Pharmacologic treatment of acute agitation in the pediatric population: What to do when oral therapy is not an option

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Objectives:

- Identify potential etiologies of acute agitation
- Discuss the treatment options for acute agitation
- Distinguish the unique characteristics of the available intramuscular (IM) formulations of antipsychotics
- Assess the available efficacy and safety literature on acute agitation treatment in the pediatric population
- Devise a treatment plan for acute agitation in the pediatric population

Background

Definitions[1-5]

I. Acute agitation = uncontrollable behavior, such as excessive motor or verbal activity, that can escalate to aggression resulting in harm to the patient, their family or healthcare workers if they do not receive intervention
   a. Aggression = any kind of behavior that has the potential to damage or harm objects, the patient or others
   b. Covert/proactive aggression versus reactive/impulsive aggression

II. Chemical restraint = involuntary use of a psychoactive medication in a crisis situation to help a patient contain out-of-control aggressive behavior[2]

III. Typical antipsychotic = first generation antipsychotics such as fluphenazine, haloperidol, etc

IV. Atypical antipsychotic = second generation antipsychotics such as ziprasidone, olanzapine, etc

I. Epidemiology[6-7]
   a. An average of 30 million children present to an emergency department (ED) in the US
   b. 3-4% have a psychiatric or behavioral chief complaint
   c. One pediatric ED in Boston, MA reported use of restraints (physical, chemical or both) in around 6.8% of all of is psychiatric evaluations in a 2 year period[7]

II. Pathophysiology[4,8]
   a. Not well known and can mostly be associated with the mechanism of the underlying disorders that manifest with agitation

Table 1. Proposed pathophysiology of acute agitation.

Disorder	**Mechanism**
Agitated depression	Increased serotonergic responsivity; decrease in GABA
Mania	Increase in dopamine
Panic disorder and generalized anxiety disorder	Increase in norepinephrine; decrease in GABA
Dementia	Decrease in GABA
Delirium	Multiple underlying causative mechanisms
Substance-induced agitation	Increase in dopamine
Acute psychosis	Increase in dopamine
Akathisia	Decrease in dopamine; increase in norepinephrine
Aggression	Increase in norepinephrine; decrease in serotonin

III. Potential etiologies[1,3,4]
   a. Medical diagnosis
      i. Ingestion of unknown substance, intoxication or withdrawal, medication side effects, pain, brain injury or trauma, acute medical illness, or worsening of a chronic condition

b. Psychiatric diagnosis
    i. Attention-deficit hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, bipolar disorder, childhood psychosis, autism, developmental disorders, and post-traumatic stress disorder (PTSD)

IV. Adult guidelines[4]
a. Workgroup of the American Association for Emergency Psychiatry
b. Sought to outline best-practice pharmacologic approaches to use when agitation requires emergent management before stabilization of the underlying etiology
c. General recommendations:
    i. The use of medication as a restraint should be discouraged
    ii. Nonpharmacologic approaches, such as verbal de-escalation and reducing environmental stimulation should be attempted, if possible, before medications are administered
    iii. Medication should be used to calm patients, not to induce sleep
    iv. Patients should be involved in the process of selecting medication to whatever extent possible
    v. If the patient is able to cooperate with taking oral medications, these are preferred over intramuscular preparations
d. Recommendations by etiology:

