazepines are still being preferred to treat pediatric agitation<sup>39, 40</sup> even though standardized studies assessing the usefulness and adverse effects of benzodiazepine monotherapy in treating inpatient aggression in children or adolescents are lacking.

## THE ASSESSMENT OF AGGRESSION AND NONPHARMACOLOGICAL TREATMENT APPROACHES

Aggression in children and adolescents can be "reactive" (impulsive and emotional in response to a trigger) and/or "proactive" (intentional and planned to fulfill a preconceived objective). 41 However, any form of aggression has the potential of severe and unexpected adverse outcomes on child inpatient units. Distinguishing the root cause, type, and identifying the warning signs of aggression may be beneficial in developing the individual treatment plan. For example, the "reactive" form of aggression shows more response to medication than the "proactive" form of aggression.42

Nevertheless, even if the aggression is mostly "reactive" on a child psychiatry inpatient unit, a behavioral approach such as collaborative problem solving (CPS) can be successfully implemented to help manage the aggression, which may minimize the use of medications.43 Relaxation techniques,44 creative art therapy,44 and maintaining the inpatient milieu<sup>45</sup> are also found to be helpful in reducing aggression in children and adolescents.



FIGURES 1. Pharmacological management of child and adolescent inpatient aggression

KEY: CPS=collaborative problem solving; \*Mild distress, no property destruction, no threatening behavior; \*\*Moderate-to-severe distress, patient exhibiting property destruction and/or threatening behavior

# CONCLUSIONS AND RECOMMENDATIONS

Based on the available literature, the authors have developed a flow chart to illustrate the recommended treatment approach for managing child and adolescent inpatient aggression (Figure 1). Treatment should address the primary psychiatric condition, which may decrease the pathological aggression. Standing psychotropic medications should be started or optimized for the most impairing primary psychiatric disorder. A similar protocol was developed for pediatric patients in the emergency room, which

begins with nonpharmacological interventions and then progresses to oral "symptom-specific" medication followed by "general agitation" medication if agitation persists.<sup>40</sup>

PRN medication should not be used unless the patient clearly exhibits severe aggression, and psychosocial interventions and/or standing medications (when indicated) have not proven sufficient to reduce aggression to manageable levels. 46 If a patient does not actually need a medication, prescribing one will put him or her at unnecessary risk of dangerous side effects, such as NMS when an antipsychotic is used. If an acute safety issue arises, the PRN medication choice should be restricted to safe, effective, and rapid-acting medication.

Medication must also be appropriate to the severity of the aggression. Mild aggression, such as no property destruction (with or without threatening behavior), can be managed with psychosocial interventions. A weight-based dose of diphenhydramine PRN can be considered for mild aggression but it should be noted that the beneficial effect may be due to a placebo effect. Moderate-to-severe aggression or threatening behavior with severe distress can be treated with either IM ziprasidone (20mg for both children and adolescents) or olanzapine (5mg for children and 10mg for adolescents). However, if the pediatric patient is imminently dangerous to self or others, it may be necessary to rapidly address the situation through the use seclusion and/or restraints with or without psychotropic medication. These recommendations are made based on the available limited evidence that was discussed in this review article. Further prospective, controlled studies are needed on oral and IM psychiatric medications for the treatment of child and adolescent inpatient aggression.

Comprehensive recommendations cannot be made until other psychotropic medications are studied for their potential to treat child and adolescent inpatient aggression. The recommendations in this article are intended to serve as helpful general guidelines, but all decisions about

medicating a patient (including the choice of medication and the dose) must always be individualized by a trained clinician based on the patient's medical history, diagnoses, and other pertinent factors.

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