Dealing with Delirium: The Pediatric Perspective

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- ► The presenter has no financial relationship with any commercial interests pertinent to this presentation.

Pharmacist Objectives

- Describe the epidemiology of pediatric delirium (PD), particularly in intensive care units
- List the signs and symptoms of delirium in pediatric patients
- Discuss the validated assessment tools which are currently available for pediatric patients
- Review treatment options available for PD

Pharmacy Technician Objectives

- List the signs and symptoms of delirium in pediatric patients
- Recall assessment tools which are currently available for pediatric patients
- Identify medication therapy available for the treatment of pediatric delirium

Background

- Neurocognitive disorder due to a somatic illness or its treatment
- Prevalence up to 57% in pediatrics and greater than 80% in adults
 - ► Highest in cardiac intensive care units (ICUs)
- Strongly associated with poor outcomes
 - Increased mortality
 - Increased length of stay
 - Increased ventilator time
 - Long-term cognitive impairment in adults

Pathophysiology

- Neuroinflammatory hypothesis
- Neurotransmitter hypothesis
- Oxidative stress hypothesis

Etiology

1	Infections	Encephalitis, meningitis, urinary tract infections, pneumonia
W	Withdrawal	Alcohol, barbiturates, benzodiazepines
A	Acute metabolic	Electrolyte imbalance, hepatic or renal failure
T	Trauma	Head injury, postoperative
С	CNS pathology	Stroke, hemorrhage, tumor, seizure disorder
Н	Нурохіа	Anemia, cardiac failure, pulmonary embolus
D	Deficiencies	Vitamin B ₁₂ , folic acid, thiamine
Е	Endocrinopathies	Thyroid, glucose, parathyroid, adrenal
A	Acute vascular	Shock, vasculitis, hypertensive encephalopathy
T	Toxic or drugs	Toxins, substance intoxication, medications
Н	Heavy metals	Arsenic, lead, mercury

Risk Factors

Non-Modifiable

- Age < two years</p>
- Developmental delay
- Higher severity of illness
- Mechanical ventilation
- Prior coma

Modifiable

- Immobilization
- Restraints
- Deep sedation
- Cardiac bypass surgery
- Prolonged ICU stay
- Benzodiazepines
- Anticholinergic medications

Assessment Question #1

- ▶ In which of the following settings is pediatric delirium reported as being the highest?
 - a. Cardiac ICUs
 - b. Neonatal ICUs
 - c. General Medicine Floors
 - d. Pulmonary Floors

Assessment Response #1

- In which of the following settings is pediatric delirium reported as being the highest?
 - a. Cardiac ICUs
 - b. Neonatal ICUs
 - c. General Medicine Floors
 - d. Pulmonary Floors

Meet DJ

- ▶ DJ is a 23-month-old girl admitted to your pediatric ICU (PICU) for acute respiratory failure and sepsis secondary to an upper respiratory tract infection.
- ➤ On PICU day two, she requires intubation and is now being mechanically ventilated. She is receiving fentanyl and midazolam drips for pain and sedation, with a goal RASS of 0 to -2.

What risk factors does DJ have for developing delirium?

Diagnostic Criteria

- Disturbances in attention and awareness
- Changes cannot be accounted for by pre-existing neurocognitive disorder
- Acute onset and fluctuating course
- Disturbance is probably the result of a medical condition or its treatment

Delirium Subtypes

Hyperactive 8%

Hypoactive 46%

Mixed 45%

Clinical Presentation

- Changes in psychomotor activity
- Emotional lability
- Hallucinations
- Disordered sleep
- Change from baseline

Assessment Question #2

- ▶ All of the following symptoms are consistent with the diagnosis of hyperactive delirium except:
 - a. Restlessness
 - b. Aggression
 - c. Hypervigilance
 - d. Lethargy

Assessment Response #2

- ▶ All of the following symptoms are consistent with the diagnosis of hyperactive delirium except:
 - a. Restlessness
 - b. Aggression
 - c. Hypervigilance
 - d. Lethargy

DJ's Symptoms

During rounds on PICU day three, DJ's nurse mentions that DJ was extremely agitated overnight and was very restless in bed, requiring an increase in her sedation. When her sedation was turned off in the early morning for a sedation holiday, DJ cried for an extended period of time, despite all attempts of consoling her. This has not happened during her previous sedation holidays and her parents state that normally coddling puts her straight to sleep.

