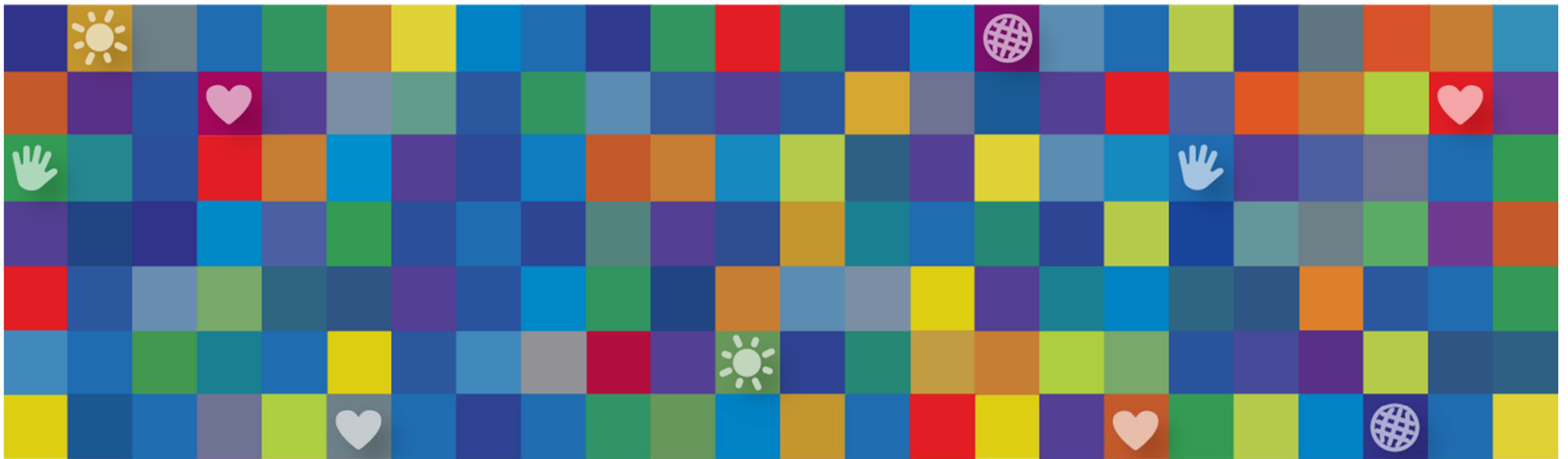




Pediatric Delirium: Typical or Atypical?



Pharmacy Grand Rounds
October 25, 2016

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The Basics



Delirium: Definition

- Disturbance of consciousness and cognition that develops acutely with a fluctuating course of mental status, inattention, and an impaired ability to receive, process, store, or recall information directly triggered by a general medical condition, substance intoxication or withdrawal, exposure to a toxin, or is due to multiple etiologies
 - Psychosis
 - ICU syndrome
 - Acute confusional state
 - Encephalopathy
 - Acute brain failure
 - “Sun-downing”

Smith HA, et al. Crit Care Clin. 2009;25(3):593-614
Van munster BC, De rooij SE. Clin Med. 2014;14(2):192-5.
Smith HA, et al. Pediatr Clin North Am 2013; 60:741-760
BMC Med. 2014;12:141.

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Delirium: Incidence

- 30-80% of critically ill adults
- 20-30% of critically ill children
 - 75% of PICU patients are <3 years old
 - 50% are < 1 year old

Smith HA, et al; *Pediatr Clin North Am* 2013; 60:741-760
Van tuijl SG, et al. *Minerva Anesthesiol.* 2015;81(3):333-41.
Brahmbhatt K, Whitgob E. *Pediatrics.* 2016;137(3):e20151940.

