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Evidence-Based Updates: Current Topics in Pediatrics

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Disclosure

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All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

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Current Topics in Pediatrics: ICU Delirium

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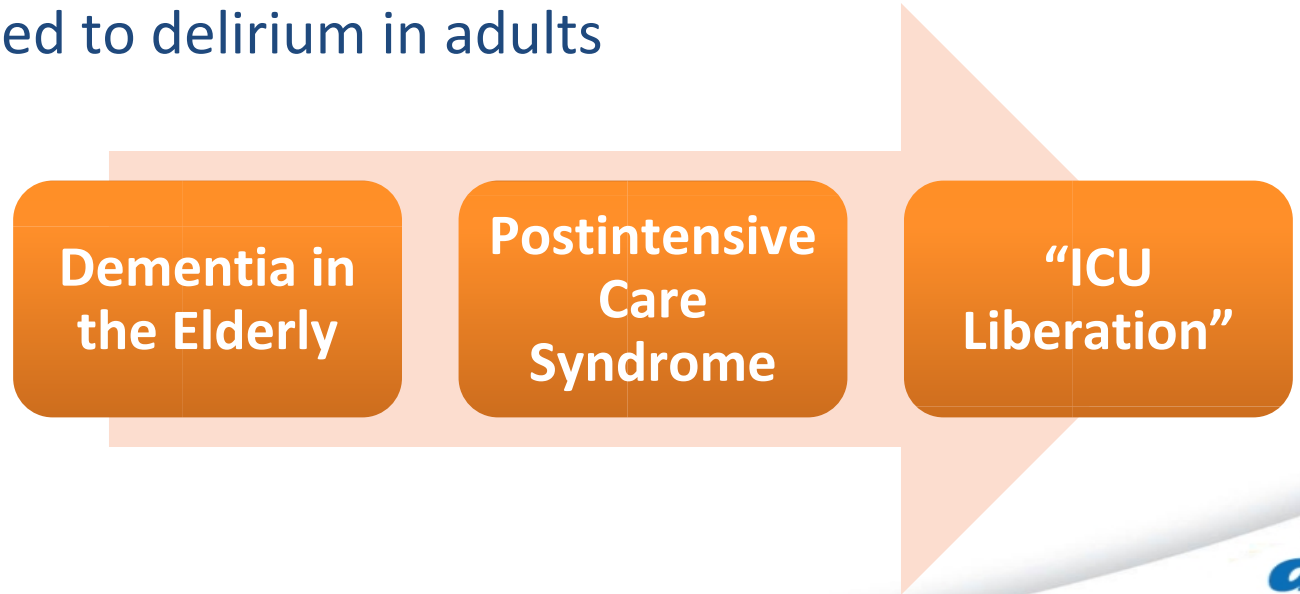
Objectives

- Recognize risk factors associated with the development of pediatric delirium (PD)
- Compare the available delirium assessment tools validated in children
- Generate evidence based management plans for prevention and treatment of PD

A Look Back in Time

- The last 20 years have provided an explosion of research related to delirium in adults

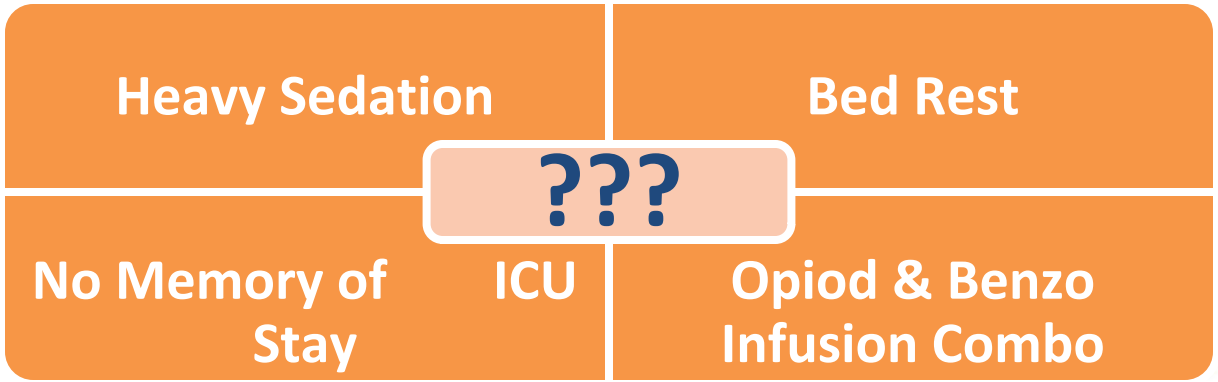


Crit Care Med 2017; 45:1562-1564

ICU = Intensive Care Unit

The Pursuit in Pediatrics

- Five years ago, the journey toward “ICU Liberation” and a clear understanding of delirium in pediatrics ignited
- Our gold-standard treatments are being questioned



Crit Care Med 2017; 45:1562-1564

Benzo = Benzodiazepine

Audience Poll

- How many centers utilize a sedation protocol in your ICU's?
- Is your standard of care to provide an opioid and benzodiazepine infusion combination?

