Management of Acute Agitation in Pediatric Patients

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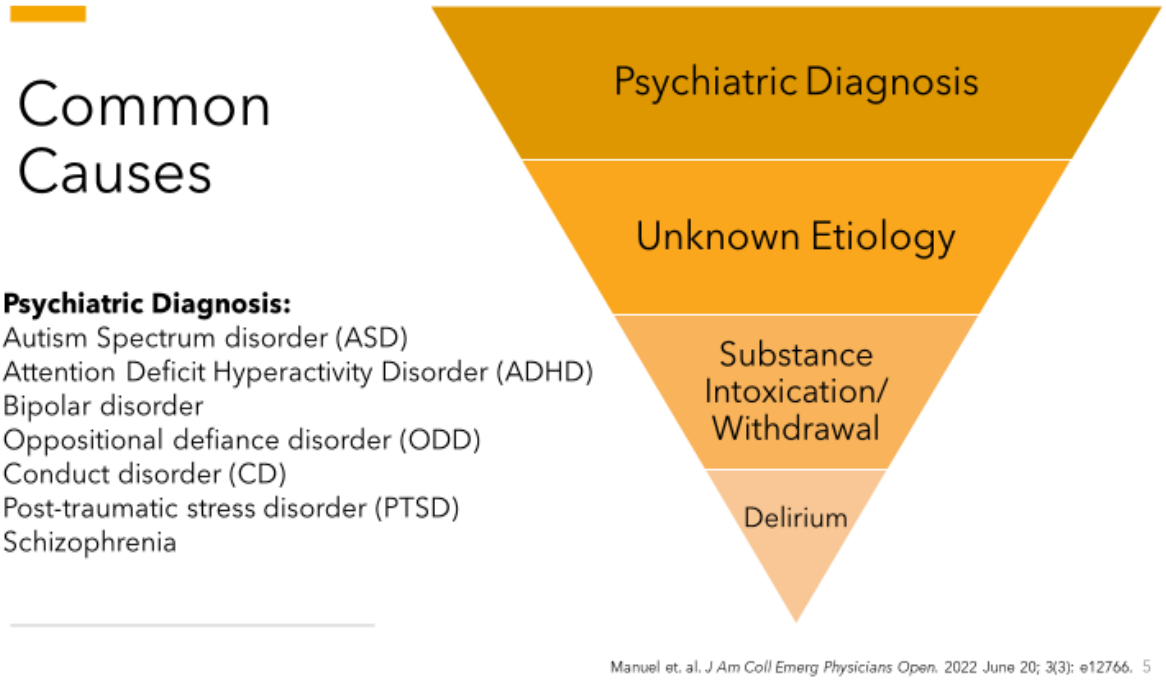

Neurotransmitter	Imbalance in Agitation	Causing…
Dopamine	Excess	Poor impulse control Increased aggression Mania
Norepinephrine	Excess	Hyperactivity Panic attacks Restlessness
Serotonin	Deficient	Increased anxiety Impulsive aggression
GABA	Deficient	Hallucinations Disorganized behavior

BETA Consensus Document

A. Goals of Therapy
   a. Collaborative practice
   b. Treat based off etiology
      i. Example: If a patient is hungry, find the patient something to eat.
   c. Non-pharm management first
      i. Verbal de-escalation is key in management of acute agitation

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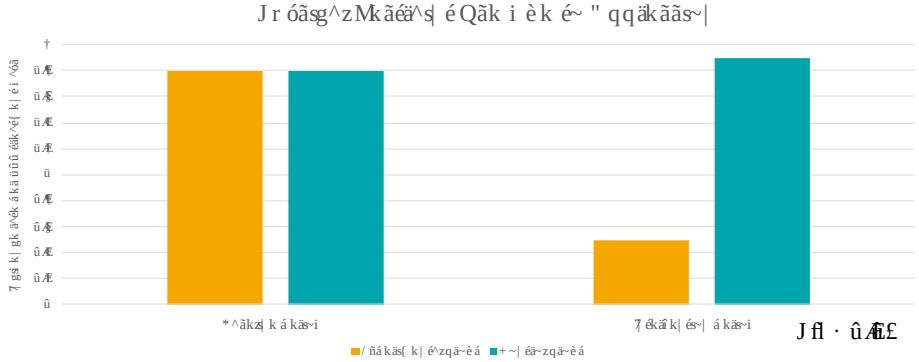

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Recommended Medications

Antipsychotics
- Haloperidol
- Chlorpromazine
- Olanzapine
- Ziprasidone
- Quetiapine
- Risperidone