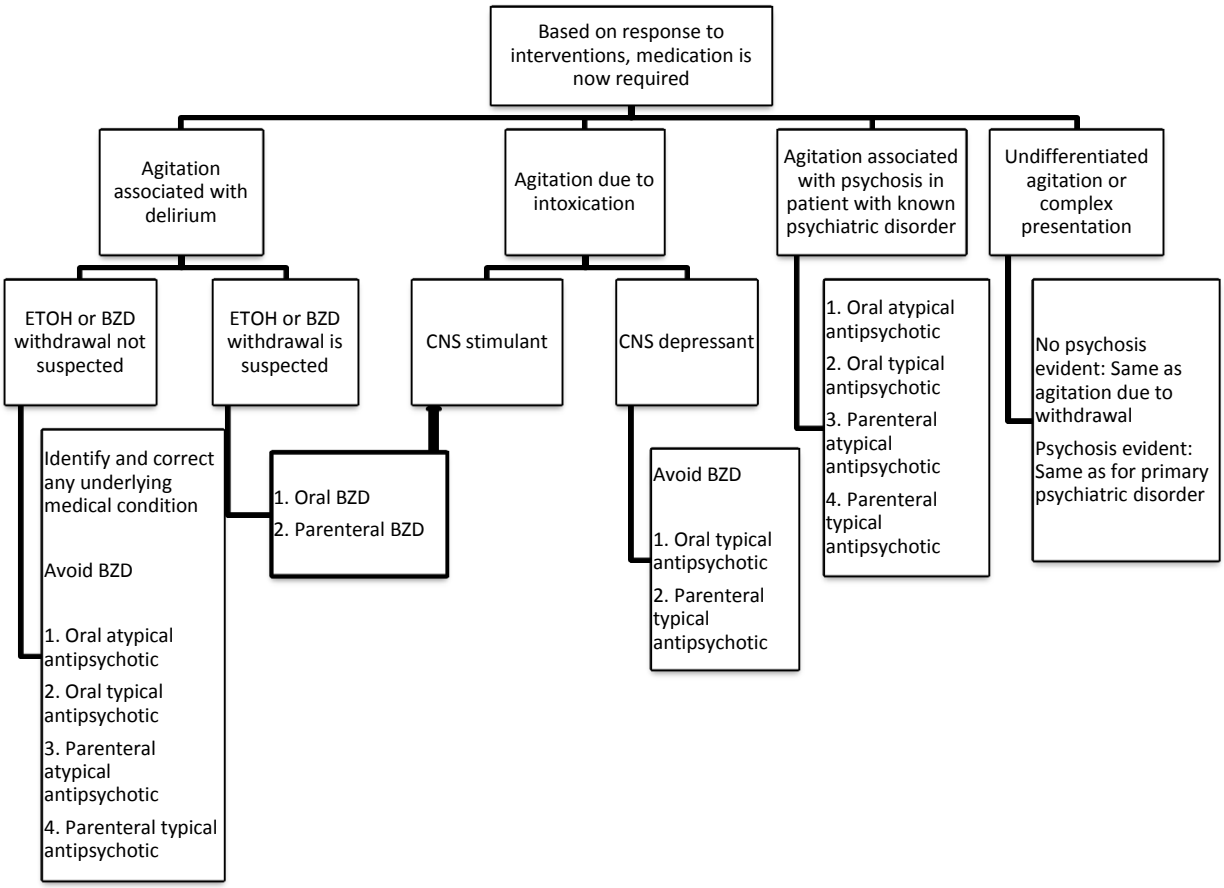

Figure 1. Adult guidelines for acute agitation in the emergency department.

V. TRAAY recommendations[9]
   a. Conduct comprehensive psychiatric diagnostic interviews with patients and parent(s)/guardian(s) before adding or adjusting to medications
   b. Standardized symptom and behavior rating scales with proven reliability and validity should be used to measure the severity and frequency of target symptoms before treatment and at regular intervals
   c. Use psychosocial and educational treatment before and during medications
   d. Use appropriate treatment for primary disorders as a first-line treatment
   e. Use an atypical antipsychotic first rather than a typical antipsychotic to treat aggression
   f. Use a conservative dosing strategy
   g. Use psychosocial crisis management techniques before medication for acute or emergency treatment of aggression
   h. Avoid frequent use of emergency medications
   i. Assess side effects routinely and systematically
   j. Ensure adequate trial before changing medications
   k. Use a different atypical antipsychotic after a failure to respond to an adequate trial of the initial first-line atypical
   l. Consider adding a mood stabilizer after a partial response to an initial first-line antipsychotic
   m. If a patient is not responding to multiple medications, consider tapering one or more medications
   n. Taper and consider discontinuing antipsychotics in patients who show a remission in aggressive symptoms for six months or longer

VI. Goals of treatment[3,4]
   a. To calm the patient without excessive sedation so that he/she can be more accurately assessed to determine etiology
   b. To decrease dangerous and aggressive behaviors prior to any harmful actions
   c. To accurately and adequately treat the underlying disorder

VII. Assessment scales[10]
   a. Overt Agitation Severity Scale (OASS) – see appendix A
   b. Behavioral Activity Rating Scale (BARS)
      i. Describes the level of activity of a patient by assigning a score as an overall assessment

Table 2. BARS score definitions

Score	Description
1	Difficult or unable to arouse
2	Asleep but responds normally to verbal or physical contact
3	Drowsy, appears sedated
4	Quiet and awake (normal level of activity)
5	Signs of over (physical or verbal) activity, calms down with instructions
6	Extremely or continuously active, not requiring restraint
7	Violent, requires restraint

Current Therapy Options

VIII. Medication options[11-27]

Table 3. Pharmacokinetic profile comparisons

Medication	Formulation	Onset of action	Peak effect	Half life	Repeat dosing
Diphenhydramine	Tab/Cap/Liq	1 hr	1.3 hr	5.4 hr	6 hr
Hydroxyzine	Cap	1 hr	2 hr	7.1 hr	6 hr
Lorazepam	Tab	Rapid	2 hr	10-16 hr	6 hr
Haloperidol	Tab	1 hr	2 hr	15 hr	8 hr
Risperidone	Tab/Liq/ODT	1 hr	1 hr	3-20 hr	12 hr
Olanzapine	Tab/ODT	5 hr	5 hr	37 hr	24 hr
Ziprasidone	Cap	5 hr	5 hr	3-4 hr	12 hr
Aripiprazole	Tab/Liq/ODT	2 hr	2 hr	75 hr	24 hr
Diphenhydramine	IM	Rapid	1.3 hr	5.4 hr	Max 300mg/day
Hydroxyzine	IM	Rapid	4-6 hr	7.1 hr	4 hr
Lorazepam	IM	5-20 min	3 hr	10-16 hr	10-15 min
Haloperidol	IM	30 min	60-90 min	26 hr	60 min
Olanzapine	IM	15-45 min	15-45 min	21-51 hr	2nd dose: 2 hr 3rd dose: 4 hr Max 30mg/day
Ziprasidone	IM	15 min	<60 min	3-4 hr	10mg: 2 hr 20mg: 4 hr Max 40mg/day
Aripiprazole	IM	60 min	1-3 hr	75 hr	2 hr Max 30mg/day