Delirium

Change in Cognition

Acute Onset with Fluctuating Course

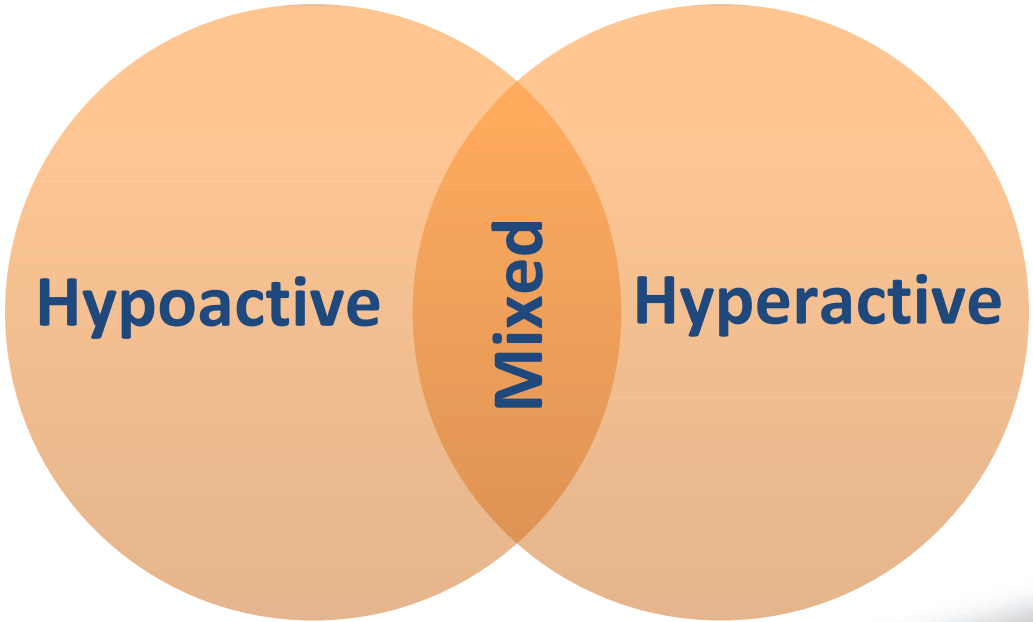
Disturbance of Consciousness

Associated with Serious Medical Illness

Acute Brain Dysfunction

Minerva Anestesiol 2015; 81:333-341
Pediatr Clin N Am 2013; 60:741-760

Types of Delirium



Pediatr Clin N Am 2013; 60:741-760

GABA = Gamma-aminobutyric acid

Prevalence

- Large, multicenter, multinational point prevalence study
  - Established delirium as a frequent complication of pediatric ICU care
  - Point prevalence of 25% across multiple institutions
  - Children requiring mechanical ventilation had prevalence of 53%
- Consistent with previous single center studies

