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Pharmacologic Management of Agitation and Aggression in a Pediatric Emergency Department – A Retrospective Cohort Study

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BACKGROUND Benzodiazepine and antipsychotic use for acute management of agitation and aggression in the pediatric emergency department (ED) setting has not been well described.

OBJECTIVES To describe medication utilization in the management of agitation and aggression in a pediatric ED and to assess the safety of their use.

METHODS This was a retrospective observational study. Patients less than 20 years of age who presented to our pediatric ED and had agitation or aggression as part of their chief complaint were included if they received at least 1 dose of benzodiazepine or antipsychotic. Outcomes included frequency of benzodiazepine and antipsychotic use, dosing of medications, and reported adverse events.

RESULTS During the 5-year study period, there were 128 visits of 120 patients who met the inclusion criteria. Lorazepam was most commonly given (70%), followed by chlorpromazine (20%). Most patients (82%) required a single dose of medication. Intoxication was associated with needing more than 1 dose of medication. Patients with autism or Asperger syndrome were more likely to receive an antipsychotic medication compared to not having these conditions (75% vs. 28%, respectively). Adverse events were documented in 6 visits: oxygen desaturation (n = 1), dizziness and nausea (n = 2), dizziness (n = 1), and paradoxical excitation (n = 2). The Naranjo Score indicated a probable adverse drug reaction for the cases of paradoxical excitation.

CONCLUSIONS Benzodiazepine and antipsychotic drug therapy for acute agitation and aggression in children appears to be safe and well tolerated when used as a single agent and at the recommended doses in this setting.

ABBREVIATIONS ADHD, attention-deficit/hyperactivity disorder; ED, emergency department; IM, intramuscular; n/a, not applicable; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor

KEYWORDS aggression; antipsychotic agents; benzodiazepines; emergency service; hospital; pediatrics

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Introduction

Hostile and violent behaviors are associated with mental health conditions, toxic substance exposure, central nervous system infections, neurologic and metabolic disorders.[1,2] Agitation and aggression in hospitalized children is not well described, but it is thought to occur more frequently in the emergency department (ED) compared to the pediatric inpatient ward.[1] Management of children with agitation and aggression in the ED setting is challenging, particularly as it can be associated with delay in assessment and diagnosis. The primary goal of managing agitation is to avoid harm to patients, protect caregivers, and ensure safety of hospital staff.[2,3]

Most children presenting with agitation and aggression need chemical or physical restraint.[1,4,5] Chemical restraint refers to the use of a medication for behavior control or movement restriction and is not otherwise part of the standard treatment of a patient's condition.[2,4] In a prospective cohort study at a tertiary children's hospital in Australia, 40 patients had 75 episodes of aggression (6–24 years, median 15 years) over a 14-month period.[1] Restraint was required in 53% of episodes and 31% required pharmacologic management.[1]

The primary therapeutic classes of medications used to manage acute agitation in children are antihistamines, benzodiazepines, and antipsychotics, and management is mostly extrapolated from evidence in adult care.[2,3] Guidelines by the American Association of Emergency Psychiatry[6] and consensus statements by the Postgraduate Medical Association of North America[7,8] recommend benzodiazepines and/or antipsychotics for agitation for patients with a primary

psychiatric disorder and benzodiazepines for agitation because of substance intoxication in the adult ED.[6–8] They recommend cautious use of medication in children and do not provide consensus for first-line therapy.[6–8]

Although guidelines for *chronic* management of agitation or aggression in children in the inpatient and outpatient setting are available,[9] no guidelines are available for acute ED management. Furthermore, the safety of benzodiazepines and antipsychotics has not been well described when used in the acute management of agitation and aggression in children. The objective of this study was to describe medication utilization in the management of acute agitation and aggression in children in the ED and assess their safety.

Methods

This was a retrospective observational cohort study using ED medical records of patients who received pharmacologic intervention for the indication of agitation or aggression between January 1, 2010, and December 31, 2014, in our tertiary academic pediatric center. Our pediatric ED has approximately 55,000 visits per year and is staffed by attending physicians with training in pediatric emergency medicine. Children less than 20 years may present to our ED for assessment and treatment. Approximately 2% of our ED visits are for mental health related reasons. Although pediatric psychiatrists are available for consult, they are not often involved in the choice of medication.