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Delirium: Causes

I	Infection	Encephalitis, meningitis, UTI, pneumonia
W	Withdrawal	Alcohol, barbiturates, benzodiazepines
A	Acute metabolic	Electrolyte imbalance, hepatic or renal failure
T	Trauma	Head injury, postoperative
C	CNS Pathology	Stroke, hemorrhage, tumor, seizures
H	Hypoxia	Anemia, cardiac failure, pulmonary embolus
D	Deficiencies	Vitamin B12, thiamine, folic acid
E	Endocrinopathies	Thyroid, glucose, parathyroid, adrenal
A	Acute vascular	Shock, vasculitis, hypertensive encephalopathy
T	Toxic or drugs	Toxins, anaesthetics, anticholinergics, opioids, etc
H	Heavy metals	Arsenic, lead, mercury

Wise M (1987). In Hales R and Yudofsky S (eds) *Textbook of Neuropsychiatry*. Washington: American Psychiatric Press, pp.89-106

Van tuijl SG, et al. *Minerva Anesthesiol*. 2015;81(3):333-41.

Silver GH, et al. *Am J Psychiatry*. 2010;167(10):1172-7.

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Delirium: Clinical Presentation

Neuropsychiatric Symptoms

Adults & Children

Impaired alertness,
waxing/waning mental status,
sleep-wake disturbances,
disorientation, and inattention

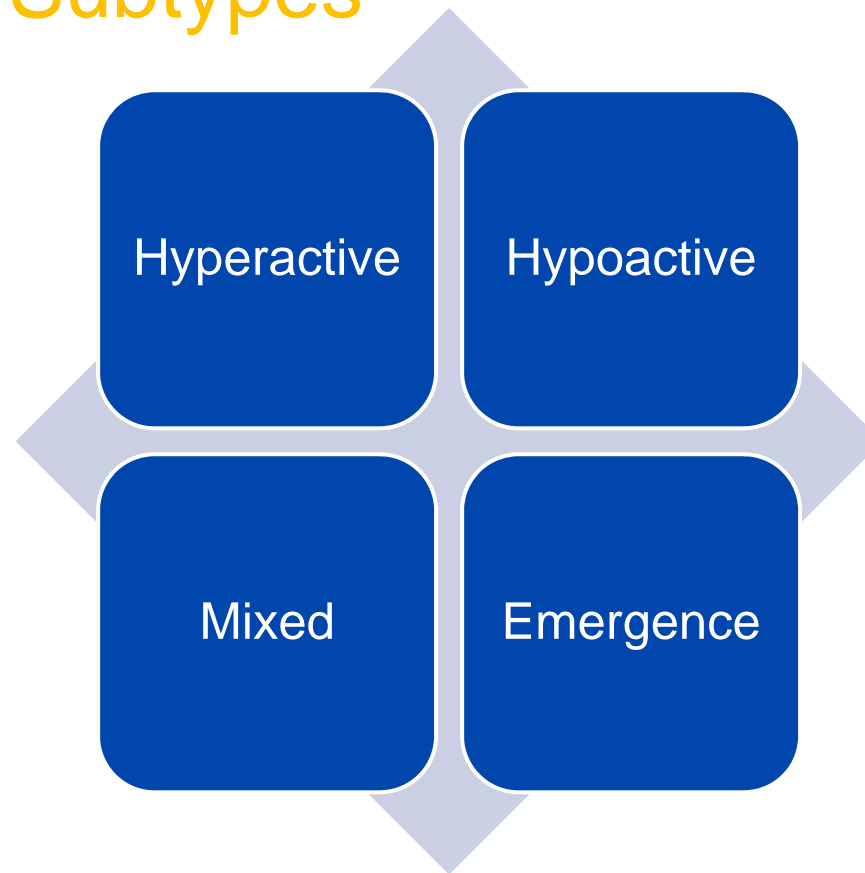
Children

Purposeless actions,
labile affect, inconsolability

Morandi A, et al. Intensive Care Med 2008;34:1907–341915
Smith HA, et al;Pediatr Clin North Am 2013; 60:741-760

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Delirium: Subtypes



Smith HA, et al;Pediatr Clin North Am 2013; 60:741-760

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Delirium: Subtypes

Hyperactive

- Restlessness
 - Agitation
 - Emotional lability, inconsolability
 - Delusions/Hallucinations
 - Autonomic dysregulation
- ↑ dopamine
 - ↓ acetylcholine

Hypoactive

- Apathy
 - Decreased responsiveness
 - Withdrawal
 - Little spontaneous movement
- ↓ dopamine
 - ↑ acetylcholine or GABA_a



Delirium: Recognition Tools

- Pediatric Confusion Assessment Method (pCAM-ICU)
 - Adapted from CAM-ICU
 - Age: ≥ 5 years
 - psCAM-ICU
- Cornell Assessment for Pediatric Delirium (CAPD)
 - Adapted from Pediatric Anesthesia Emergence Delirium (PAED)
 - Age: 0-21 years

Silver GH, et al. Am J Psychiatry. 2010;167(10):1172-7.