Which of DJ's symptoms are consistent with a diagnosis of delirium?

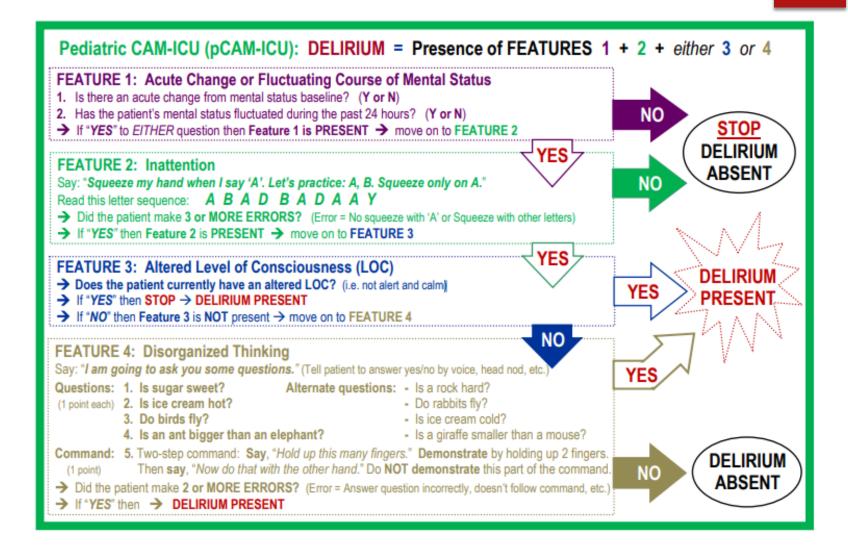
Validated Assessment Tools

- Pediatric Anesthesia Emergence Delirium scale (PAED)
- Pediatric Confusion Assessment Method for ICU (pCAM-ICU)
- PreSchool Confusion Assessment Method for ICU (psCAM-ICU)
- Cornell Assessment of Pediatric Delirium (CAPD)
- Sophia Observation withdrawal Symptoms-Pediatric Delirium scale (SOS-PD)

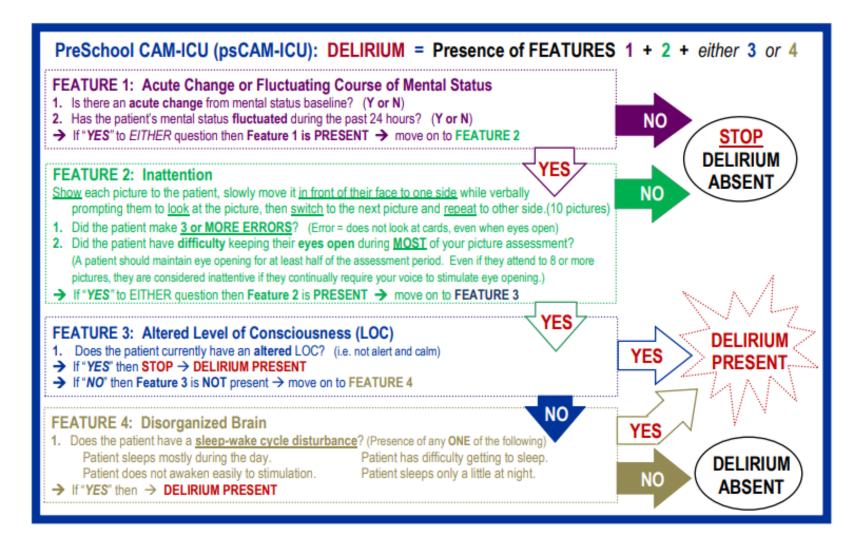
PAED

Behavior	Not at all	Just a little	Quite a bit	Very much	Extremely
Makes eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surroundings	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