NA = not applicable

IX. Adverse Drug Reactions[1,14-18]

a. Extrapyramidal Symptoms (EPS) = involuntary movements[28,29]
   i. Acute dystonia = muscle rigidity and spasms
   ii. Akathisia = feeling of restlessness
   iii. Pseudoparkinsonism = tremor, hypokinesia, rigidity and postural instability
   iv. Risk factors: young, muscular males, higher potency antipsychotic, and extremes in age
   v. EPS incidence with oral risperidone and olanzapine is 12% and 8% respectively in the pediatric population[1]

b. QTc prolongation[30-32]
   i. Risk factors: electrolyte disturbances, bradycardia, congenital QTc prolongation, cardiovascular disease, female sex, baseline prolongation, other QTc medications
   ii. In the adult population, PO ziprasidone can show up to a 22.5msec change from baseline QTc, and the pediatric population showed a similar change around 22.9msec
   iii. Comparative effects on QTc with oral formulations: thioridazine > ziprasidone > quetiapine > olanzapine, risperidone, and haloperidol

c. Neuroleptic Malignant Syndrome (NMS)[33-36]
    i. DSM-IV criteria: fever and severe muscle rigidity plus 2 other signs, symptoms or laboratory findings[33]
    ii. Risk factors include catatonia, agitation, dehydration, restraint, preexisting abnormalities of CNS dopamine activity, iron deficiency, high potency antipsychotics, parenteral routes, higher titration rates, and total dose
    iii. 16% of cases developed within the first 24 hours, 66% within the first week and almost all cases were present within 30 days[36]
    iv. There are 23 NMS case reports with oral atypical antipsychotics in 20 children and adolescents between the years 1990-2008[35]
        1. Highest reported incidences: risperidone, olanzapine, aripiprazole

Table 4. Summary of ADR profiles for medications available as IM formulations[1,3,11-17,28-36]

Drug	Paradoxical reactions	EPS	QTc prolongation	NMS	Sedation	Orthostatic hypotension	Respiratory depression
Diphenhydramine	Moderate	Rare	NR	NR	High	Low	Low
Hydroxyzine	Moderate	Rare	NR	NR	High	High	Low
Lorazepam	Moderate	Rare	NR	NR	High	Low	High
Haloperidol	NR	High	Low	Low	Low	Low	Low
Olanzapine	NR	Moderate	Low	Rare	High	High	Moderate
Ziprasidone	NR	Low	High	Rare	Moderate	Moderate	Low
Aripiprazole	NR	Moderate	Low	Rare	Moderate	Moderate	Moderate

Pediatric Considerations

X. Pharmacokinetics[37-41]
    a. Absorption: the relatively low proportion of skeletal muscle to fat in younger children tend to produce unpredictable plasma concentrations after IM administration
    b. Metabolism: IM route avoids first pass metabolism
    c. Elimination: drug clearance can continue to increase and the most rapid elimination of drugs is seen in school-aged children

XI. Physical considerations[11-17,42]
    a. Varying concentrations of medications can cause large amounts of fluid to deliver dosage
    b. Standardized max volumes per muscle site might prevent delivery of full dosage

XII. Trauma
    a. Physical restraint and the physical pain associated with injections can be traumatizing and confusing to a child or adolescent who might not have the capacity to understand everything that is going on around them
    d. This experience for a child or adolescent who has had a history of physical or sexual abuse can be even more profound if it triggers memories of their past
    e. Confusion about the situation and their surroundings in addition to this added pain could actually cause more agitation

Literature Review

XIII. Case Reports[43]

a. In 2004, Hazaray and colleagues published 3 case reports using ziprasidone IM as needed (PRN) for acute agitation and aggression

i. Case 1 was a 13 year old male with conduct disorder and ADHD who had received 77 doses of PRN medications for severe agitation including PO olanzapine, PO and IM chlorpromazine, and PO and IM lorazepam in an 8 week period. Subsequently, 4 episodes that were deemed unresponsive to these previous medications were treated with ziprasidone 10mg IM. Each dose was followed by a calming period and then sleep. His behaviors improved, PRN medications decreased and no further seclusion was necessary.

ii. Case 2 involved a 12 year old male with a history of explosive outbursts that eventually led to legal charges. After 23 episodes of aggression treated with olanzapine 5mg PO PRN, he was started on ziprasidone 20mg PO daily. During a following episode unresponsive to PO olanzapine, patient received one dose of IM ziprasidone 10mg. He calmed down and was asleep within 15 minutes. Patient no longer required any PRN medications and was discharged after continued improvement in behavior for 2 months.

iii. Case 3 described a 12 year old male with diagnoses including oppositional defiant disorder, generalized anxiety disorder and bipolar disorder, NOS. He was currently being treated with ziprasidone 80mg PO BID which was reduced to 40mg BID on admission. In the first 6 weeks, the patient had multiple rage attacks that was treated with 16 doses of PRN medications of PO olanzapine or IM haloperidol. Ziprasidone 10mg IM was used for 2 severe rage attacks a week apart. He responded with immediate calming followed by somnolence. After the second dose he had a syncopal episode 1.5 hours after administration, but recovered minutes after with no changes in ECG or EEG. During his 1 year stay, the intensity and frequency of his outbursts and need for PRN medications were reduced.

