Pharmacologic Management of the Agitated Child

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Abstract: Agitation is a chief complaint that causes many children and adolescents to present to emergency medical attention. There are many reasons for acute agitation, including toxicologic, neurologic, infectious, metabolic, and functional disorders. At times it may be necessary to pharmacologically treat the agitation to prevent harm to the patient, caregivers, or hospital staff. However, one should always be mindful that the differential diagnosis is broad, and a complete although timely assessment with targeted testing must be done before concluding that the agitation is rooted solely in nonorganic causes. There are various pharmacologic choices for the treatment of agitation, and they will be reviewed here. While treatment of agitation may be necessary to keep the patient as well as staff safe, as well as to facilitate medical evaluation in some cases, care must be taken to treat the patient with compassion, never using pharmacologic treatment for reasons of punishment or staff convenience. The focus is on the pharmacologic management of acute agitation of patients in the pediatric age group, in the context of a full evaluation for possible nonfunctional causes of agitation. Goals, risks, and benefits of medication use will be reviewed.

Key Words: typical antipsychotics, atypical antipsychotics (AAPs), extrapyramidal symptoms (EPSs), QTc prolongation, neuroleptic malignant syndrome

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TARGET AUDIENCE

This CME activity is intended for pediatricians, pediatric emergency medicine physicians, clinical registered nurse practitioners, and physician assistants providing care in pediatric emergency care settings.

LEARNING OBJECTIVES

After completion of this article, the reader should be better able to:

1. Develop a process for the rapid evaluation of the agitated pediatric patient presenting to an emergency care setting.
2. Utilize predictive indicators for agitation and rule out other causes, based on history, physical examination, and targeted testing.
3. Assess the risks and benefits of common pharmacologic management for the agitated pediatric patient and create a rationale for specific management plans.

Agitation is a physical sign and, as such, needs to be addressed so that an accurate diagnosis can be made before the medical professional can create a treatment plan. As with any patient seen in the emergency department (ED), airway, breathing, and circulatory issues need to be addressed first and treated with no delay. Vital signs, including O_2 saturation and temperature, need to be quickly assessed, as well as blood glucose level if the patient is acutely altered. As part of a rapid physical assessment, care should be taken to assess hydrational level, as agitation is frequently associated with a degree of dehydration. In addition, a rhythm strip or 12-lead electrocardiogram should be obtained if possible (Table 1).

It is important to identify and treat the causes of agitation and treat them for several reasons. The agitated state may reflect a life-threatening emergency that can be halted if recognized and addressed. In addition, the acutely agitated patient poses danger to himself as well as to the health care personnel treating him. Furthermore, complications of prolonged motor agitation include rhabdomyolysis and potentially life-threatening hyperthermia.

Positive predictors of potential violent behavior include male sex, history of prior violent behavior, arrival in the ED in police custody, being a victim of violence, having a history of alcohol or drug abuse, and having a history of psychiatric illness.[1,2] Dorfman and Mehta[3] examined the frequency of restraint use in 1 urban pediatric ED and noted that 1 of 15 children undergoing psychiatric evaluation was restrained. The form of restraint included physical, chemical, or both. The same group did a follow-up study to compare the use of restraint for children undergoing psychiatric evaluations in institutions housing emergency medicine residencies and pediatric emergency medicine fellowships.[4] Their surveys revealed that the great majority of the programs reported having used restraint of some form, but in very rare (5% or less) of cases. However, while the majority of the programs had policies in place for physical restraint, the minority of programs had policies for chemical restraint (only 5/28 pediatric EM fellowship programs), and a large percentage of programs surveyed did not give formal education to their trainees on the appropriate rationale and implementation of restraint.

Initial Evaluation

It is important that the initial evaluation identify any preexisting medical problems, psychiatric past medical and psychiatric family history, medications being routinely taken or possible drug or alcohol exposure, medications available to the patient (especially with children who may have had accidental ingestions), and allergies. The family should be questioned about past episodes of agitation, if any, as well whether this episode was of sudden onset.

A detailed physical examination must be done, as it may provide clues as to the etiology of the acute agitation. Care should be taken to identify signs of injury, especially trauma to the head. The presence of hemotympanum or cerebrospinal fluid rhinorrhea

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Dr. Marzullo has disclosed that the U.S. Food and Drug Administration has not approved the use of Haloperidol, Risperidone, Ziprasidone, or Olanzapine for the treatment of agitation in the pediatric population as discussed in this article. Please consult the product's labeling for approved information.