Traube C et al. Crit Care Med. 2014;42(3):656-63.

Turkel SB, Hanft A. Paediatr Drugs. 2014;16(4):267-74.

Joyce C, et al. J Child Adolesc Psychopharmacol. 2015;25(9):666-70.

Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. J Neuropsychiatry Clin Neurosci. 2001;13(2):229-42.

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Costs of Delirium

- Increased length of hospital stay
- Higher \$\$ to patient and hospital
- Increased time on mechanical ventilation
- Delusional memories
- High morbidity and mortality

Silver GH, et al. Am J Psychiatry. 2010;167(10):1172-7.
Traube C et al. Crit Care Med. 2014;42(3):656-63.
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Traube C et al. Crit Care Med. 2016 [Epub ahead of print]

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Q1: If confronted with the need for pharmacological treatment for delirium, which drug would be your first choice?

- A. Haloperidol
- B. Olanzapine
- C. Quetiapine
- D. Risperidone
- E. Ziprasidone
- F. None of the above



Treatment



Non-Pharmacological Management

- **Ultimate goal:** “Normal” routine
 - Reassurance and reorientation
 - Repeat frequently
 - Calendars, clocks
 - Pictures of people and objects
 - Familiar toys, music, blankets
 - Lighting, noise
 - Early mobilization, avoiding restraints
 - Psychiatry consult

Turkel SB, Hanft A. Paediatr Drugs. 2014;16(4):267-74.
Joyce C, et al. J Child Adolesc Psychopharmacol. 2015;25(9):666-70

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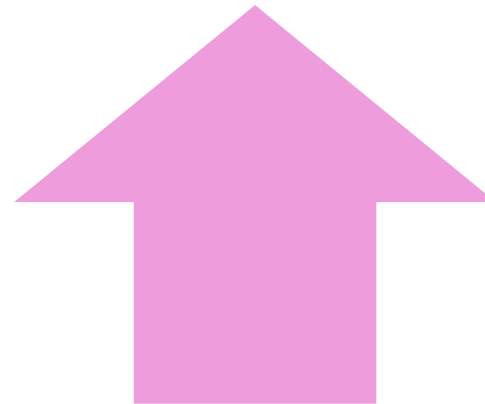
Individualization



Antipsychotic
adverse
effects



Untreated
delirium



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Pharmacologic Management

Historically: Haloperidol

Atypicals → Olanzapine,
quetiapine, risperidone,
ziprasidone

Optimal therapy???

Why Antipsychotics?

- Established clinical efficacy
- Decreased symptoms and severity
- Shorter time to clinical improvement
- Decreased need for other medications
- Can assist in weaning off of other medications

Turkel SB, et al. J Child Adolesc Psychopharmacol. 2012;22(2):126-30.

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Haloperidol: Oldie but Goodie?



Most studied
Only IV agent that can be administered safely
Relatively less sedation than other agents
Blocks dopamine

Significant cardiac effects may be more common in children <12
Extrapyramidal symptoms (EPS), dystonia, akathisia, and hyperpyrexia

Turkel SB, et al. J Child Adolesc Psychopharmacol. 2012;22(2):126-30.
Turkel SB, Hanft A. Paediatr Drugs. 2014;16(4):267-74.