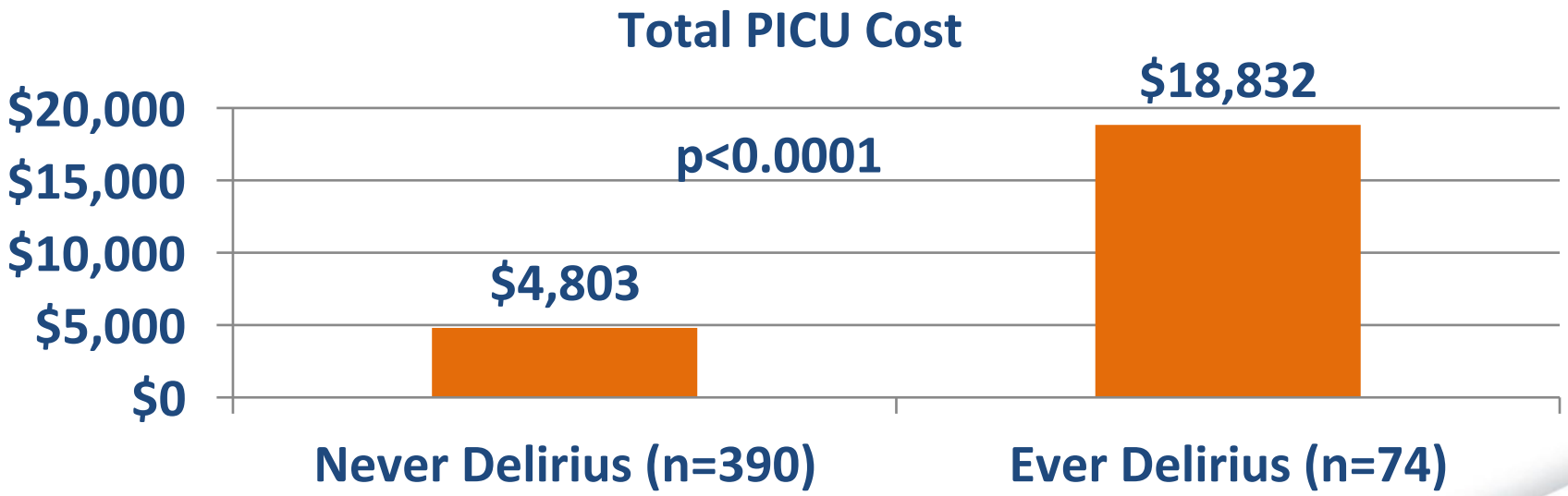
Crit Care Med 2017; 45:584-590

Financial Impact

- Prospective, observational study to determine the cost associated with delirium in critically ill children
- Urban, academic, tertiary-care PICU
- Evaluated 464 PICU admissions from September to December 2014
- Hospital costs compared for patients with delirium and those never delirius