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TABLE 1. Common Classification of Agitation

A. Nontoxic Causes
Neurological/structural
Parenchymal contusion, especially frontal
Subarachnoid hemorrhage
Subdural hematoma, epidural hematoma
Space-occupying lesions (tumor)
Hydrocephalus
Seizure/postictal state
Stroke
Infectious
Meningitis
Encephalitis
Brain abscess
Sepsis
Metabolic
Hypoglycemia/hyperglycemia
Hyponatremia
Hypercalcemia
Renal failure
Hypercarbia
Acute hypoxemia (of any cause)
Hypothermia/hyperthermia
Hepatic encephalopathy
Hypertensive encephalopathy
Thyrotoxicosis/hypothyroidism
Functional/psychiatric
Agitated depression
Schizophrenia
Personality disorder
Bipolar disorder
Extreme anxiety
B. Toxic Causes
Anticholinergic agents
Antihistamines, antipsychotics, antispasmodics, antidepressants, antiemetics, atropine
Adrenergic agonists
Cocaine, amphetamines, ephedrine, pseudoephedrine, xanthenes
Phencyclidine
Hallucinogens
LSD, mushrooms
Aspirin
Lithium
Alcohol
Carbon monoxide
Steroids
Hydrocarbons
Serotonin agonist overdose (serotonin syndrome)
Withdrawal syndromes
Sedative-hypnotics, γ-hydroxybutyrate, ethanol, opiates

should be ruled out. Signs of blood loss or other injury also need to be identified. A neurological examination should be done as thoroughly as circumstances permit, with close attention to mental status. Physical findings on examination that lead to a diagnosis of a particular toxidrome should be assessed, especially signs of anticholinergic or sympathomimetic poisoning, 2 classes of ingestions frequently presenting with agitation. Pupil size and reactivity are important to note, as small, poorly reactive pupils are seen with metabolic encephalopathies, and large pupils suggest adrenergic stimulation or cholinergic blockage. If a fundoscopic examination can be done, one should look for signs of papilledema or hemorrhages. Breath should be assessed for odors such as ketones seen in diabetes mellitus or hints of ingestions such as hydrocarbons or alcohol. Hyperventilation can be seen with anxiety associated with the agitation itself, but may be associated with fever and metabolic acidosis (seen in metabolic emergencies such as decompensated diabetes or salicylate ingestion). Hyperventilation is also an early sign of increased intracranial pressure.

In general terms, we can divide the causes of agitation into 5 main categories: (1) toxic, (2) neurologic (structural), (3) infectious, (4) metabolic, and (5) functional disorders.[5] A complete list of nonpsychiatric causes of agitation is beyond the scope of this review, but the following is a good introduction to the process of evaluation that should occur when a child or young adult presents with a prominent finding of agitation.

Toxins

In the class of toxic exposures, one needs to consider the categories of (1) recreational exposure to illicit drugs, (2) accidental overdose of a medication, idiosyncratic response to a medication, or interaction of concurrently used medications, (3) suicidal ingestion, or (4) exposures to environmental agents. Common recreational drugs that induce agitation include cocaine, amphetamines, phencyclidine, and the hallucinogens. Suicidal ingestions often start with delirium, but as time passes, decreased level of consciousness ensues. This group includes medications with anticholinergic properties (including antihistamines). Delirium can also be induced by serotonergic medications or combinations of them, causing the serotonin syndrome.[6]

Urine should be collected on all agitated patients for assessment of urine drug screen. In regard to drug intoxication, Claassen and Gilfillan studied psychotic patients seeking care in an urban ED[7] and found that 21% had used alcohol or an illegal drug before coming to the ED. However, only 21% of those patients had self-reported abuse, and only 29% of patients that clinicians suspected to be "under the influence" actually tested positive by laboratory tests. Thin-layer chromatography can assess many more toxins if indicated, but is not helpful in the immediate time frame. Care must be taken not to be lulled into doing a less than thorough assessment, as an agitated person with a positive finding present on the qualitative drug screen could also have a closed head injury causing his acute findings on physical examination.