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Antipsychotic Summary

		Haloperidol	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Available Formulations		Tablet, IV, IM, suspension	Tablet, ODT, IM	Tablet	Tablet, ODT, liquid	Capsule, IM
MOA	D2	+++	+	+	++	++
	α 1	+	+	+++	++	+
	H1	+	+++	+++	+	++
	ACh	+	++	+	+	+
Renal		No adjustment	No adjustment	No adjustment	<30mL/min	Use IM with caution
Hepatic		No adjustment	No adjustment	No adjustment	Child-Pugh C	No adjustment
Drug-Drug Interactions		CYP2D6 & CYP3A4	CYP1A2	CYP 3A4	CYP2D6, P-glycoprotein	Minor

Turkel SB, Hanft A. Paediatr Drugs. 2014;16(4):267-74.
 Lexicomp®; Joyce C, et al. J Child Adolesc Psychopharmacol. 2015;25(9):666-70

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Q2: Haloperidol's main mechanism of action is:

- A. Serotonin agonist
- B. Serotonin antagonist
- C. Dopamine antagonist
- D. Dopamine agonist
- E. None of the above



Adverse Effects



Antipsychotic Adverse Effects

- CNS: akathisia, sedation, lower seizure threshold, laryngeal spasm, neuroleptic malignant syndrome (NMS)
- Metabolic: metabolic syndrome, obesity, hyperglycemia, elevated cholesterol, increased risk for DM Type 2, ASCVD

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Summary Table of Adverse Effects

	Anti-Cholinergic	EPS	NMS	Orthostasis	QTc	Sedation	Weight gain
Haloperidol	+	+++	+	♥	♥♥ (40)	+	++
Olanzapine	+++	+	+	♥	♥ (10)	+++	+++
Quetiapine	+++	+	+	♥♥	♥ (6.4)	+++	++
Risperidone	++	++	+	♥♥	♥ (14.5)	++	+++
Ziprasidone	++	+	+	♥♥	♥ (20.6)	++	+

+++→ greater than 30% (except for NMS in haloperidol just is –rare but highest risk since highest potency antipsychotic)
 ++→>10%
 +<10%

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 Turkel SB, Hanft A. Paediatr Drugs. 2014;16(4):267-74.

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Current Literature



Atypical Antipsychotic Medications to Control Symptoms of Delirium in Children and Adolescents (2012)

Objective

Describe the use of atypical antipsychotics in controlling symptoms of delirium in children/adolescents

Methods

Retrospective chart review

Children's Hospital Los Angeles (CHLA)

24 month period

Patients 1-18 years (~1/2 of patients < 12, >12)

Diagnosed with delirium; DRS-R-98

110 pediatric patients

Intervention

Olanzapine, risperidone, or quetiapine

Results

DRS-R-98 score decreased significantly ($p < 0.001$) with antipsychotics without significant adverse side effects

Mean Antipsychotic Dosages

(mg)	Olanzapine (n=78)	Risperidone (n=13)	Quetiapine (n=19)
Starting Daily Dose	4 (0.625-30)	0.6 (0.25-1)	30 (12.5-100)
Ending Daily Dose	5.4 (1.25-20)	0.7 (0.25-2)	70 (12.5-300)
Minimum Daily Dose	3 (0.625-5)	0.5 (0.15-1)	25 (12.5-50)
Maximum Daily Dose	10 (1.25-60)	1 (0.25-2)	75 (12.5-300)
Average Daily Dose	10 (1-52.5)	1.3 (0.375-4)	56 (12.5-125)
Usual Dosing	2.5-20	0.2-3	50-800
Days on Med	26.5 days (1-132, 178)	17.5 days (2-54)	35.1 days (1-108, 118)

Atypical Antipsychotic Medications to Control Symptoms of Delirium in Children and Adolescents

Discussion

- Causes: multifactorial; mainly infection or drug (opioids or benzodiazepines)
- Dosages were the highest when delirium was drug induced
- Length of treatment wasn't significantly different ($p>0.3$)
- Not able to determine decreased DRS-R-98 scores was due to antipsychotic
- ODT and liquid formulations seemed to remove the need for IV
- No distinction between hypoactive, hyperactive, or mixed

Conclusion

- Atypical antipsychotic medications appear to be effective and safe
- Variability in starting doses
- Younger children should be started on the lower end of the range