XIV. Observational chart review[44]

a. In 2004, JA Staller published an observational study describing the characteristics, outcomes and safety of 49 children and adolescents receiving ziprasidone IM from a retrospective chart review.

i. 32 (65.3%) were females and 35 (71.4%) were Caucasian

ii. The most common indications were agitation and agitation/anxiety/threat. Psychosis was listed only for 2 patients.

iii. Dosing in 87% of subjects received 20mg and the remaining received a 10mg dose

iv. Only 2 patients continued to exhibit agitation and aggression during the ensuing shift after a 20mg dose

v. 1 patient required a repeat dose within 4 hours of the initial injection according to nursing notes

vi. No nursing notes indicated any adverse reactions

<table>
<tr><td>Study 1[45]</td><td>Barzman DH, DelBello MP, Forrester JJ, et al. A retrospective chart review of intramuscular ziprasidone for agitation in children and adolescents on psychiatric units: prospective studies are needed. J Child Adolesc Psychopharmacol. 2007;17(4):503-9.</td></tr>
<tr><td>Trial design</td><td>Retrospective chart review</td></tr>
<tr><td>Purpose</td><td>To evaluate the effectiveness and tolerability of intramuscular ziprasidone for impulsivity and agitation in psychiatrically hospitalized children and adolescents</td></tr>
<tr><td>Outcomes</td><td>• Primary: change from baseline to end point BARS score
• Secondary: response rate defined as an end point CGI-I score of ≤2</td></tr>
<tr><td>Inclusion criteria</td><td>All children and adolescents admitted to Cincinnati Children’s Hospital Medical Center psychiatric units between January 1, 2002 and July 11, 2005 who receive a dose of IM ziprasidone</td></tr>
<tr><td>Exclusion criteria</td><td>No doses of IM ziprasidone administered or no documentation of symptom and behavioral changes</td></tr>
<tr><td>Methods</td><td>• Computerized search of patients to identify initial cohort of patients with a prescription for IM ziprasidone
• BARS, Clinical Global Impression-Severity (CGI-S) and Improvement (CGI-I) scores were based on systematic and detailed review of the inpatient medical records and assigned by 2 board-certified child and adolescent psychiatrists who had established interrater reliability for all rating instruments
• Wilcoxon Signed-Rank test, Regression analyses</td></tr>
<tr><td>Results</td><td>• Out of 218 patients identified, 59 patients who received a total of 77 injections met all inclusion/exclusion criteria

Table 5. Baseline demographics
<table>
<tr><th>Characteristic</th><th>n (%)</th></tr>
<tr><td>Male</td><td>39 (66)</td></tr>
<tr><td>5-7 years old</td><td>2 (3)</td></tr>
<tr><td>8-12 years old</td><td>14 (24)</td></tr>
<tr><td>12-19 years old</td><td>43 (73)</td></tr>
<tr><td>Bipolar disorder</td><td>22 (37)</td></tr>
<tr><td>Major depressive disorder</td><td>12 (20)</td></tr>
<tr><td>Mood disorder NOS</td><td>12 (20)</td></tr>
<tr><td>Psychotic disorder</td><td>12 (20)</td></tr>
<tr><td>Disruptive disorder</td><td>10 (17)</td></tr>
<tr><td>Impulse control disorder</td><td>8 (14)</td></tr>
<tr><td>ADHD</td><td>6 (10)</td></tr>
</table>
<table>
<tr><th>Co-administered medications</th><th>n (%)</th></tr>
<tr><td>Antipsychotic</td><td>29 (38)</td></tr>
<tr><td>Antidepressant</td><td>23 (30)</td></tr>
<tr><td>Alpha-2 agonist</td><td>7 (9)</td></tr>
<tr><td>Stimulant</td><td>7 (9)</td></tr>
<tr><td>Mood stabilizer</td><td>6 (7.8)</td></tr>
<tr><td>Other antiepileptic drug</td><td>5 (6.4)</td></tr>
<tr><td>Anticholinergic</td><td>3 (3.8)</td></tr>
<tr><td>Other</td><td>3 (3.8)</td></tr>
</table>
• Ziprasidone 10mg, n=15 (19%)
• Ziprasidone 20mg, n=62 (81%)
• Baseline BARS: 6.5 ± 0.7
• Baseline CGI-S: 6.2 ± 0.9
• 8 (10%) episodes included subjects already receiving oral ziprasidone on a scheduled basis and 88% of these episodes utilized IM ziprasidone 20mg</td></tr>
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- **Primary outcome**

Table 6. Post treatment BARS scores

<table>
<tr><td></td><td colspan="7">BARS Scores</td></tr>
<tr><td></td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr>
<tr><td>All doses</td><td>3 (4%)</td><td>30 (39%)</td><td>13 (17%)</td><td>24 (31%)</td><td>4 (5%)</td><td>1 (1%)</td><td>2 (3%)</td></tr>
<tr><td>10mg</td><td colspan="3">4 (27%)</td><td>6 (40%)</td><td colspan="3">5 (33%)</td></tr>
<tr><td>20mg</td><td colspan="3">42 (68%)</td><td>18 (29%)</td><td colspan="3">2 (3%)</td></tr>
</table>