In terms of toxidrome identification, one should pay particular attention to the vital signs, skin, and pupils. Adrenergic agonists include amphetamines and cocaine. Intoxication with these agents is often associated with tachycardia, hypertension, hyperthermia, and tachypnea. Pupils are enlarged. Skin is flushed and diaphoretic. Peristalsis is increased. Phencyclidine presents similarly, but the pupils are small and reactive, and nystagmus is prominent.

Another class of medications that are commonly associated with agitation is the anticholinergics and includes the antihistamines, atropine, and some antiemetics, antipsychotics, and anticonvulsants. Blood pressure and respiratory rate may be normal, but tachycardia and hyperthermia may be seen, as well as visual hallucinations. Pupils are enlarged with this class of toxins also and may be sluggish to react. The skin is flushed, but hot and dry. The gastrointestinal and genitourinary tracts are slowed.

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Opioid withdrawal is associated with acute agitation. Mental status should be preserved. Patients may be hypertensive and tachycardic, but with normal respiratory rate and temperature. Pupils are dilated. Nausea, vomiting, and diarrhea may be present.

In ethanol withdrawal, dilated pupils are also present, as well as tremor, hypertension, tachycardia, tachypnea, hyperthermia, and diaphoresis. Central nervous system (CNS) irritability might lead to seizures. Delirium could be severe to life-threatening.

Agitated delirium is associated with the rare serotonin syndrome. Tachycardia, hypertension, hyperthermia, diaphoresis, and myoclonus may be seen.

Neurologic

The neurologic category of causes of agitation needs to be considered in those with evidence of trauma or focal signs on neurologic examination. Anything on examination concerning for intracranial injury should prompt evaluation for brain contusions, subdural hematoma, subarachnoid bleeds, or space-occupying lesions such as epidural hematoma. One also needs to consider a space-occupying lesion that might reflect tumor in someone with no sign of trauma but a suspicious neurological examination or new-onset changes in mood or behavior. Antecedent seizure with postictal state may also present as agitation. The neurologic examination needs to assess any evidence of either focal or global brain dysfunction. A focal neuroexamination in terms of asymmetry of cranial nerve findings, motor strength, and so on suggests a structural lesion. Lack of orientation and waxing and waning consciousness suggest delirium. None of these findings should exist in a patient with a functional psychiatric disorder.

The mental status examination deserves special attention. Delirium, or an organic, acute confusional state, refers to an acute cognitive impairment with disorientation to some extent, attention deficit, and fluctuating level of consciousness.[8] There is often impairment of at least some vital signs. The mood is most often labile. Patients with delirium often have no prior psychiatric history. Psychosis is a disorder characterized by well-organized hallucinations or delusions.[5] Alertness, orientation, and cognition are not usually affected in psychosis, which is a psychiatric diagnosis. Vital signs and mood are usually constant. Whereas hallucinations can be seen in delirium and psychosis, in delirium the hallucinations are usually visual, but in psychosis they are most often auditory.

Infections

Central nervous system infections may present with delirium. Physical examination needs to assess for the presence of fever, hypoxia, meningeal irritation, the stigmata of petechiae or purpura, or cutaneous signs of intravenous (IV) drug use. History of immunosuppression or recent treatment for sinusitis is also important historical information. Common infectious reasons for delirium or other agitated states include CNS abscess as an extension of sinusitis, meningitis, encephalitis, or sepsis. In addition, isolated hypoxia from a non-CNS issue such as pneumonia can induce acute agitation.

Metabolic

Metabolic causes of agitation should not be overlooked in the initial evaluation. The most common metabolic cause of agitation is hypoglycemia.[5] Hypoglycemia can be seen secondary to ethanol ingestion as well as for many other reasons. If metabolic cause for agitation is suspected, it would be wise to assess for sodium status, acid-base status (including the presence of hypercarbia), anion gap, renal function, liver function, and thyroid function. Laboratory markers for rhabdomyolysis are associated with muscle breakdown. Urinalysis, creatine phosphokinase levels, and potassium levels should be sought. Physical examination findings may also aid in narrowing down some of the metabolic possibilities. For instance, recent weight loss, polyuria and polydipsia, and vomiting might suggest undiagnosed diabetes mellitus. Recent weight loss, tachycardia, diaphoresis, and poor sleep might indicate thyroid dysfunction. Both hyperthyroidism and hypothyroidism have been associated with agitation. Rarely, the agitation might be due to a late-presenting metabolic disorder such as late-onset urea cycle defect or porphyria.