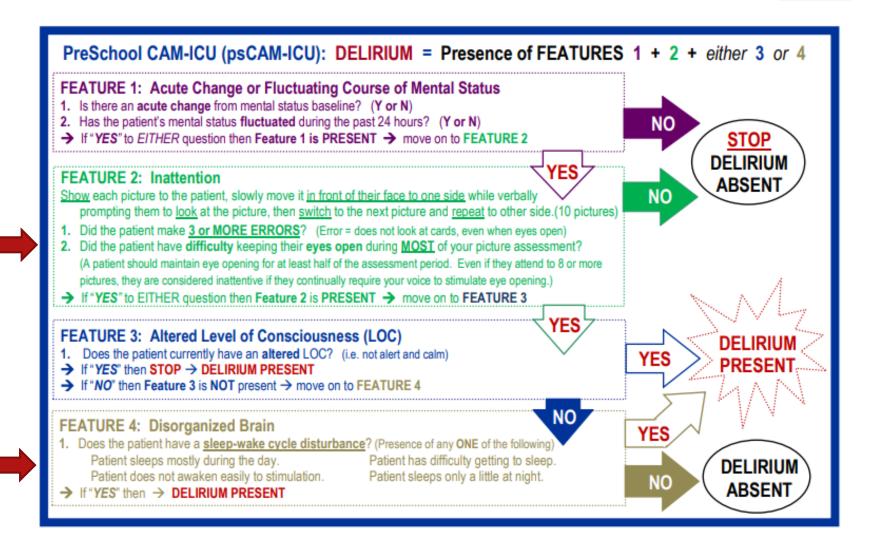
pCAM-ICU



psCAM-ICU



psCAM-ICU



CAPD

RASS Score ____ (if -4 or -5 do not proceed)

Please answer the following questions based on your interactions with the patient over the course of your shift:

	Never	Rarely	Sometimes	Often	Always	Score
	4	3	2	1	0	
1. Does the child make eye contact with the caregiver?						
2. Are the child's actions purposeful?						
3. Is the child aware of his/her surroundings?						
4. Does the child communicate needs and wants?						
	Never	Rarely	Sometimes	Often	Always	
	0	1	2	3	4	
5. Is the child restless?						
6. Is the child inconsolable?						
7. Is the child underactive—very little movement while awake?						
8. Does it take the child a long time to respond to interactions?						
					TOTAL	



Parents do not recognize their child's behavior			Tick if yes Parents perceive their child's behavior as very different or unrecognizable in comparison with what they are accustomed to when the child is ill or in hospital; "this is not my child".					
Step 2	Withdrawal	Delirium						
Tachycardia			Heart rate exceeds baseline by ≥ 15%.					
Tachypnea	ŌŌ		Breathing rate exceeds baseline by ≥ 15%.					
Fever	00		Body temperature exceeded 38.4° C now or in past 4 hours.					
Sweating	00	00	Without apparent reason.					
Agitation	00	00	E.g.: irritable, restless, agitated, fumbling (trying to pull out catheters, venous lines, gastric tubes etc.).					
Anxiety	00	00	Child shows anxious facial expression (eyes wide open, raised and tensed eyebrows). Behavior varies from panicky to introvert.					
Tremors		00	Trembling, involuntary sustained rhythmic movements of hands and/or feet.					
Motor disturbance			Involuntary movements of arm and/or legs; little muscle twitches.					
Muscle tension	00	00	Clenching wrists and toes and/or hunched shoulders. Or: abnormal tensed position of head, arm and/or legs caused by muscle tension.					
Attentiveness		00	If you (nurses) or parents fail to attract or hold the child's attention. Child is not aware of surroundings; living in "his own world"; Apathy.					
Purposeful acting			If child has difficulty in doing things that normally are no problem; e.g. cannot grab pacifier or cuddly toy					
Lack of eye contact		00	No or little eye contact with caregiver or parents.					
Inconsolable crying	00	00	Inconsolable (shown by refusing food, pacifier or not wanting to play). Score silent crying in ventilated children as inconsolable crying.					
Grimacing		00	Eyebrows contracted and lowered, nasolabial fold visible.					
Sleeplessness	00	00	Child doesn't sleep more than one hour at a stretch; catnaps.					
Hallucinations	00	0 0*	Child seems to see, hear of feel things that were not there.					
Disorientation			Only for children >5 years. Child doesn't know whether it is morning, afternoon or evening,					
Distriction			is not aware where it is, does not recognize family or friends.					
Speech			If speech is incomprehensible, unclear or child cannot tell a coherent story (not age ap- propriate).					
Acute onset of symptoms		\circ	Acute change of symptoms compared to before hospital admission.					
Fluctuations		00	The occurrence of symptoms strongly varies over the past 24 hours.					
Vomiting	00		At least once in past 4 hours.					
Diarrhea	00		At least once in past 4 hours.					
Total score								
SOS score* PD score*			Withdrawal score (max. is 15) Count ticked boxes Delirium score (max. is 16/17) Count ticked boxes					