  - Mean BARS score: 3.1 ± 1.3, $p < 0.0001$

- **Secondary outcomes**
  - CGI-I ≤2 (much improved): 62 (81%)
  - CGI-I 3 (minimally improved): 12 (16%)
  - CGI-I 4 (no change): 1 (1.3%)
  - CGI-I 5 (minimally worse): 1 (1.3%)
  - CGI-I 6 (much worse): 1(1.3%)
- **Adverse events reported**
  - Increase in seizure frequency: 1 (1.3%)
  - Dizziness: 1 (1.3%)
  - Nosebleed: 1 (1.3%)
  - Sore muscles/general aches: 1 (1.3%)
  - Confusion: 1 (1.3%)
  - Drowsiness/sleeping: 46 (60%)

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<tr><td>Conclusion</td><td>

- Placebo-controlled studies are needed to demonstrate efficacy and safety (with baseline and post-administration ECGs) of IM ziprasidone for agitation in children and adolescents on inpatient psychiatric units

</td></tr>
<tr><td>Critique</td><td>

- Strengths
  - Inter-rater reliability
  - Large age range
- Weaknesses
  - Retrospective study (selection bias and missing data)
  - Potential for missing adverse event documentation
  - No blinding or control data
  - Subjective assessment scale

</td></tr>
</table>

<table>
<tr><td>Study 2[46]</td><td>Khan SS, Mican LM. A naturalistic evaluation of intramuscular ziprasidone versus intramuscular olanzapine for the management of acute agitation and aggression in children and adolescents. J Child Adolesc Psychopharmacol. 2006;16(6):671-77.</td></tr>
<tr><td>Trial design</td><td>Naturalistic, retrospective chart review</td></tr>
<tr><td>Purpose</td><td>To compare the efficacy and safety of IM ziprasidone versus IM olanzapine in treating aggression in youth</td></tr>
<tr><td>Outcomes</td><td>• Restraint outcomes: number of restraints and time in restraints after study medication and time in restraints after emergency medication
• Study outcomes: length of stay (LOS), days on study agent, aggressive episode, number of doses of emergency medications and number of doses of study agent</td></tr>
<tr><td>Inclusion criteria</td><td>Patients less than 18 years old in the child and adolescent inpatient psychiatric unit at Austin State Hospital between January 1, 2003 and January 24, 2005 who received either IM ziprasidone or olanzapine for acute agitation or aggression</td></tr>
<tr><td>Exclusion criteria</td><td>Patients 18 years and older diagnosed with moderate, severe or profound mental retardation, subjects receiving both IM ziprasidone and IM olanzapine at some point during their hospitalization</td></tr>
<tr><td>Methods</td><td>• The state hospital computer system was utilized to obtain 100 medical charts that met study criteria
• Chi-squared and two tailed Student t-tests were used to compare categorical data and continuous variables respectively
• A post hoc one-way analysis of covariance was conducted to control for age and gender effects on time in restraint and number of restraints</td></tr>
<tr><td>Results</td><td>Table 7. Baseline demographics
<table>
<tr><td></td><td>Olanzapine, n=50</td><td>Ziprasidone, n=50</td></tr>
<tr><td>Children (age ≤12 years), n (%)</td><td>15 (30)</td><td>5 (10)</td></tr>
<tr><td>Adolescents (13-17 years), n(%)</td><td>35 (70)</td><td>45 (90)</td></tr>
<tr><td>Male, n (%)*</td><td>34 (68)</td><td>16 (32)</td></tr>
<tr><td>Diagnosis with psychosis, n (%)</td><td>18 (36)</td><td>16 (32)</td></tr>
<tr><td>Scheduled oral antipsychotic, n (%)</td><td>41 (82)</td><td>48 (96)</td></tr>
<tr><td>Oral ziprasidone/olanzapine</td><td>0/--</td><td>--/13</td></tr>
<tr><td>Clozapine treatment</td><td>0</td><td>4</td></tr>
<tr><td>Number of doses administered</td><td>163</td><td>251</td></tr>
</table>
*Significant difference (p<0.001) between the two treatment groups

Table 8. Reported dosing
<table>
<tr><td></td><td>Olanzapine</td><td>Ziprasidone</td></tr>
<tr><td>Mean study dose, mg (SD)</td><td>8.19 ± 2.43</td><td>19.07 ± 2.63</td></tr>
<tr><td>Mean child dose, mg (SD)</td><td>5.92 ± 2.18*</td><td>15.66 ± 4.35</td></tr>
<tr><td>Mean adolescent dose, mg (SD)</td><td>9.17 ± 1.77*</td><td>19.45 ± 2.13</td></tr>
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*Significant difference (p<0.001) in child vs adolescent dosing</td></tr>
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- **Results**

Table 9. Restraint outcomes

Outcome	Olanzapine	Ziprasidone	p-value
Documented effective, (%)	90.2	84.9	p=0.733
Mean number of restraints within 4 hours after study medication	0.32	0.44	p=0.555
Mean time in restraint after study medication, min	41	38	p=0.218
Mean time in restraint after emergency medication, min	31	46	NS