Functional

After the history, physical examination, and at least consideration for the above diagnoses have been made, and the toxicologic, radiologic, and laboratory evaluations have been considered or performed if indicated, then the diagnosis of functional agitation may be entertained and treated. This category includes schizophrenia, personality or behavior disorders, anxiety disorders, bipolar disorders, and other primary psychiatric diagnoses. Hallucinations, paranoid delusions, and irritable, angry mood are typical conditions for the development of acute agitation.[9]

Treatment: General Principles

Because of underfunded and sparse mental health access, the pediatric ED has increasingly borne the burden of managing mental health emergencies.[10] The pediatric ED routinely treats patients through the second decade, so the presentations are extremely variable, ranging from medical/traumatic causes of agitation, to inadvertent ingestion of medications, to purposeful intoxication and drug withdrawal, to primary mental illness.

Much has been written about the goals of treating agitation.[3] One primary goal is to keep the patient from hurting himself and from hurting staff. The risk to staff is increased with the age, size, and strength of the agitated patient. In addition, "rapid tranquilization" has often been promoted not only to prevent injury, but also to allow for a proper medical evaluation to be conducted.[9] When agitation becomes severe, it can be accompanied by such dyscontrol of behavior that the immediate treatment concern becomes alleviating the threat of assault to the patient himself and to others (including care providers) and damage to the environment. At that juncture, some form of restraint needs to be used and is often given on an involuntary basis. This assumes that patient seclusion from an agitating, sensory-overloaded environment has been attempted, that agitating family members have been removed, attention to the comfort needs for food and warmth has been addressed, and that "talk down" procedures have been implemented and exhausted.[1,11]

An imperative of any restraint policy should be that it not be used as punishment for the patient or as convenience for the staff.[12]

Agitation is still poorly understood at the cellular level but is believed to be associated with pathological increases in dopamine and norepinephrine, as well as decrease in γ-aminobutyric acid. In addition, a milieu of too much or too little serotonin has been associated with agitation.[9,13]

When emergency medications for agitation are considered, the patient should always be given the option of taking an oral medication first. This approach has several benefits[10]:

1. Patient relief that the situation is being taken care of by adults.
2. It gives the child some control over his treatment.
3. It may cause "anticipatory" tranquillization.

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TABLE 2. General Guidelines for Treatment of Agitation

- Clearly introduce yourself, assure patient that you are there to keep him/her safe; this is your job
- Use simple language, soft voice, slow movements
- Stay 37–4 feet away from the patient
- Relaxed body language
- Ask caregiver or patient about why they are upset and offer ways to calm them
- Maintaining privacy and respect, nonjudgmental attitude, active listening, remain engaged
- Address hunger, thirst, comfort, warmth
- Offer distracting toys/sensory modalities
- Explain what is to come next. Discuss restraint and offer reward for calmer behavior
- Reduce environmental stimulation (dim lights, reduce noise, minimize visitors, redirect traffic near room)
- Remove access to breakable objects/equipment
- Prepare with staff for the next step if the calming strategies fail—do medication calculations, etc
- Engage consultants: security, social work, psychiatry
- Consider the need of physical restraints
- Prepare an algorithm for pharmacologic management if the above methods fail, including attention to the clinical situation, preexisting medications, intoxication status, medical history, allergies

4. It avoids the trauma of an involuntary injection.

With the use of any chemical restraint, proper monitoring guidelines need to be followed according to the Joint Commission on the Accreditation of Healthcare Organizations standards (Tables 2 and 3).[10,14]

Typical Antipsychotics

Early pharmacologic management of agitation was aimed at putting the patient into a stuporous state, but this did not address the underlying pathology and frequently resulted in adverse sequelae or even death.[9] In addition, medications that left the patient unconscious took away the patient's ability to take part in diagnostic testing or crisis intervention. Therefore, new treatment is generally aimed at getting the patient to be calmed, but still be interactive. This is why the advent of antipsychotics (so-called typical antipsychotics) was revolutionary in the treatment of agitation, as they had a calming effect on the patient as well as treating the underlying psychosis.[9] They also have a high therapeutic index and lack addictive potential.[1] All typical antipsychotics act by inhibiting dopaminergic transmission in the brain via their D_2 receptor affinity.[10]