^{*} Consult child-psychiatrist if: Step 1b is positive AND/OR Step 2 score is ≥ 4 or symptom with * is positive.



Step 2	Withdrawal	Delirium	
Tachycardia	00		Heart rate exceeds baseline by ≥ 15%.
Tachypnea	00		Breathing rate exceeds baseline by ≥ 15%.
Fever			Body temperature exceeded 38.4° C now or in past 4 hours.
Sweating	00	00	Without apparent reason.
Agitation	00	00	E.g.: irritable, restless, agitated, fumbling (trying to pull out catheters, venous lines, gastric tubes etc.).
Anxiety	00	\circ	Child shows anxious facial expression (eyes wide open, raised and tensed eyebrows). Behavior varies from panicky to introvert.
Tremors	00	00	Trembling, involuntary sustained rhythmic movements of hands and/or feet.
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Sleeplessness	00	00	Child doesn't sleep more than one hour at a stretch; catnaps.
Hallucinations	00	0 0*	Child seems to see, hear of feel things that were not there.
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Acute onset of symptoms		\circ	Acute change of symptoms compared to before hospital admission.
Fluctuations		00	The occurrence of symptoms strongly varies over the past 24 hours.
Vomiting	00		At least once in past 4 hours.
Diarrhea			At least once in past 4 hours.

^{*} Consult child-psychiatrist if: Step 1b is positive AND/OR Step 2 score is ≥ 4 or symptom with * is positive.

Comparison of Assessment Tools

	PAED	pCAM- ICU	psCAM- ICU	CAPD	SOS-PD
Age group	1 – 17 years	> 5 years	6 months – 5 years	0 – 21 years	0 – 16 years
Sensitivity	91%	83%	78%	94%	97%
Specificity	98%	99%	86%	79%	92%

- European Society for Pediatric and Neonatal Intensive Care guidelines recommend the use of CAPD to assess PD (grade of recommendation = A) every 8 to 12 hours
- ▶ 71% of respondents in an international survey stated that delirium screening was not practiced in their PICUs

Assessment Question #3

- Which of the following assessment tools has the highest specificity for pediatric delirium?
 - a. PAED
 - b. pCAM-ICU
 - c. CAPD
 - d. SOS-PD

Assessment Response #3

- Which of the following assessment tools has the highest specificity for pediatric delirium?
 - a. PAED
 - b. pCAM-ICU
 - c. CAPD
 - d. SOS-PD

Delirium Assessment in DJ

RASS Score (if -4 or -5 do not proceed) Please answer the following questions based of your shift:	on your ir	nteraction	ns with the pa	itient ov	er the co	urse of
your sinit.	Never	Rarely	Sometimes	Often	Always	Score
	4	3	2	1	0	
1. Does the child make eye contact with the caregiver?			*			
2. Are the child's actions purposeful?			*			
3. Is the child aware of his/her surroundings?		*				
4. Does the child communicate needs and wants?		*				
	Never	Rarely	Sometimes	Often	Always	
	0	1	2	3	4	
5. Is the child restless?					28	
6. Is the child inconsolable?						
7. Is the child underactive—very little movement while awake?		*				
8. Does it take the child a long time to respond to interactions?			*			
			1		TOTAL	