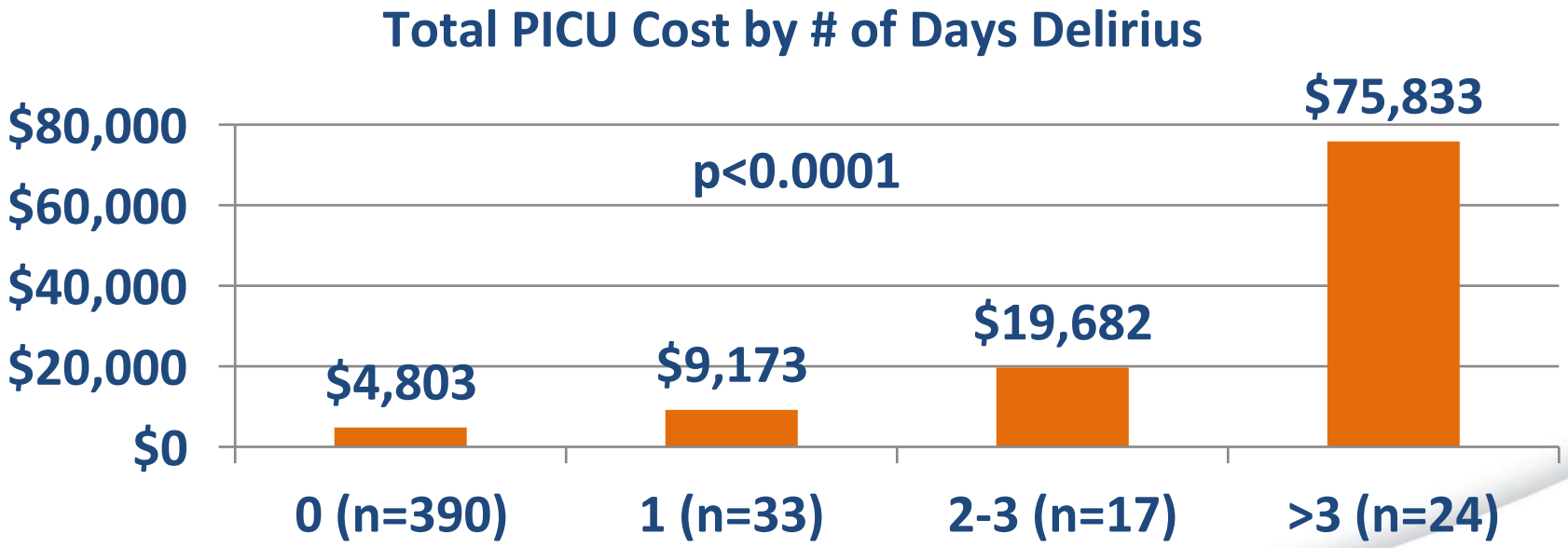
PICU = Pediatric Intesive Care Unit

Financial Impact



Adapted from Crit Care Med 2016; 44:e1175-1179

Financial Impact



Adapted from Crit Care Med 2016; 44:e1175-1179

Other Implications

1. Longer length of ICU stay
2. Longer length of hospital stay
3. Independently associated with in-hospital mortality

Crit Care Med 2017; 45:891-898

Risk Factors

Modifiable

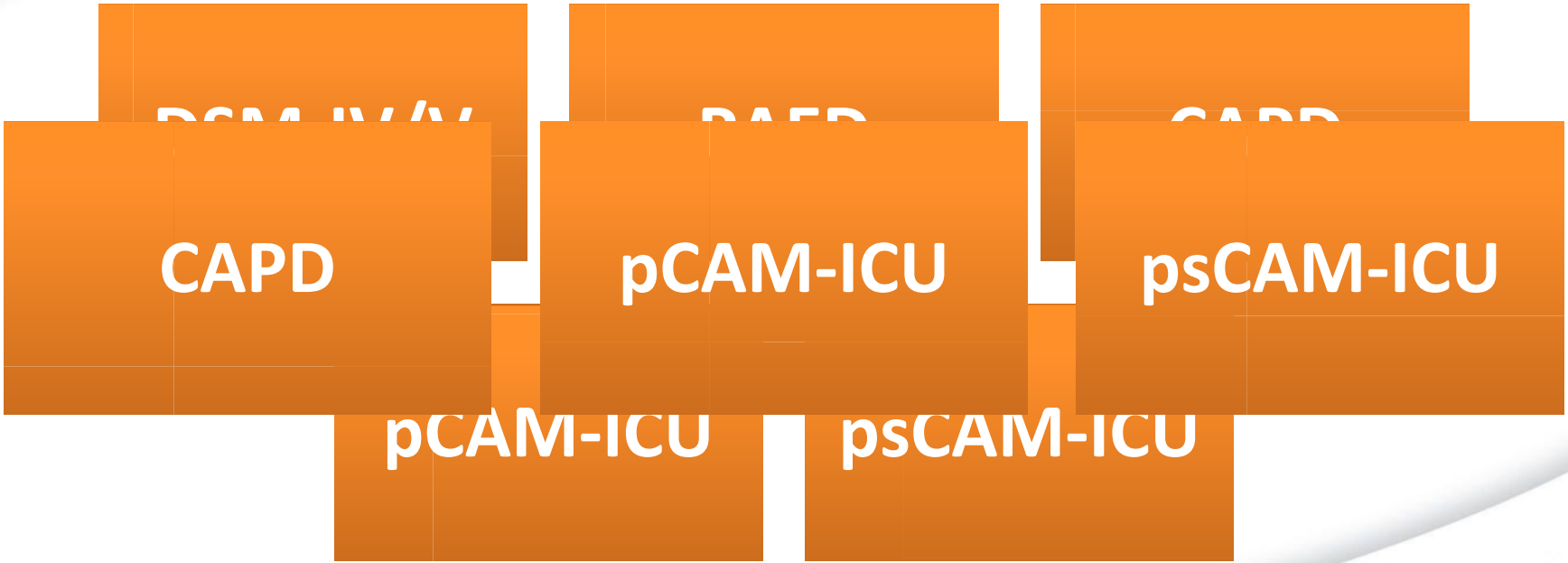
- Benzodiazepines
- Opiods
- Anticholinergics
- Steroids
- Restraints

Non-Modifiable

- Age < 5 Years
- Developmental Delay
- Severity of Illness
- Mechanical Ventilation
- Vasoactive Medications

Ped Crit Care Med 2015;16: 303-309, Crit Care Med 2017; 45:891-898
Crit Care Med 2017; 45:1427-1435, Crit Care Med 2017; 45:1562-1564

Assessment Tools



DSM-IV/V: Diagnostic and Statistical Manual of Mental Disorders, PAED: Pediatric Anesthesia Emergence Delirium Scale, CAPD: Cornell Assessment of Pediatric Delirium
pCAM-ICU: Pediatric Confusion Assessment Method for the ICU, psCAM-ICU: Preschool Confusion Assessment Method for the ICU

Audience Poll

- How many centers are using a validated tool to screen for delirium daily in your ICU's?

- If so, which tool are you utilizing?
  a. CAPD
  b. pCAM-ICU + psCAM-ICU
  c. Other

CAPD

- An adaptation of the PAED
- Designed to detect all three types of delirium
- Validated with a sensitivity of 94% and a specificity of 79%
  - Developmental delay – sensitivity of 96%, specificity of 51%
- Takes 2 minutes or less to complete
- Eight elements correlate directly with DSM-IV definition of delirium

Crit Care Med 2014; 42:656-663

CAPD

RASS Score = _____ (If -4 or -5, do not proceed)
Answer based on interactions with patient over course of your shift.
(4 = Never, 3 = Rarely, 2 = Sometimes, 1 = Often, 0 = Always)

	Score
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?	

Adapted from Crit Care Med 2014; 42:656-663

RASS = Richmond Agitation-Sedation Scale

CAPD

RASS Score = _____ (If -4 or -5, do not proceed) Answer based on interactions with patient over course of your shift. (4 = Never, 3 = Rarely, 2 = Sometimes, 1 = Often, 0 = Always)	
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 =	

Adapted from Crit Care Med 2014; 42:656-663

RASS = Richmond Agitation-Sedation Scale

CAPD

- Developmental anchor points created to better assess children < 2 years of age

	8 Week Old	1 Year Old
1. Does the child make eye contact with caregiver?	Follows moving object past midline, regards hand holding object, focused attention.	Holds gaze. Prefers primary parent. Looks at speaker.