The goal is to treat the agitation acutely, but also to treat the primary psychiatric illness. However, it is important to note that for a patient already on an antipsychotic medication, this medication should be optimized before adding additional medication regimens aimed at treating undifferentiated agitation or starting a new antipsychotic. Many studies have shown the effectiveness of the use of neuroleptics (typical antipsychotics) to control agitation caused by psychosis.[15] Less efficacy has been seen with neuroleptic use if there is no definitive diagnosis. Issues with neuroleptics have included the risk of dystonic reactions, lowering of seizure threshold, and impairing the body's ability to dissipate heat. Haloperidol, a high-potency butyrophenone, has been the most studied and broadly used typical antipsychotic. It can be administered orally, intramuscularly, or intravenously. Onset of action by the intramuscular (IM) or IV route is within 30 to 60 minutes, and duration of effect is up to 24 hours.[9]

The most problematic consequences of haloperidol use are extrapyramidal symptoms (EPSs), which include dystonia, akathisia, and Parkinson-like effects. These respond to anticholinergic medications such as diphenhydramine or benztropine. Dystonic reactions manifest as involuntary movements due to muscular spasms that include torticollis, tongue protrusion, facial grimacing, or opisthotonos. More frightening manifestations of dystonic reactions include oculogyric crisis, a spasm of the extraocular muscles resulting in an upward stare, and laryngospasm, clearly an airway emergency.[10] Akathisia is a motor restlessness that is accompanied by anxiety and may mimic the agitation symptoms themselves.

The typical antipsychotics also carry a risk of neuroleptic malignant syndrome (NMS). Neuroleptic malignant syndrome is an idiosyncratic event that is rare but is a potentially fatal syndrome that presents with hyperthermia, altered mental status, autonomic instability, and severe muscle rigidity. Creatinine phosphokinase levels are elevated. Causes of death attributed to NMS have included rhabdomyolysis with secondary renal failure, disseminated intravascular coagulation, aspiration pneumonia, and cardiopulmonary arrest.[8] Although such a reaction is dramatic, the last pediatric fatality from NMS was reported in 1986.[10] Neuroleptic malignant syndrome risk increases with the dopamine receptor-binding potency of the typical antipsychotic.

Extrapyramidal symptoms and NMS are more common with the high-potency typical antipsychotics (haloperidol) than with the low-potency typical antipsychotics. However, Liebold et al[16] described a case of NMS in an adolescent medicated with ziprasidone, an atypical antipsychotic (AAP). Their discussion also made the good point that the use of AAPs is increasing, so we need to be on alert that the negative effects heretofore associated with the older drugs, the typical antipsychotics, need to be noted carefully as the number of patients being treated

TABLE 3. General Emergency Pharmacology Guidelines

- If patient is already on psychotropic medications, consider dosing those if possible, unless there is suspicion of toxicity
- Offer PO medication option first
- Delirium present: treat underlying medical derangement
- Avoid benzodiazepines if there is evidence of EtOH/CNS depressant intoxication
- Symptom-specific medication
  - °Anxiety: lorazepam, consider diphenhydramine
  - °Mania or psychotic thoughts: haloperidol, risperidone, olanzapine, ziprasidone
  - °General agitation: can give benzodiazepine or antipsychotic. Can mix haloperidol and lorazepam. With other antipsychotics, can add benzodiazepine after 30 min

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with the new generation drugs increases. Treatment of NMS includes supportive care, with attention to cooling, sedation with benzodiazepines, and volume resuscitation for hypotension.[17] Cessation of the offending antipsychotic is imperative. Medication treatment has included bromocryptine. In addition, dantrolene has also been used in NMS, as an extrapolation of its usefulness for the rigidity and hyperthermia of malignant hyperthermia. However, there is no clear evidence that either of these dopamine agonists should be routinely used.