Delirium Assessment in DJ

RASS Score (if -4 or -5 do not proceed)						
Please answer the following questions based of your shift:	on your ir	nteractio	ns with the pa	itient ov	er the co	urse of
	Never	Rarely	Sometimes	Often	Always	Score
	4	3	2	1	0	
1. Does the child make eye contact with the caregiver?			*			
2. Are the child's actions purposeful?			*			
3. Is the child aware of his/her surroundings?		23				
4. Does the child communicate needs and wants?		*				
	Never	Rarely	Sometimes	Often	Always	
	0	1	2	3	4	
5. Is the child restless?					*	
6. Is the child inconsolable?					2	
7. Is the child underactive—very little movement while awake?		*				
8. Does it take the child a long time to respond to interactions?			*			
					TOTAL	21

Delirium Assessment in DJ

RASS Score (if -4 or -5 do not proceed) Please answer the following questions based o your shift:	n your ir	nteractio	ns with the pa	itient ov	ver the co	urse of	
	Never	Rarely	Sometimes	Often	Always	Score	
	4	3	2	1	0		
1. Does the child make eye contact with the caregiver?			*				
2. Are the child's actions purposeful?			*				
3. Is the child aware of his/her surroundings?							
4. Does the child communicate needs and wants?		*					
	Never	Rarely	Sometimes	Often	Always		
	0	1	2	3	4		
5. Is the child restless?					*		
6. Is the child inconsolable?					23		
7. Is the child underactive—very little movement while awake?		*					
8. Does it take the child a long time to respond to interactions?			*				
					TOTAL	21	+ Deli

Delirium Management in Adults

- Prevention
 - ► Early mobilization
 - Dexmedetomidine over benzodiazepine infusions
- Pharmacologic therapy
 - ▶ Haloperidol: no evidence of reduced duration of delirium
 - Atypical antipsychotics: may reduce duration of delirium
 - ▶ Quetiapine 50 mg PO every 12 hours (starting dose)

Non-Pharmacologic Therapy

- Address the underlying cause
- Repeated reorientation
- Early mobilization
- Noise reduction
- Sleep management
- Soothing stimulation of all five senses

Indications for Pharmacologic Therapy

- Continued symptoms despite optimal environment
 - Extreme agitation or anxiety
 - Hallucinations or delusions
 - Symptoms leading to stress, discomfort, or danger
 - Delirium leads to extreme stress in parents
 - Interferes with care
- Start low and go slow!

Pharmacologic Therapy

- Avoidance of agents that can precipitate delirium
- Antipsychotics
 - Haloperidol
 - Risperidone
 - Olanzapine
 - Quetiapine
- Delirium due to withdrawal
 - ▶ Benzodiazepines and clonidine for benzodiazepine withdrawal
 - Clonidine and methadone for opioid withdrawal

Pharmacologic Therapy

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Haloperidol

Mechanism: nonselectively blocks postsynaptic D2 receptors

≥ 3 Months	Adults
Load with 0.15 – 0.25 mg IV over 30 – 45 min followed by maintenance of 0.05 – 0.5 mg/kg/day IV divided	0.5 – 10 mg IV; may repeat bolus dose if inadequate response

- Dosage Forms: PO (solution, tablet), IM, IV
- Pharmacokinetics/Pharmacodynamics (PK/PD)
 - ▶ Time to peak: 2 to 6 hours (PO); 20 minutes (IM)
 - ▶ Metabolism: 50-60% glucuronidation
 - ► Half-life: 14 to 37 hours (PO); 14 to 26 hours (IV); 20 hours (IM)
- Side effects: extrapyramidal symptoms (EPS), QT prolongation

Risperidone¹

Mechanism: high antagonistic activity at $5HT_2$ and D_2 receptors; also antagonizes a_1 , a_2 , and histaminergic receptors strongly