- Score > 9 indicative of delirium

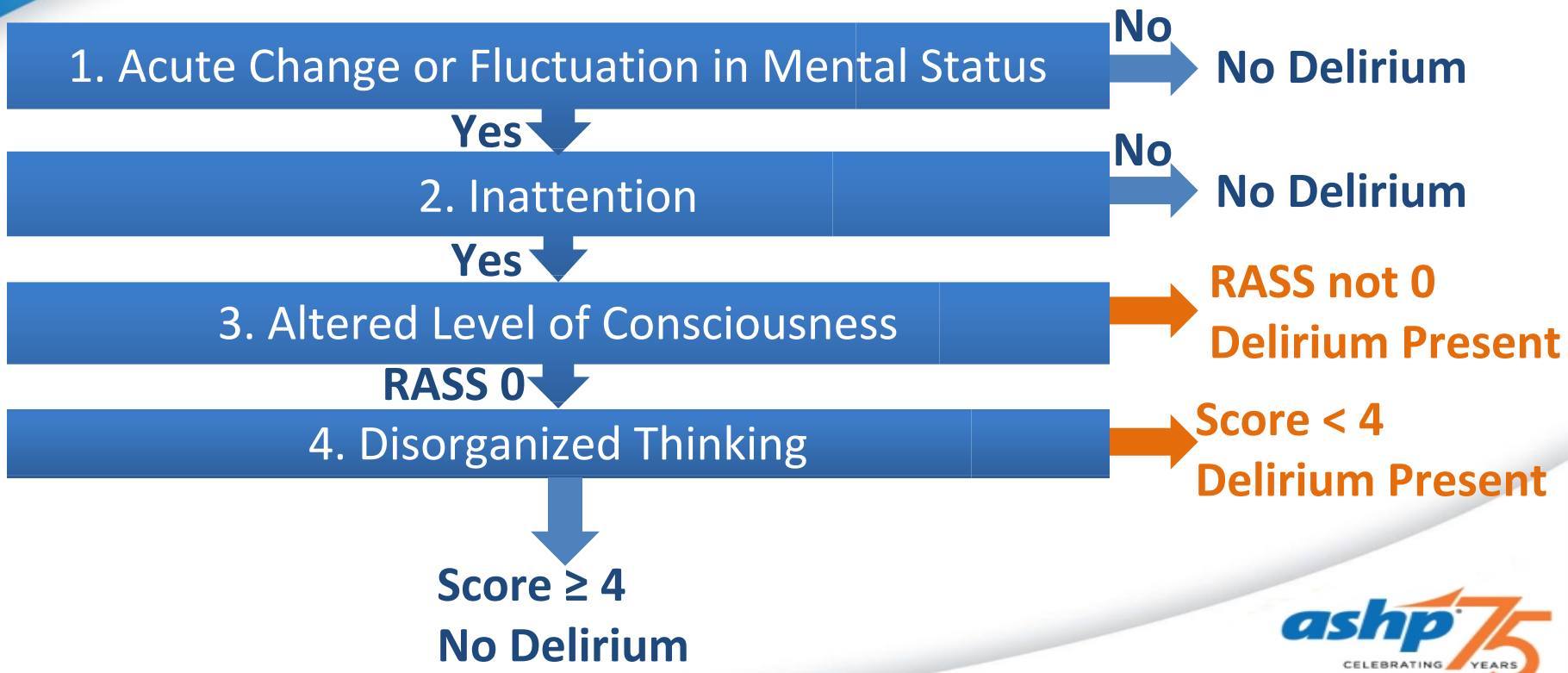
Crit Care Med 2014; 42:656-663

pCAM-ICU

- Adapted from the CAM-ICU for children > 5 years old
- Validated with a sensitivity of 83% and specificity of 99%
- Requires presence of inattention
- Evaluates 4 features of DSM delirum diagnosis
- (Feature 1 and Feature 2) + (Feature 3 or Feature 4) indicative of delirium

Crit Care Med 2016; 44:592-600
Crit Care Med 2011; 39:150-157

pCAM-ICU



Adapted from Crit Care Med 2011; 39:150-157

pCAM-ICU

- Assessment of Inattention
  - Squeeze my hand when you hear the letter “A”
    - Read the following letters…..”ABADBADAAY”
- Assessment of Disorganized Thinking
  - Is sugar sweet?
  - Is ice cream hot?
  - Hold up 2 fingers. Now add 1 more.