Following institutional research ethics board approval, patients were identified through the National Ambulatory Care Reporting System of the Canadian Institute for Health Information, an administrative database of outpatient activity, including ED encounters. ED encounters were linked to the institutional pharmacy database and those who met the inclusion criteria were selected for review.

We included patients less than 20 years of age who received at least 1 dose of benzodiazepine (e.g., lorazepam) or antipsychotic (e.g., chlorpromazine, haloperidol, risperidone, olanzapine) for the treatment of agitation or aggression in the ED. All medications were used off-label for the treatment of agitation and aggression in this setting. We excluded patients who received benzodiazepines or antipsychotics for other indications or if we were unable to locate the patient's ED chart.

The primary outcome of this study was the frequency with which antipsychotics and benzodiazepines were used to manage agitation and aggression in the ED. Secondary outcomes included median dose used, number of doses needed, and adverse events of therapy.

Demographic information and outcome measures were collected from the patient ED medical record by 1 individual and data collection was validated by 1 of the investigators. Adverse events were assigned a Naranjo Score[10] by 2 independent investigators to determine the likelihood of the event being a result of the medication administered. If there was a discrepancy in score, a third investigator was asked to score the adverse event. The Naranjo Scale is a validated tool to estimate the probability that a medication caused an adverse event; probability is assigned based on the score (0 = doubtful, 1–4 = possible, 5–8 = probable, ≧9 = definite).[10] Interventions in response to adverse events, such as discontinuing the medication, administration of fluids or other medications, were recorded.

Data were entered into REDCap. Descriptive statistics were employed to summarize demographic and clinical features using Microsoft Excel (2010) and GraphPad (2016). The χ^2 test was used to compare groups, with an *a priori* level of significance of $p = 0.05$.

Results

During the study period, 4963 patients with mental health complaints were identified from the National Ambulatory Care Reporting System database and 451 patients who were dispensed 1 of the target medications were identified from the pharmacy database. After cross-referencing the 2 databases, 194 potentially eligible patients were screened for inclusion. Seventy-four (38%) patients were excluded following chart review: 53 (27%) received no target medication, 15 (8%) received target medication for another indication, 6 (3%) charts were missing. In total, 120 patients (128 visits) were included (Table 1). Seventy-three patients (61%) had a documented psychiatric history and 53 (44%) had a history of aggression as part of their past medical history. Sixteen patients (13%) were intoxicated with alcohol and 12 (10%) had autism or Asperger syndrome.

A total of 138 doses of medication were given (Table 2). Lorazepam was the most common, followed by chlorpromazine (Tables 2 and 3). Two patients received adjunctive diphenhydramine. Medication was most commonly given orally, and 14% of doses were given parenterally. Doses administered are presented in Table 3. Patients received standard doses of medication, based on age and/or weight. In 45 (35%) visits, patients received a nonpharmacologic intervention in addition to receiving a medication (Table 2).

Benzodiazepines were given as the first medication regardless if the patient was intoxicated or not (69% vs. 66%, respectively). Diagnosis of intoxication was associated with needing more than 1 dose of medication (75% vs. 10%, $p < 0.0001$). In patients with autism or Asperger syndrome, antipsychotics were used more often as the first line of treatment, compared to children without autism or Asperger syndrome (75% vs. 28%, $p = 0.0022$).

Adverse events were documented in 6 (4.7%) visits. One adolescent patient who received 2 doses of midazolam 5 mg intramuscular (IM) and 1 dose of chlorpromazine 25 mg IM had transient oxygen desaturation requiring oxygen by mask. Two adolescent patients

Table 1. Patient Demographics (N = 120)