Table 10. Study outcomes

Mean number of doses of study agent, n (SD)	3 ± 4	5 ± 8	p=0.157
Mean doses of emergency medication, n (SD)	11 ± 9	21 ± 26	p=0.009
Mean days on study agent, days (SD)	3.1 ± 3.8	4.6 ± 6.6	p=0.152
Mean number of aggressive episodes, n (SD)	9 ± 8	14 ± 15	p=0.497
Mean LOS, days (SD)	26 ± 17	34 ±24	p=0.053

- **Adverse Events**
  - Olanzapine: somnolence 33 (20%); 2 other possible side effects reported – itching and pseudoparkinsonism
  - Ziprasidone: somnolence 40 (16%); 3 other possible side effects reported – itching, nausea, and stiffness in the joints
  - No pattern of clinically relevant changes in blood pressure, pulse rate or QTc with either treatment groups

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<tr><td>Conclusion</td><td>

- Overall, the results suggest IM ziprasidone and olanzapine may be equally effective in treating agitation and aggression in children and adolescents

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<tr><td>Critique</td><td>

- Strengths
  - Comparator group
  - Clinically relevant outcomes
  - Standardized treatment forms
  - Larger number of doses
- Weaknesses
  - Retrospective study (selection bias and missing data)
  - Potential for missing adverse event documentation
  - Lack of standardized objective measurements
  - No severity assessment

</td></tr>
</table>

<table>
<tr><td>Study 3[47]</td><td>Jangro WC, Preval H, Southard R, Klotz SG, Francis A. Conventional intramuscular sedatives versus ziprasidone for severe agitation in adolescents: case-control study. Child Adolesc Psychiatry Ment Health.2009;3(1):9-14.</td></tr>
<tr><td>Trial design</td><td>Retrospective, naturalistic observational study</td></tr>
<tr><td>Purpose</td><td>To compare IM ziprasidone to conventional IM medications (haloperidol combined with lorazepam) for the treatment of severe agitation in adolescents</td></tr>
<tr><td>Outcomes</td><td>• Primary: restraint duration and need for adjunctive medication
• Secondary: change in BARS, blood pressure, pulse</td></tr>
<tr><td>Inclusion criteria</td><td>All adolescents presenting to the SUNY Stony Brook psychiatric emergency services with severe agitation episodes (defined as requiring physical restraint)</td></tr>
<tr><td>Exclusion criteria</td><td>Ziprasidone with lorazepam, oral or IM sedatives within 1 hour prior, and concomitant IM agents such as diphenhydramine, amobarbital, lorazepam, or chlorpromazine</td></tr>
<tr><td>Methods</td><td>• A computerized search of restraint records for episodes of agitation was used to identify patients
• All sedatives given within 1 hour after was considered a rescue medication
• Comparisons made by t-test, repeated measures ANOVA, and chi-squared tests</td></tr>
<tr><td>Results</td><td>Table 11. Baseline characteristics
<table>
<tr><td>Characteristic</td><td>Ziprasidone</td><td>Haloperidol/lorazepam</td><td>p-value</td></tr>
<tr><td>Age (years) (SD)</td><td>15.5 ± 1.5</td><td>15.9 ± 1.2</td><td>NS</td></tr>
<tr><td>Gender, male (%)</td><td>12 (42.9)</td><td>15 (62.5)</td><td>NS</td></tr>
<tr><td>Positive toxicology (%)</td><td>7 (25)</td><td>10 (41.7)</td><td>NS</td></tr>
</table>
• 52 adolescents aged 12-17 years old
○ Ziprasidone 10mg, n=4
○ Ziprasidone 20mg, n=24
○ Haloperidol with lorazepam, n=24 (avg dose 4.8 and 1.9 respectively)
• Mean baseline BARS score was 6.9 (n=7)