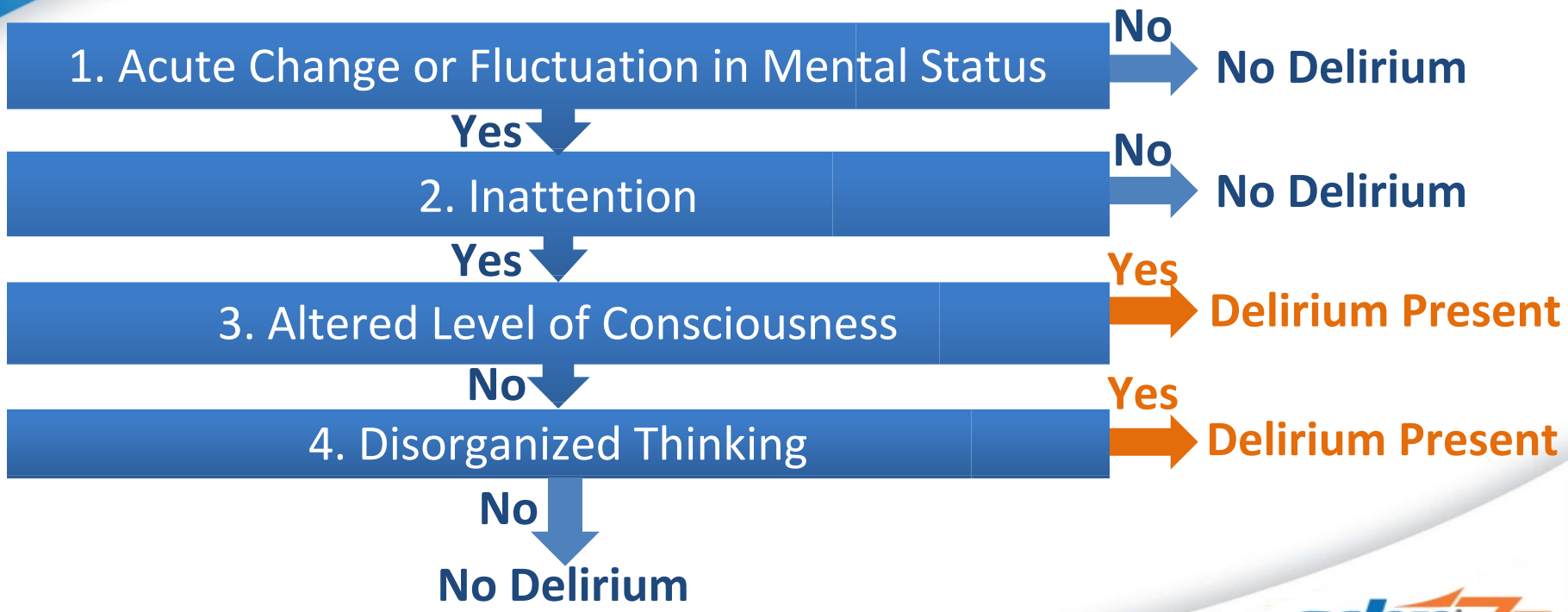
Crit Care Med 2011; 39:150-157

psCAM-ICU

- Adapted from pCAM-ICU for children 6 months to 5 years old
- Validated with a sensitivity of 75% and specificity of 91%
- Requires presence of inattention
- Evaluates 4 features of DSM delirum diagnosis
- (Feature 1 and Feature 2) + (Feature 3 or Feature 4) indicative of delirium

Crit Care Med 2016; 44:592-600

psCAM-ICU



Adapted from Crit Care Med 2016; 44:592-600

psCAM-ICU

- Assessment of Inattention
  - Show alternating pictures/mirrors while giving verbal prompts
    - “Is this a truck?”
- Assessment of Disorganized Brain
  - Is there a sleep/wake cycle disturbance?
    - Sleeps most of the day
    - Does not awaken easily to stimulation