Quetiapine as treatment for delirium in critically ill children: A case series (2013)

	Case 1 8 months	Case 2 3 years	Case 3 6 years	Case 4 14 years	Range
Starting daily dose	15mg* 1.7mg/kg	25mg 2.1 mg/kg	30mg* 1.6mg/kg	50mg 1.3mg/kg	15-50mg/day 1.7 mg/kg/day
Max daily dose	20mg 2.2mg/kg	100mg 8.3mg/kg	100mg 5.3mg/kg	137.5mg 3.6mg/kg	20-137.5mg 3.6/mg/kg/day
Duration of therapy	15 days; DC+taper	20 days; DC+taper	9 days	12 days	9-20 days

- CAPD screening tool
- Delirium improved in first 24 hours
- Successful treatment from infancy to adolescents

*Compounded liquid solution

Traube C, et al. Journal of Pediatric Intensive Care. 2013;2(3):121-126

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Evaluation of the Safety of Quetiapine in Treating Delirium in Critically Ill Children: A Retrospective Review (2015)

Objective

Systematically evaluate the safety of short-term quetiapine use in pediatric patients for the purpose of treating ICU delirium

Methods

Retrospective Chart Review

Weill Cornell Center of New York Presbyterian Hospital

22 month period

Patients 2-20 years (median-4.5 years old), diagnosis of delirium; CAPD

50 patients

Intervention

Quetiapine

Results

Length of use, days 12 (4.5-22)

Dosage, mg/kg/day 1.3 (0.4-2.3)

Episodes of prolonged QTc 3

Evaluation of the Safety of Quetiapine in Treating Delirium in Critically Ill Children: A Retrospective Review

Discussion

- Largest systematic evaluation of the side effect profile in pediatrics
- Therapy initiation at Weill Cornell Center:
 - 1.5 mg/kg/day, divided in 3 doses
 - Extra 0.5 mg/kg for breakthrough agitation
 - Maximum dose is limited to 6mg/kg/day

Conclusion

- Quetiapine is a safe drug for short-term use with >2,400 doses used
- Administration is safe even in our youngest children
- Start patients on quetiapine 1.5mg/kg/day divided q8h
- Monitoring QTc is important, but increase may not be clinically significant



Detection and Management of Delirium in the Neonatal Unit: A Case Series (2016)

Description	Case 1 DOL 119	Case 2 DOL 77	Case 3 DOL 28
Consult	PICU and psych	PICU and psych; CAPD	Psych; CAPD
Symptoms	Hyperactive, inconsolable, poor attention, altered sleep wake cycle	Inconsolable, purposeless movements, insomnia, agitation	Agitation, restlessness, frequent flailing of arms and legs
Treatment	Quetiapine	Quetiapine	Quetiapine
Dose	1.5mg/kg/day - q 8hr - q 6h -titrated off	1.5mg/kg/day - q 8hr - continued for 2 months	1.5mg/kg/day - q 8hr - continued for 5 weeks

Q3: 9 y/o boy (20kg) with mixed delirium and difficulty sleeping. All non-pharmacologic measures have been maximized. What would be the best drug therapy to start?

- A. Haloperidol IV STAT
- B. Quetiapine 0.5mg/day prn
- C. Risperidone 3mg/kg/day
- D. Quetiapine 1.5mg/kg/day
- E. I wouldn't start drug therapy

Future Research

- MIND-USA Trial
 - Multi-center, double-blind, randomized, placebo-controlled trial
 - 561 Adults
 - Haloperidol IV vs. Ziprasidone IV vs. placebo
 - Objective: define the role of antipsychotics in the management of delirium in vulnerable critically ill patients
 - Study completion: July 2019



Summary

- Hypoactive: avoid potent antipsychotics
- Hyperactive: haloperidol or quetiapine
- Renal and/or liver dysfunction: avoid risperidone
- Drug-Drug Interactions: ziprasidone
- IV: haloperidol
- Sedation: start at bedtime
- Daily dose = control symptoms
- Discontinue/taper: improved clinical status or SEs

SEs: side effects

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Questions & Discussion

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