< 5 years	≥ 5 years & Adolescents
0.1 – 0.2 mg PO once daily qHS	0.2 – 0.5 mg PO once daily qHS; usual dose of 0.2 – 2.5 mg/day in divided doses 2 to 4 times daily

- Dosage Forms: PO (solution, orally disintegrating tablet, tablet), IM
- ▶ PK/PD
 - ▶ Time to peak: 1 hour; rapid oral absorption
 - Metabolism: CYP2D6
 - ► Half-life: 20 hours (PO)
- Side effects: EPS, metabolic side effects, hyperprolactinemia

Olanzapine

Mechanism: potent antagonism of serotonin 5-HT_{2A} and 5-HT_{2C}, dopamine D_{1-4} , histamine H_1 , and a_1 -adrenergic receptors

Adults

5 mg PO once daily for up to 5 days

- Dosage Forms: PO (orally disintegrating tablet, tablet), IM
- ► PK/PD
 - ▶ Time to peak: ~ 5 hours
 - Metabolism: direct glucuronidation and CYP1A2, CYP2D6
 - ► Half-life: ~37 hours
- Side effects: metabolic side effects

Quetiapine

Mechanism: potent antagonism of serotonin 5-HT_{1A} and 5-HT₂, dopamine D₁ and D₂, histamine H₁, and a₁ and a₂ receptors

Adults

50 mg PO twice daily; may increase in increments of 50 mg up to a maximum of 400 mg daily

- Dosage Forms: PO (tablet)
- ▶ PK/PD
 - ▶ Time to peak: 0.5 to 3 hours
 - Metabolism: CYP3A4
 - ► Half-life: 5.3 hours
- Side effects: metabolic side effects, orthostasis

Antipsychotics for PD

- Design: descriptive, single center, 4-year study
- Population: PICU patients diagnosed with PD
 - Child neuropsychiatrist diagnosis using DSM-IV criteria
 - Agreed upon by multidisciplinary team
- Intervention: non-pharmacologic therapy + antipsychotics
 - ► Haloperidol 0.15-0.25 mg IV load, 0.05-0.5 mg/kg/day IV maintenance
 - ▶ Risperidone 0.1-0.2 mg PO load, 0.2-2 mg/day PO maintenance

Antipsychotics for PD Results

- Results
 - 40 patients diagnosed with PD (5%)
 - ▶ 27 patients (67.5%) received haloperidol
 - ▶ 7.4% experienced acute dystonia
 - ▶ 10 patients (25%) received risperidone
 - ▶ 1 patient (2.5%) received both in succession
- Beneficial results observed rapidly in most cases
- Conclusion: PD responds well to treatment once recognized

	Haloperidol (n = 27)	Risperidone (n = 10)
"Emerging"	12 (45%)	4 (40%)
Hyperactive	9 (33%)	4 (40%)
Hypoactive	6 (22%)	2 (20%)

Atypical Antipsychotics for PD

- Design: retrospective, single-center chart review
- ▶ Population: patients 1–18 years of age with a diagnosis of PD who received antipsychotic therapy (n = 110)
- Intervention
 - ► Olanzapine (n = 78)
 - Quetiapine (n = 19)
 - ► Risperidone (n = 13)

Atypical Antipsychotics' Effect on Delirium Scoring

	Olanzapine (n = 78)	Quetiapine (n = 19)	Risperidone (n = 13)	P value
Age (yrs)	10.8 (4.9)	10.8 (4.5)	8.6 (5.4)	0.33
Pretreatment Delirium Score	20.4 (5)	16.9 (5.1)	21 (5.7)	0.03
Posttreatment Delirium Score	4.7 (3)	4.3 (3)	6.7 (4.3)	0.17
Difference in Delirium Score*	15.7 (5.6)	12.4 (5.2)	15.3 (6)	0.11
Average daily dose (mg) [†]	10 (1 – 52.5)	56 (12.5 – 125)	1.3 (0.375 – 4)	n/a
Duration (days)†	26.5 (1 – 132, 178)	35.1 (1 – 108, 118)	17.5 (2 – 54)	n/a