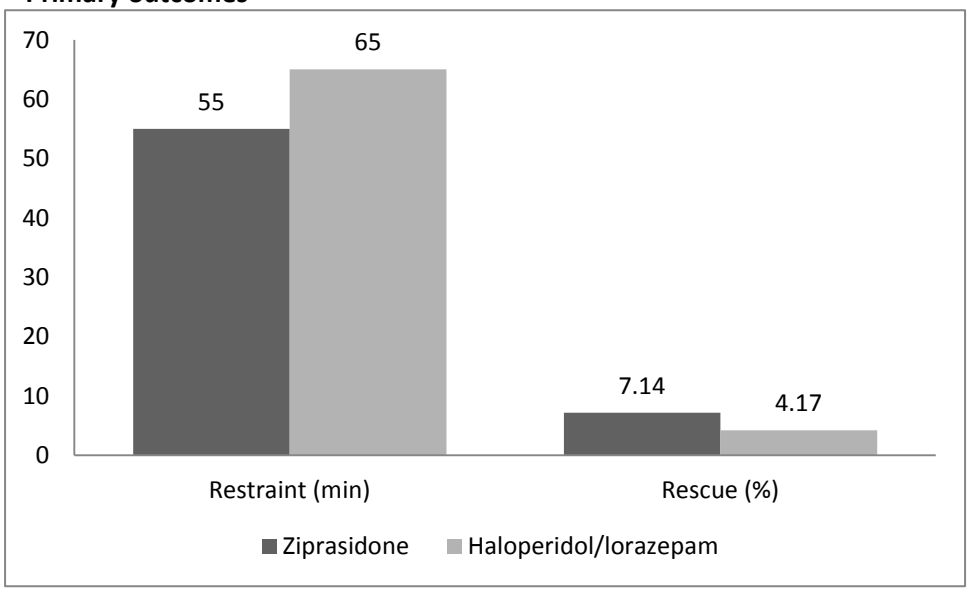
• Primary outcomes


Figure 2. Time spent in restraints and use of rescue medications between treatment groups.</td></tr>
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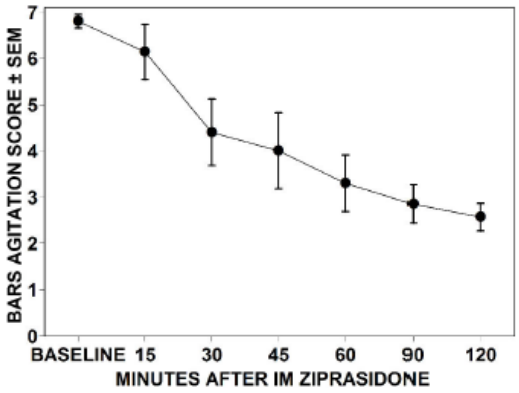
• Secondary outcomes


Figure 3. BARS scores for 7 patients

Table 12. Change in heart rate in 30 patients
<table>
<tr><th>Treatment group</th><th>Decrease in pulse</th><th>p-value</th></tr>
<tr><td>Ziprasidone (SD), n=18</td><td>8.9 ± 4.24</td><td rowspan="2">NS</td></tr>
<tr><td>Haloperidol/lorazepam (SD), n=12</td><td>8.3 ± 2.4</td></tr>
</table>
○ No significant changes in blood pressure in either treatment group
○ No EPS reported for either treatment group
○ Only 4 ECGs available, but all reported normal QTc intervals
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<tr>
<td>Conclusion</td>
<td>• Reduction in severe agitation in the ziprasidone IM monotherapy group was comparable to the haloperidol IM combined with lorazepam IM group</td>
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<tr>
<td>Critique</td>
<td>
• Strengths
○ Patient population and setting
○ Baseline severity
○ Clinically relevant outcomes
○ Comparator group
• Weaknesses
○ Retrospective study (selection bias and missing data)
○ Limited sample size
○ Lack of standardized adverse event reporting
○ Lack of standardized objective measure for most patients
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Recommendations

1) Nonpharmacological approaches should always be attempted prior to any medication, but also after medication is administered
2) Ziprasidone is the preferred agent unless patient has a known cardiac disorder, other risk factors for QTc prolongation, or previous intolerance
3) Start with lowest available dose, especially for young children and antipsychotic naïve patients
4) Training should take place for support staff on monitoring via assessment scales, as well as, recognition of important side effects
5) Repeat dosing should follow package insert recommendations to avoid excessive drug accumulation
6) Physical attributes of the child should be considered before drug administration for proper dosing and ideal administration site

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Appendices

A. OASS assessment questions and ratings[10]

Intensity (I)	Frequency (F)					
Behavior	Not present	Rarely	Some of the time	Most of the time	Always present	Severity score (SS) (I x F = SS)
A. Vocalizations and oral/facial movements						
1. Whimpering, whining moaning, grunting, crying	0	1	2	3	4	= _____
2. Smacking or licking of lips, chewing, clenching jaw, licking, grimacing, spitting	0	1	2	3	4	= _____
3. Rocking, twisting, banging of head	0	1	2	3	4	= _____
4. Vocal perseverating, screaming, cursing, threatening, wailing	0	1	2	3	4	= _____
B. Upper torso and extremity movements						
1. Tapping fingers, fidgeting, wringing of hands, swinging or flailing arms	0	1	2	3	4	= _____
2. Task perseverating (eg opening and closing drawers, folding and unfolding clothes, picking at objects, clothes or self)	0	1	2	3	4	= _____
3. Rocking (back and forth), bobbing (up and down), twisting or writhing of torso, rubbing or masterbating self	0	1	2	3	4	= _____
4. Slapping, swatting, hitting at objects or others	0	1	2	3	4	= _____
C. Lower extremity movements						
1. Tapping toes, clenching toes, tapping heel, extending, flexing or twisting foot	0	1	2	3	4	= _____
2. Shaking legs, tapping knees and/or thighs, thrusting pelvis, stomping	0	1	2	3	4	= _____
3. Pacing, wandering	0	1	2	3	4	= _____
4. Thrashing legs, kicking at objects or others	0	1	2	3	4	= _____
				Total OASS		= _____
			Subtract baseline OASS			= _____
				Revised OASS		= _____

Instructions for completing form

Step one: For each behavior, circle the corresponding frequency

Step two: For every behavior exhibited, multiply the intensity score by the frequency and record as the severity score

Step three: For the OASS total, all severity scores and record as total OASS

Step four: Does this patient have a neuromuscular disorder (ie Parkinson's disease, tardive dyskinesia) affecting total OASS? Yes No

Step five: If yes, please establish a baseline OASS in non-agitated state and subtract from above total OASS for revised OASS

B. Clinical Global Impression Scales (CGI)[48]

a. Clinical global impression scale severity (CGI-S)