In addition, use of haloperidol has been associated with a low but real association with QTc prolongation and subsequent cardiac arrhythmias, but a clear causation from the drug use to a fatal arrhythmia has not been shown.[18]

Benzodiazepines

Benzodiazepines facilitate γ-aminobutyric acid transmission, and this is the likely mechanism for tranquilization of the acutely agitated patient.[9] They are both sedative and anxiolytic, and both of these properties are likely helpful in acute agitation. The therapeutic effect is linked to the decrease in arousal, but beyond this, there is little effect in their isolated use in the underlying psychiatric symptoms.

Benzodiazepines cause sedation, respiratory depression, and ataxia. This CNS effect can be additive with other CNS depressants, so they need to be used cautiously in settings in which ethanol, barbiturate, or opioid intoxication is coexisting.

The most used benzodiazepine in the treatment of agitation has been lorazepam.[9] It is the only drug of this class with consistent, rapid, and complete IM absorption. Like haloperidol, it can be given orally, intramuscularly, or intravenously. Its metabolite is inactive and has few drug-drug interactions.[19] It has been used very effectively in acute alcohol withdrawal. They have an added benefit if stopping and preventing seizures.

Paradoxical reactions with the use of benzodiazepines are more common in children than adults,[20] as well as in children with developmental delay, mental retardation, autism, or other organic brain syndromes.

Benzodiazepines have been used successfully in combination with typical antipsychotics, and several studies have shown increased efficacy beyond either drug used alone.[9,21,22] Most studies have examined the use of haloperidol and lorazepam used together, and this combination reflects the most commonly used clinical practice. In the only double-blind prospective study looking at haloperidol or lorazepam alone or in combination, it was found that within 1 hour of treatment, the combination-treated patients had a decrease in agitation not achieved by the single medication groups until 2 to 3 hours after treatment.[21] An added benefit is that both drugs are stable for several hours when mixed in the same syringe; thus, only 1 injection is needed if being given parenterally. An additional benefit to combination therapy is that the benzodiazepine confers protection from EPSs compared with the use of typical antipsychotics used alone.[22]

Atypical Antipsychotics

Atypical antipsychotics differ from the typical, older antipsychotics in that they target both the dopamine D_2 receptor as well as serotonin receptors. This blockage of both the dopamine and serotonin receptors improves negative symptoms associated with schizophrenia and decreases the adverse effects of isolated dopamine antagonism, such as EPSs.[10] The majority of published data on the use of AAPs given IM in the treatment of acute agitation have involved medically stable, nonintoxicated patients.[9] There are no controlled studies examining the efficacy of the AAPs in patients with severe agitation, intoxicated patients, or those who are medically complicated. While the AAP class is generally less associated with EPSs than the typical antipsychotics, meta-analyses of randomized controlled trials showed that the risk is still present with AAP use.[17] Neuroleptic malignant syndrome has also been seen with the AAP, but to a lesser degree and with less serious outcomes.[23]

The considerations regarding the enhanced tolerability of the AAP as compared with the typical antipsychotics might suggest a benefit to their use first line in the treatment of acute agitation, but more studies need to be done to elucidate their safety profile and their use in the previously cited patients who are not agitated solely because of a psychiatric cause. Another benefit of the AAP is that they lend themselves to an ease of transition to long-term, oral (PO) therapy for particular psychiatric diagnoses.[22] This is especially important when one considers the lack of outpatient compliance for psychiatric medications due to negatively perceived adverse effects. However, there is not enough evidence at present to completely substitute the use of AAP for the typical antipsychotics in the emergency setting. The choice of an AAP seems to make the most sense if the prescriber is trying

TABLE 4. Choices for Pharmacologic Treatment for Agitation

Medication Name	Medication Class	Doses	Route of Administration	Onset of Action	Adverse Effects
Lorazepam	Benzodiazepine	0.05–0.1 mg/kg per dose (usually 1–2 mg)	PO/IM/IV	5–10 min IM/IV 20–30 min PO	Respiratory depression, sedation, idiosyncratic disinhibition
Haloperidol	Typical antipsychotic	0.025–0.075 mg/kg/dose; usually 2–10 mg	PO/IM	20–30 min IM 45–60 min PO	EPS, NMS, hypotension, QTc prolongation
Risperidone	AAP	0.25–2 mg	PO (tablet, liquid, rapid dissolve)		EPS, NMS, QTc prolongation
Ziprasidone	AAP	10–20 mg (over 12)	PO/IM	30–45 min IM	QTc prolongation (risk greater than haloperidol, risperidone, or olanzapine), EPS, NMS
Olanzapine	AAP	2.5–10 mg	PO/IM/ODT	15–30 min IM	QTc prolongation, EPS, NMS, bradycardia, hypotension (not recommended to combine with benzodiazepines), anticholinergic symptoms

ODT indicates oral disintegrating tablet.