Data presented as mean (standard deviation) unless otherwise specified; Delirium score calculated using the Delirium Rating Scale-Revised-98 *includes 75 cases with both pre- and posttreatment scores; † mean (range); n /a = not available

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Atypical Antipsychotic Safety

- Adverse Reactions
 - Mild dystonia in one patient treated with olanzapine
 - Four patients died of underlying medical condition
 - ▶ 2 olanzapine, 1 quetiapine, 1 risperidone
 - No other significant adverse events reported
- Conclusion: atypical antipsychotics appeared to be safe and effective for PD treatment

Quetiapine for PD

- Design: single-center, retrospective, chart review
- Population: PICU patients diagnosed with PD who received quetiapine (n = 50)
 - Median age of 4.5 years (2 months 20 years)
 - Preexisting developmental delay in 34% of patients
- Intervention: quetiapine initiated at 1.5 mg/kg/day divided q8h
 - ▶ Additional 0.5 mg/kg given as needed for breakthrough agitation
- Clinical data were collected for the first 10 days after initiation

Quetiapine Conclusions

- Results, median (interquartile range)
 - ► Length of quetiapine use: 12 (4.5 22) days
 - Quetiapine dosage: 1.3 (0.4 2.3) mg/kg/day
 - Number of doses administered: 2428
 - ▶ 39% of doses administered to patients < 2 years
- Adverse events
 - 3 episodes of prolonged QTc reported, with no subsequent arrhythmias
 - Quetiapine dose 3.3 6.3 mg/kg/day
- Conclusion: quetiapine can safely be used for short-term management of PD

Study Limitations

- Small sample sizes
- Omission of clinically important outcomes
- Limited dosing information
- ► Lack of control groups

Assessment Question #4

- ▶ What class of medications is most commonly used to treat pediatric delirium that is not due to withdrawal?
 - a. Benzodiazepines
 - b. Opioids
 - c. Antipsychotics
 - d. Anticholinergics

Assessment Response #4

- What class of medications is most commonly used to treat pediatric delirium that is not due to withdrawal?
 - a. Benzodiazepines
 - b. Opioids
 - c. Antipsychotics
 - d. Anticholinergics

DJ's Treatment

How would you manage DJ's delirium?

DJ's Treatment

How would you manage DJ's delirium?

- Non-pharmacologic therapy
 - Repeated reorientation, noise reduction, sleep management, soothing stimulation of all five senses

DJ's Treatment

How would you manage DJ's delirium?

- Non-pharmacologic therapy
 - Repeated reorientation, noise reduction, sleep management, soothing stimulation of all five senses
- Pharmacologic therapy
 - Discontinue midazolam as soon as possible
 - Only haloperidol and risperidone come as an oral solution

Summary

- Validated assessment tools should be used at least once per shift in ICU patients to allow for early identification and appropriate treatment of PD.
- ► Nonpharmacologic therapies have been shown to reduce the incidence of PD.
- Antipsychotics can potentially be used for the treatment of PD, although long-term benefit and safety have not been evaluated.

Assessment Question #5

- ▶ Which type of delirium is most common?
 - a. Hyperactive
 - b. Mixed
 - c. Hypoactive

Assessment Response #5

- Which type of delirium is most common?
 - a. Hyperactive
 - b. Mixed
 - c. Hypoactive

Assessment Question #6 - Techs

- Which of following medications used for the treatment of pediatric delirium is only commercially available as a tablet?
 - a. Haloperidol
 - b. Lorazepam
 - c. Olanzapine
 - d. Quetiapine

Assessment Response #6

- ▶ Which of following medications used for the treatment of pediatric delirium is only commercially available as a tablet?
 - a. Haloperidol
 - b. Lorazepam
 - c. Olanzapine
 - d. Quetiapine

Dealing with Delirium: The Pediatric Perspective

Anasemon Aioub, PharmD
PGY-1 Pharmacy Practice Resident