Score	Description
1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients

b. Clinical global impression scale improvement (CGI-I)

Score	Description
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

C. Medication profile summaries[1,2,11-13,19-21]

	Diphenhydramine	Hydroxyzine	Lorazepam
Pediatric indications	Symptomatic relief of allergic symptoms, adjunct to epinephrine in anaphylaxis, nighttime sleep aid, prevention of motion sickness, antitussive, and management of Parkinsonian syndrome including drug-induced EPS	Treatment of anxiety/agitation, adjunct to pre- and postoperative analgesia and anesthesia, antipruritic and antiemetic	PO: anxiety and insomnia due to anxiety or situational stress in adolescents
Pediatric oral dosing	2 - <6 years: 6.25mg Q4 hr; max 37.5mg/day 6 - <12years: 12.5mg Q4 hr; max 75mg/day ≥12 years: 25-50mg Q4-6 hr; max 300mg/day	<6 years: 50mg daily in divided doses ≥6 years: 50-100mg daily in divided doses	0.02-0.09mg/kg Q4-8 hours or 0.01-0.03mg/kg and may repeat Q20 min as needed
Pediatric IM dosing	5mg/kg/24hr or 150mg/m2/24hr; max 300mg/day	0.5-1mg/kg/dose	0.02-0.09mg/kg Q4-8 hours or 0.01-0.03mg/kg and may repeat Q20 min as needed
Onset of action	PO: 15-20 min IM: rapid	PO: 15-30 min IM: rapid	PO: 30-60 min IM: 20-30 min IV: 5-20 min

Time to peak	1-3 hr	4-6 hr	3 hr
Metabolism	Extensively via CYP2D6, minor via CYP1A2, 2C9 and 2C19	Hepatic to many metabolites	Conjugation to inactive metabolite
Half-life	Children: 5 hours (4-7 hour range) Adults: 9 hours (7-12 hour range)	Adults: about 20 hours	16.8 hours
Excretion	Urine	Urine	Urine 88%
Special considerations	Potential for overdosage that can cause hallucinations, convulsions or even death	Burning sensation during administration of IM formulation	Larger Vd and longer half-life in children and adolescents compared to adults

D. Typical antipsychotic profile summaries[1-5,14,23]

	Droperidol	**Haloperidol**
Pediatric indication	Nausea and vomiting associated with surgical or diagnostic procedures	Schizophrenia, control of tics and vocal utterances of Tourette's disorder, severe behavioral problems
Pediatric oral dosing	N/A	0.01-0.03mg/kg/day
Pediatric IM dosing	0.1mg/kg slowly	1-3mg Q6-8 hours; max 0.15mg/kg/day
Onset of action	3-10 min	30-60 min
Time to peak	30 min	60-90 min
Metabolism	Hepatic	Mostly glucuronidation and CYP3A4 to inactive metabolites
Half-life	Children: 101.5 ± 26.4 min Adults: 134 ± 13 min	Adults: 20 hours
Excretion	75% urine	Urine and feces
Special considerations	Associated with a >9% increase in the average baseline QTc in children	Often given as a mixture with lorazepam

E. Atypical antipsychotic profile summaries[1-5,15,16,18,24,25,27]

	Olanzapine	**Ziprasidone**	**Aripiprazole**
Pediatric oral Indication	1. Treatment of schizophrenia in kids 13 years and older 2. Treatment of bipolar disorder in kids 13 years and older	None	1. Treatment of acute mania or mixed episodes in kids ≥10 years with bipolar disorder 2. Treatment of irritability associated with autistic disorder in kids ≥6 years 3. Treatment of schizophrenia in kids ≥13 years
Pediatric oral Dosing	2.5 – 20mg/day; target dose 10mg daily	5 – 20mg/day	2 – 30mg/day; target dose 10mg daily
Pediatric IM Dosing	Children: 5mg/dose Adolescents: 10mg/dose	Children: 5mg/dose Adolescents: 10mg/dose	No experience in pediatric population

Adult IM Indication	Acute agitation in patients with schizophrenia and related psychotic disorders and bipolar mania	Acute agitation associated with schizophrenia	Acute treatment of agitation associated with schizophrenia or bipolar I disorder
Receptor Affinity	High: 5-HT2A, 5-HT2C, D1-4, H1 and alpha1 Moderate: 5-HT3 and muscarinic receptors Weak: GABA-A, BZD, and beta-adrenergic receptors	High: D2, D3, 5-HT2A, 5-HT1A, 5-HT2C, 5-HT1D and alpha1 Moderate: H1	High: D2, D3, 5-HT1A, and 5-HT2A Moderate: D4, 5HT2C, 5-HT7, alpha1, and H1 Partial agonist: D2 and 5-HT1A
Metabolism	Direct glucuronidation, CYP1A2, CYP2D6	Aldehyde oxidase; minor via CYP3A4 and CYP1A2	CYP2D6 and CYP3A4
Excretion	57% urine	66% feces	55% feces
Special considerations	Caution in combination with IM benzodiazepines due to reported fatalities. IM max concentration 5 times that of oral.		Higher propensity to cause akathisia which can be mistaken as continued or increased agitation IM max concentration on average 19% higher and AUC 90% higher than oral