Demographic	Result
Age, yr (mean ± SD)	13.6 ± 3.2
Male, n (%)	57 (48)
Weight, kg (mean ± SD)	55 ± 20
More than 1 ED visit, n (%)	7 (6)
Documented history of aggression, n (%)	53 (44)
Psychiatric diagnosis, n (%)	73 (61)
Anxiety	40 (33)
ADHD	25 (21)
Autism or Asperger syndrome	12 (10)
Depression	30 (25)
Eating disorder	5 (4)
Obsessive compulsive disorder	7 (6)
More than 1 psychiatric diagnosis, n (%)	44 (37)
Psychiatric medication, n (%)	80 (67)
Antipsychotic	33 (28)
ADHD medication	17 (15)
Benzodiazepine	20 (17)
SSRI	42 (35)
Other	20 (17)
Reasons for ED visit, n (%)	
Aggression	39 (30)
Anxiety	55 (43)
Behavioral problem	40 (31)
Depression	11 (8)
Intoxication/ingestion	16 (12)
Psychosis	8 (6)
Self-harm	16 (12)
Suicidal	16 (12)
Other	18 (14)

ADHD, attention-deficit/hyperactivity disorder; ED, emergency department; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor

who received a single dose of lorazepam orally (1 and 2 mg, respectively) had dizziness and nausea, 1 was given ondansetron and offered bed rest. Another patient who had received lorazepam 1 mg orally (0.025 mg/kg) had dizziness that resolved with no additional therapy. Two patients (age 9 and 11 years) who received lorazepam orally developed paradoxical excitation, with increasing agitation and aggression. One of these patients had received 2 doses of lorazepam (total dose 1.5 mg [0.05 mg/kg]) and required no treatment, and the other patient had received 1 dose of lorazepam 1 mg (0.025 mg/kg) and required treatment with chlorpromazine. The Naranjo Score indicated that the adverse events were probably related to the medication in the 2 cases of paradoxical excitation (Naranjo Score 5) and possibly related to the medication in the remaining cases (median Naranjo Score 3; range 3–4). Seven (5%) children in the cohort were admitted to the hospital, 6 of them to a psychiatry unit. The median (range) duration of stay in the ED was 4.8 hours (1.5–18.6 hours).

Table 2. Emergency Department Management of Agitation or Aggression (N = 128)

Intervention	n (%)
Nonpharmacologic	45 (35)
Quiet room	29 (23)
Restraints	12 (9)
Restraints and quiet room	4 (3)
First medication given	
Lorazepam	85 (66)
Midazolam	1 (1)
Chlorpromazine	21 (16)
Olanzapine	1 (1)
Risperidone	4 (3)
Quetiapine	13 (10)
Haloperidol	3 (2)
Number of medications given	
1	116 (91)
2	12 (9)
Number of doses given	
1	105 (82)
2	17 (13)
≥3	6 (5)

Discussion

We found that benzodiazepines were more commonly administered than antipsychotics in our cohort of children with agitation and aggression arriving to a tertiary ED. Chlorpromazine was the most commonly administered antipsychotic and haloperidol was rarely used in our cohort. Adjunctive antihistamine was uncommonly used and is not part of routine practice in our ED. In the literature, practice varies.

Among children 6 to 18 years old who presented with aggression to 5 EDs in Australia over a 5-year period, antipsychotics were used in 62 (22%) of 279 presentations, benzodiazepines were used in 31 (11%), and physical restraint was used in 37 (13%).[11] This is in contrast to Dorfman et al[4] who surveyed use of restraints for pediatric ED patients undergoing psychiatric evaluation. The most commonly reported agents were benzodiazepines, followed by butyrophenone antipsychotics (e.g., haloperidol, droperidol) as reported by directors of emergency medicine residencies and pediatric emergency medicine fellowships in the United States.[4] The use of butyrophenone antipsychotics reported in this survey, compared to other antipsychotics, is consistent with recommendations from the adult-based literature.[6] At our institution, butyrophenone antipsychotics are used cautiously because of concern about the risk of extrapyramidal adverse effects.