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to avoid EPSs and is trying to start a medication that is likely to be converted to a chronic medication. However, one must acknowledge that we most often are treating the agitated patient without benefit of a full psychiatric evaluation, and although this may come later, it makes little sense to choose a drug for reasons that might be misguided and the benefits not realized after a psychiatric assessment is complete.

There is growing evidence that metabolic abnormalities are associated with AAP use in children. The risks include weight gain, diabetes mellitus, and dyslipidemia.[24] These findings are very concerning, as the use of the AAPs is growing, as is the trend toward childhood obesity in general.

Commonly Used AAP Medications

Risperidone (Risperdal), is a benzisoxazole derivative with high affinity for dopamine/serotonin receptors. It is available only in PO preparations[10] and is a good choice if the patient is willing to take PO medications.

Ziprasidone (Geodon) is a benzisothiazol piperazine dopamine/serotonin antagonist with a low propensity for causing EPSs. It was the first AAP that became available in an IM preparation (in 2002), reaching peak plasma concentrations in 30 to 45 minutes with a duration of at least 4 hours.[1,9] Its most common adverse effect is sedation.[10] The Food and Drug Administration has advised caution with use of ziprasidone because of its propensity to increase the QTc interval. This has raised concern of a possible relationship between prolonged QT, progressing to torsades de pointes, malignant arrhythmia, and sudden death. However, no clear causal relationship has been exposed. It prolongs the QT interval to an increased degree than haloperidol, olanzapine, or risperidone. Patient should be screened carefully for family history of sudden death; a pretreatment electrocardiogram should be considered to measure the QTc interval, and the medication should not be used in conjunction with any other medication known to prolong the QT interval.[18]

There are no known studies to date looking at the efficacy and safety of combination treatment of ziprasidone and benzodiazepines in children or adolescents.[10]

Olanzapine (Zyprexa) is in the thienobenzodiazepine class and is also a dopamine/serotonin antagonist, also approved for IM administration. Injection leads to maximum concentration in 15 to 45 minutes, and duration of action is up to 24 hours. No clinically significant changes in QTc have been noted with olanzapine.[25] Case reports, some fatal, have been associated with the use of olanzapine and have been associated with cardiorespiratory depression, hypotension, and bradycardia. A direct causal link from olanzapine has not been found, as several of these cases involved a combination of treatment with other drugs such as benzodiazepines and significant comorbidities in the patients.[9] However, because of these findings, it is suggested that olanzapine be given as a single agent and not be given with other CNS depressants.[9] Further studies are needed that examine the use of olanzapine in the medically complex, intoxicated, or severely agitated patient.

In addition, olanzapine has been noted to have significant anticholinergic properties,[1] so it is not a good choice for agitation treatment in a patient who is experiencing an anticholinergic overdose (Table 4).

Future Studies

The primary purpose of this review was to examine the use of medications for the treatment of agitation. As we have discussed, there are few controlled studies that examine the practices of chemical, as well as physical, restraints in the agitated child. Here we discussed primarily the use of medications for the treatment of agitation. Most of the drugs reviewed here are used "off-label" with regard to pediatric administration, and studies are needed to evaluate best practices, taking into account safety, efficacy of medications for targeted symptoms, and the incidence of adverse effects. Most medication patterns in the pediatric population have been by extrapolation of the practices used in adult populations (ie, the combination use of benzodiazepines and butyrophenones). However, as is applicable to most discussions of pediatric care, children are not "little adults," and as such, they differ in metabolism and kinetics, in adipose tissue and protein binding. Hence, medication studies need to be done specifically on children, with less emphasis on extrapolation from adult usage practices.