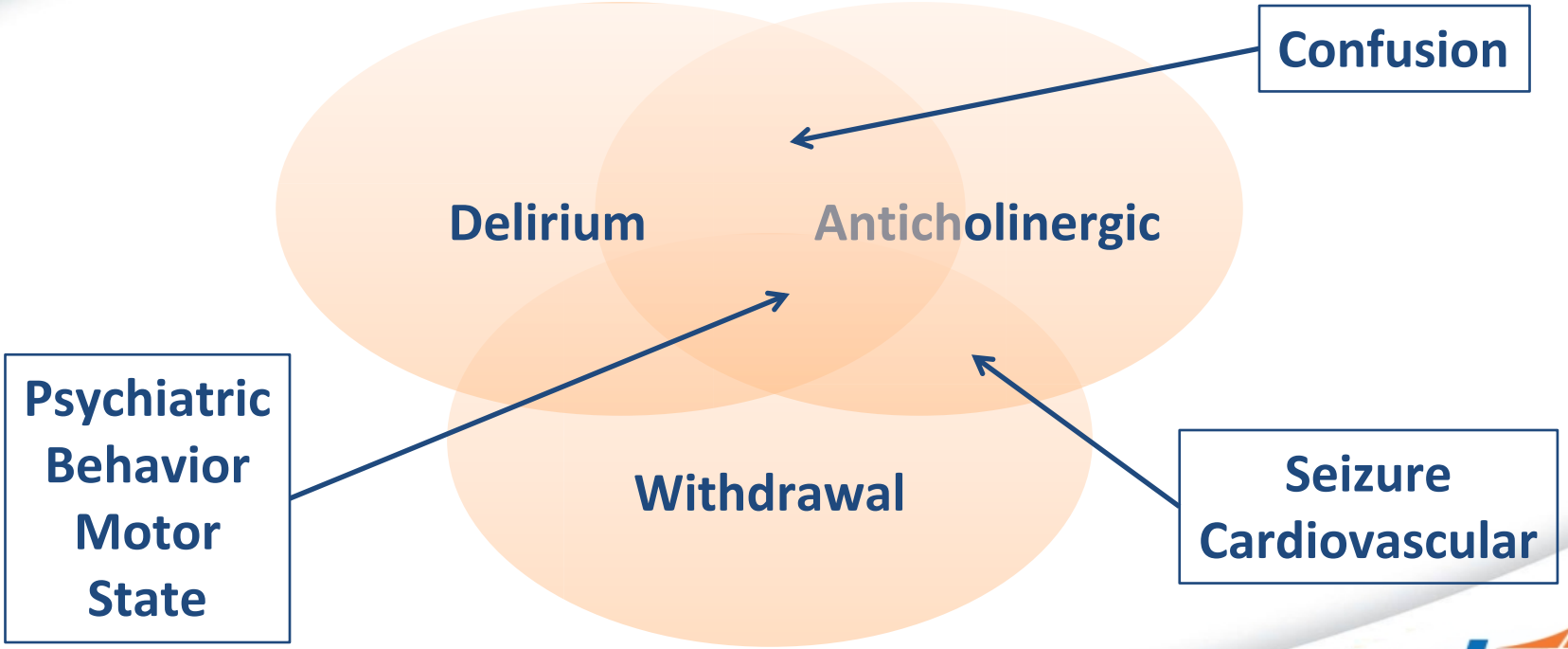
Crit Care Med 2016; 44:592-600

Which Tool to Use?

	CAPD	p/psCAM-ICU
Pros	Can be used in all ages	Objective
	Validated in developmental delay	Quick to complete
	Quick to complete	
Cons	Subjective	Not for < 6 months old
	Training on anchor points	Not validated in developmental delay
		Training on 2 tools

Intensive Care Med 2016; 42:972-986
Critical Care 2014; 18:489-499, Crit Care Med 2017; 45:584-590

A Word of Caution



Ped Crit Care Med 2017; 18:580-588

An Example

- Two year old girl with respiratory failure has been intubated for 9 days. In preparation for extubation her Midazolam was weaned to 0.2 mg/kg/hr and Fentanyl to 2 mcg/kg/hr. The following day she is:
  - Restless, doesn't make eye contact, slow to calm, startles easily, increased muscle tone, slept poorly overnight
- Other medications include lorazepam, furosemide, famotidine, and methylprednisolone

An Example

- WAT-1 = 6
  - Diagnosis = Withdrawal
  - Treatment = Fentanyl and Midazolam boluses to treat withdrawal
- CAPD = 14
  - Diagnosis = Delirium
  - Treatment = Consider antipsychotic and avoid benzodiazepines
- Anticholinergic Drug Scale = 10
  - Diagnosis = Significant risk for Anticholinergic Toxidrome
  - Treatment = Discontinue anticholinergic agents

Management

Begin by asking yourself “Why?”

Management

1. Underlying illness?
2. Iatrogenic causes?
3. Environmental causes?
4. Consider pharmacologic therapy

Crit Care Med 2017; 45:891-898

Audience Poll

- How many centers utilize a Delirium Bundle daily to prevent and manage PD?

- How many centers use a Delirium Treatment protocol to institute pharmacologic therapy?

Delirium Bundle

- A 19 bed PICU in an urban, academic medical center implemented a delirium bundle containing three components:
  - Delirium screening protocol
  - Sedation protocol
  - Early mobilization protocol
- 22 month study period
- Reduced their average monthly delirium prevalence from **19.3%** ⇨ **11.8%**

Ped Crit Care Med 2017; 18:531-540

Delirium Bundle Ideas

- Delirium, sedation, withdrawal screening tools
- Early mobilization protocol
- Day/Night Orientation
- Noise Reduction
- Clustering Care with Family Engagement
- Discontinue unnecessary medications