Benzodiazepines
- Lorazepam
- Midazolam

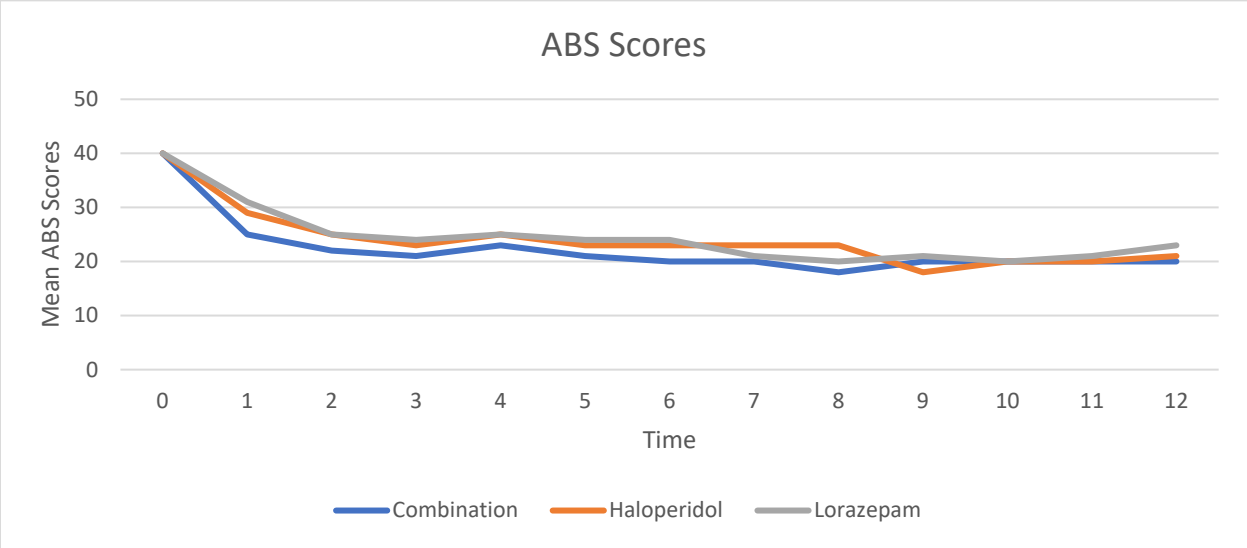
Antihistamines
- Diphenhydramine

Gerson et. al. Western J of Emer Medicine. 2019; 20(2): 409-418.20

Medication	Mechanism of Action
Haloperidol	Antagonizes dopamine-2
Ziprasidone	Antagonizes dopamine-2, serotonin, alpha-1 and histamine-1
Olanzapine	Antagonizes dopamine-1, serotonin, alpha-1, histamine-1, and muscarinic-1
Chlorpromazine	Antagonizes dopamine-2, histamine-1, and muscarinic-1
Risperidone	Antagonizes dopamine-2, serotonin, and alpha-1
Quetiapine	Antagonizes dopamine-2, serotonin, and histamine-1

Haloperidol (+lorazepam):

Methods	Primary Objective	Results	Conclusions
Double-blind, prospective, randomized study in adults in ED (n=98) IM haloperidol 5mg, IM lorazepam 2mg or combination of therapies	Change from baseline in ABS scores and BPRS scores	Combination vs. Lorazepam vs. Haloperidol: p = 0.04	Combination of lorazepam and haloperidol lower ABS scores more than monotherapy of haloperidol or lorazepam



Ziprasidone:

Methods	Primary objective	Results	Conclusion
Retrospective, nonrandom study in adolescents (n = 52)	Compare efficacy and safety of IM ziprasidone to IM haloperidol and lorazepam	**Restraint duration:** Z: 55 min, H+L: 65 min p=NS **Rescue medications:** Z: 2/28, H+L: 1/24 p=0.6	Ziprasidone is equally effective as the combination of haloperidol and lorazepam

Olanzapine:

Methods	Primary Objective	Results	Conclusions
Retrospective chart review of patients less than 18 years treated with IM ziprasidone or olanzapine	Provide information on dosing, response, safety and tolerability	**Number of doses of emergency medication**: O: 11 vs. Z: 21; p=0.009 **Number of aggressive episodes:** O: 9 vs. Z: 14; p=0.497	IM ziprasidone and IM olanzapine are equally effective

Chlorpromazine:

Methods	Primary Objective	Results	Conclusion
Retrospective chart review in patients <18 years (n=145)	Compare effectiveness and safety of IM chlorpromazine vs. IM olanzapine in treating aggression in pediatrics	Pre-IM BARS score: C: 6.26; O: 6.29 Post-IM BARS score: C: 3.21; O: 2.71 p=0.004	Olanzapine lowers BARS score more than chlorpromazine, but both are efficacious

Risperidone and Quetiapine

Methods	Primary Objective	Results	Conclusions
Prospective, rater-blinded study comparing risperidone, olanzapine, quetiapine and haloperidol	Change in baseline in MOAS total score and the MOAS categories of aggression	See below	No difference between risperidone, quetiapine and olanzapine