Most helpful would be retrospective, "head-to-head" randomized trials comparing the use of IM haloperidol/lorazepam combination versus IM ziprasidone versus IM olanzapine in the highly agitated or psychotic pediatric patient. End points to study should include time to onset of action, efficacy, tolerability, and safety when used in the young, comorbid, or intoxicated patient. Studies also need to better delineate the frequencies of electrocardiographic changes/arrhythmogenic risks in those patients with no family history or medical history of cardiac pathology.

REFERENCES

1. Coburn VA, Mycyk MB. Physical and chemical restraints. *Emerg Med Clin N Am*. 2009;27:655–667.
2. Citrome L, Volavka J. Violent patients in the emergency setting. *Psychiatric Clin North Am*. 1999;22:789–801.
3. Dorfman DH, Mehta SD. Restraint use for psychiatric patients in the pediatric emergency department. *Pediatr Emerg Care*. 2006;22:7–12.
4. Dorfman DH, Kastner B. The use of restraint for pediatric psychiatric patients in emergency departments. *Pediatr Emerg Care*. 2004;20:151–156.
5. Ford MD, Delaney KA, Ling LJ, et al. eds. *Clinical Toxicology*. WB Saunders; 2001:146–153.
6. Arora B, Kannikeswaran N. The serotonin syndrome-the need for physician's awareness. *Int J Emerg Med*. 2010;3:373–377.
7. Claassen CA, Gilfillan S, Orsulak P. et al. Substance use among patients with a psychotic disorder in a psychiatric emergency room. *Psychiatr Serv*. 1197;48:353–358.
8. Slater N, Constantino JN. Pediatric emergencies in children with psychiatric conditions. *Pediatr Emerg Care*. 1998;14:42–50.
9. Battaglia J. Pharmacological management of acute agitation. *Drugs*. 2005;65:1207–1222.
10. Sonnier L, Barzman D. Pharmacologic management of acutely agitated pediatric patients . *Pediatr Drugs*. 2011;13:1–10.
11. Dorfman DH. The use of physical and chemical restraints in the pediatric emergency department. *Pediatr Emerg Care*. 2000;16:355–360.
12. Masters KJ, Bellonci C, Bernet W, et al. Practice parameter for the prevention and management of aggressive behavior in child and adolescent psychiatric institutions, with special reference to seclusion and restraint. *J Am Acad Child Adolesc Psych*. 2002;41(suppl 2):4S–25S.
13. Lindenmayer JP. The pathophysiology of agitation. *J Clin Psychiatry*. 2000;61(suppl 14):5–10.
14. The Joint Commission. Available at: *www.jointcommission.org/*. Accessed March 23, 2013.
15. Neborsky R, Janowsky D, Munson E, et al. Rapid treatment of acute psychotic symptoms with high- and low-dose haloperidol. Behavioral Considerations. *Arch Gen Psychiatry*. 1981;38:195–199.

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16. Liebold J, Patel V, Hasan RA. Neuroleptic malignant syndrome associated with ziprasidone in and adolescent. *Clin Ther*. 2004;26:1105–1108.
17. Rasimas JJ, Liebelt EL. Adverse effects and toxicity of the atypical antipsychotics : what is important for the pediatric emergency medicine practitioner? *Clin Pediatr Emerg Med*. 2012;13:300–310.
18. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*. 2001;158:1774–1782.
19. Greenblatt DJ, Divoll M, Harmatz JS, et al. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. *J Pharm Sci*. 1982;71:248–252.
20. Gutierrez MA, Roper JM, Hahn P. Paradoxical reactions to benzodiazepines. *Am J Nurs*. 2001;101:34–39.
21. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med*. 1997;15:335–340.
22. Yildiz A, Sachs GS, Turgay A. Pharmacological management of agitation in emergency settings. *Emerg Med J*. 2003;20:339–346.
23. Neuhut R, Lindenmayer JP, Silva R. Neuroleptic malignant syndrome in children and adolescents on atypical antipsychotic medication: a review. *J Child Adolesc Psychopharmacol*. 2009;19:415–422.
24. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second generation antipsychotic medications during first time use in children and adolescents. *JAMA*. 2009;302:1765–1773.
25. Lindborg SR, Beasley CM, Alaka K, et al. Effects of intramuscular olanzapine vs. haloperidol and placebo on QTc intervals in acutely agitated patients. *Psychiatry Res*. 2003;119:113–123.

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