In our cohort, benzodiazepines were the first medication in 69% of children where intoxication was present; however, these children required more doses of medication than children who were not intoxicated. Limited information is available in the literature about

Table 3. Dosages of Medications Administered During 128 Emergency Room Visits

Medication	Medication Given Anytime During Visit, n (%)	Doses via Parenteral Route, n (%)	Median Total Dose mg (range)
Lorazepam	89 (70)	6 (7)	1 (0.25–6)
Midazolam	3 (2)	3 (100)	5 (3–10)
Chlorpromazine	26 (20)	7 (25)	25 (12.5–100)
Risperidone	4 (4)	n/a	0.38 (0.25–0.5)
Quetiapine	12 (9)	n/a	25 (12.5–200)
Haloperidol	4 (4)	3 (75)	5 (1–5)
Olanzapine	1 (0.8)	n/a	5 (n/a)

n/a, not applicable

the pharmacologic treatment of children with intoxication who present with agitation or aggression. Among 212 children 10 to 18 years presenting with alcohol intoxication to 5 EDs in Australia, aggression was reported in 28 (13%). Physical restraint was used in 4% of presentations.[12]

Most children in our cohort only required a single dose of a single medication. There is limited information in the literature to suggest which medications are most effective in children with agitation. Khan and Mican[13] retrospectively evaluated 100 children treated for agitation or aggression with an atypical antipsychotic during their inpatient hospital visit. Half of the children received olanzapine IM (mean 8 mg/dose) and the other half received ziprasidone IM (mean 19 mg/dose). Children in the olanzapine versus ziprasidone group had a mean of 9 versus 14 aggressive episodes and received a mean of 11 versus 21 doses of emergency medication. Children received concomitant lorazepam or antihistamine for the management of aggression more often in the ziprasidone group. Barzman et al[14] retrospectively evaluated children who received ziprasidone IM and were admitted to a psychiatric unit. Over 4.5 years, 59 children received 77 doses of ziprasidone IM with majority receiving a concomitant medication. Following ziprasidone administration, the Behavioral Activity Rating Scale had significantly improved.[14] Jangro et al[15] conducted a retrospective case control of adolescents who received chemical restraint in their psychiatric ED. Adolescents received ziprasidone 10 or 20 mg IM (n = 28) or haloperidol 2.5 to 10 mg IM with lorazepam 1 to 2 mg IM (n = 24). They found no difference in restraint duration or use of rescue medications between groups. In these studies, it is difficult to assess the effectiveness of the medication studied given that patients received concomitant medication or multiple doses.

Antipsychotics were most commonly the first medication given for children with autism or Asperger syndrome in our ED, which is consistent with evidence for managing challenging behaviors in this population.[16,17] Antipsychotics have been shown to be effective for the management of irritability, aggression, and self-injurious behavior in children with autism and risperidone is approved by the Food and Drug Administration for this indication.[16] Benzodiazepines are used cautiously in this population because of the potential for disinhibition.[16]

Adverse events were documented in less than 5% of visits in our cohort, all of which were either possibly or probably related to the medication. Darnis et al[18] found a lower rate of general adverse drug reactions (0.5%) in their pediatric ED through prospective surveillance of 11,095 visits over a 4-month period. Somnolence was not a reported adverse event in our cohort, possibly because this may have been a desired effect of therapy. Sedation was reported in 16% and 20% of children from Texas who received olanzapine and ziprasidone, respectively,[13] and in 60% of 59 children who received ziprasidone.[14] Increased seizure frequency (n = 1), dizziness (n = 1), nosebleed (n = 1), and myalgia (n = 1) were also reported in these 59 children.[14] It was not determined if adverse events were associated with the antipsychotic medication.

The main limitation of our study was that we were unable to assess effectiveness of medications given, because of the retrospective nature of our study and the lack of standardized assessment of agitation in our ED. Attempts to assess effectiveness based on need for subsequent doses of medication would have been confounded by the severity of the child's behavior and the choice of the first medication. Additionally, although adverse drug events and patient safety events are generally well documented in the health record as part of the ED documentation standards, it is possible that not all adverse events were captured. We chose to limit our population to those who received pharmacologic management for agitation and aggression and, therefore, we are unable to draw comparison to children who are managed without medications.

Conclusions

Benzodiazepine and antipsychotic drug therapy for acute agitation and aggression in children appears to be safe and well tolerated when used as single agents

and doses and at the recommended doses in the ED setting. Further research is needed to clarify effectiveness and optimal drug choice based on the etiology of agitation and aggression behaviors.

ARTICLE INFORMATION

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