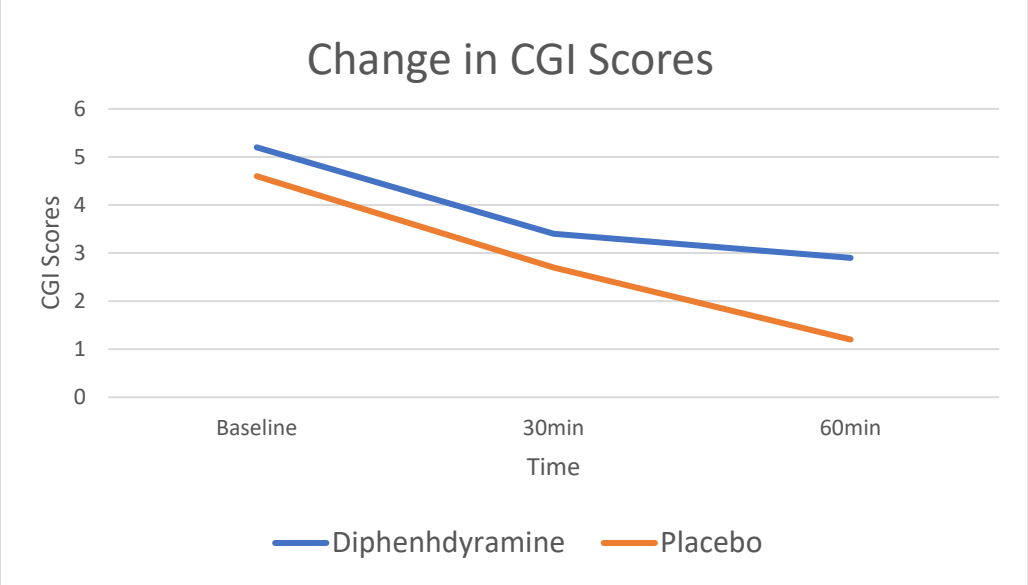
MOAS Total Score	Risperidone	Olanzapine	Quetiapine	Haloperidol	P value
Baseline	7.52	6.79	7.95	9.54	
Endpoint	0.26	0.50	0.05	0.18	0.551

Side effects of Antipsychotics:

Adverse Event	Risperidone	Olanzapine	Quetiapine	Haloperidol	P value
Abnormal gait	7.4%	8.3%	4.6%	7.1%	0.964
Dizziness	3.7%	12.5%	18%	3.6%	0.204
EPS	7.4%	0	0	21.4%	0.012
Headache	3.7%	8.3%	4.6%	7.1%	0.888
Hypotension	7.4%	17%	14%	14%	0.780
Somnolence	11.1%	21%	7%	18%	0.338

Diphenhydramine:

Patients	Method	Results	Conclusion
Male patients (n=21) aged 5-13 years	Double blind, placebo-controlled trial IM Diphenhydramine vs. placebo	See below	Diphenhydramine is no better than placebo for acute agitation



Benzodiazepines:

Methods	Methods	Results		Conclusions
Randomized, prospective, double-blind controlled trial in adults (n=111)	Compare efficacy in sedation between lorazepam, midazolam and haloperidol	Mean time to sedation: L: 32.2 min H: 28.3 min M: 18.3 min $p < 0.05$	Mean time to arousal: L: 217.2 min H: 126.5min M: 81.9 min $P < 0.05$	Midazolam sedates patients the quickest and wears off first. All medications are effective sedation medications.

Medication formulations:

Medication	IM	Tablet	Liquid	ODT
Diphenhydramine	Yes	Yes	Yes	
Haloperidol	Yes	Yes	Yes	
Chlorpromazine	Yes	Yes	Yes	
Olanzapine	Yes	Yes		Yes
Quetiapine		Yes		
Risperidone		Yes		Yes
Lorazepam	Yes	Yes	Yes	
Midazolam	Yes		Yes	

Recommendations:

I always recommend:

Medication	Patient population	With ____ agitation	Because…
PO Olanzapine, Risperidone, or Quetiapine	In patients with a known psychiatric illness and able/willing to take PO	Mild, moderate, or severe	• Targets the neurotransmitters involved with psychiatric illness and acute agitation • Proven efficacy • Improved side effect profile

IM Olanzapine	In patients with a known psychiatric illness and unable/unwilling to take PO	Moderate-severe	• Targets neurotransmitters involved with psychiatric illness and acute agitation • Proven efficacy • Improved side effect profile
PO Diphenhydramine	In patients with an unknown etiology for agitation able to take PO	Mild	• Does not target neurotransmitters involved with psychiatric illness or acute agitation • Benign side effect profile

I sometimes recommend…

Medication	Patient Population	In a situation where…	Because…
PO or IM Chlorpromazine	In patients with a known psychiatric illness	The patient is unresponsive to olanzapine, risperidone or quetiapine	• Targets neurotransmitters involved with psychiatric illness and acute agitation • Proven efficacy • Worse side effect profile compared to olanzapine, risperidone and quetiapine
PO or IM Haloperidol + Lorazepam	In patients with a psychiatric illness	The patient is Moderately-severely agitated and unresponsive to all other agents	• Only targets one neurotransmitter involved with psychiatric illness and acute agitation • Risk of dystonic reactions in pediatric patients

PO or IM Benzodiazepines	In patients with agitation due to an unknown etiology	The patient is moderately-severely agitated	• Does not target neurotransmitters involved with psychiatric illness or acute agitation • Too sedating