Minerva Anestesiol 2015; 81: 333-341, J Intensive Care Med 2017; August:1-8

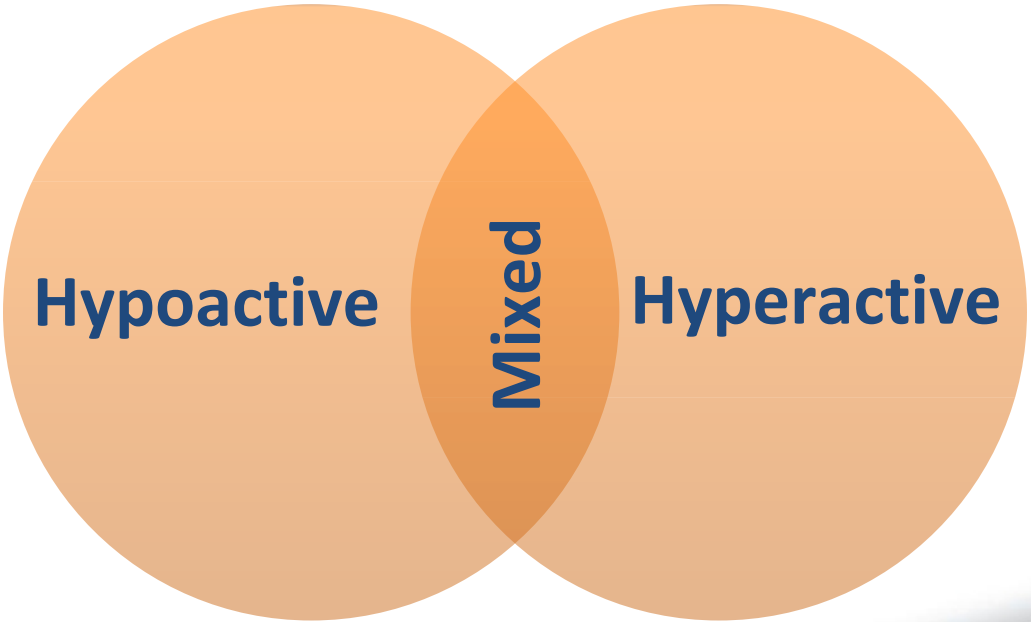
Pharmacologic Options

- Haloperidol
- Risperidone
- Quetiapine
- Olanzapine
- Ziprasidone

Types of Delirium

Atypical Antipsychotics

- ↓Dopamine
- ↑Acetylcholine
- ↑GABA



Antipsychotics

- ↑Dopamine
- ↓Acetylcholine
- ↓GABA

Antipsychotics

Pediatr Clin N Am 2013; 60:741-760

Audience Poll

- For those centers that treat delirium, which medication do you use?
  a. Quetiapine
  b. Risperdal
  c. Haloperidol
  d. Other
  e. Depends on type of delirium

Antipsychotics

	Haloperidol	Risperidone	Quetiapine
Starting Dose	0.025-1 mg	0.05-0.5 mg	0.5 mg/kg
Dosage Forms	Tab, Liquid, IV, IM	Tab, Liquid, ODT, IM	Tablet
D2 Binding	+++	++	+
ACh Binding	+	+	+
EPSE	+++	++/+++	0/+
QTc Prolongation	+++	+	+/++

Adapted from Ped Drugs 2014; 16:267-274
J Child and Adolescent Psychopharmacology 2015; 25:666-670

D2 = Dopamine, Tab = Tablet, ODT = Oral Disintegrating Tablet
Ach = Acetylcholine, EPSE = Extrapyramidal Side Effects

Haloperidol

- Retrospective review of 55 PICU patients that received Haloperidol for PD
- January 2000 to July 2011
- Median dose 0.03 mg/kg/day (0.02-0.12 mg/kg/day)
- Adverse events noted in 10% of patients
  - All female, median age 6.3 years (3.9-15 years)
  - Sedation, tremor, dystonia, fever, NMS, rigidity, oculogyric crisis

Intensive Care Med 2014; 40:1602-1603

NMS = Neuroleptic malignant syndrome

Quetiapine

- Retrospective review evaluating the safety of Quetiapine use in 55 PICU patients diagnosed with delirium
- January 2013 through November 2014
- Ages 2 months to 20 years
- Median daily dose 1.3 mg/kg/day (0.4-2.3 mg/kg/day)
- Median duration of therapy 12 days (4.5-22 days)

J Child and Adolescent Psychopharmacology 2015; 25:666-670

Quetiapine

Clinical Parameters and Adverse Outcomes of Quetiapine	
Number of doses administered	2428
Number of doses administered to children < 2 years of age	953
Episodes of prolonged QTc	3
Episodes of torsades de pointes	0
Episodes of extrapyramidal symptoms	0
Episodes of NMS	0

Adapted from J Child and Adolescent Psychopharmacology 2015; 25:666-670

Quetiapine in Neonates

- Case series in 3 NICU patients
- CGA's of 4, 11, and 17 weeks
- Complex medical problems with increasing doses of sedation
- All treated with Quetiapine 0.5 mg/kg/dose Q8 hours
- Delirium improved over course of 2-5 days
- All sedation weaned off between 7 and 18 days
- Quetiapine treatment duration 5-8 weeks
- No adverse events reported

Help Me, Don’t Harm Me

- It’s time to start our journey to “Pediatric ICU Liberation”
- Keeping our patients and devices safe is important
- Emerging research shows children can be awake, comfortable, and interactive with an endotracheal tube
- Be mindful of our patients developing brains
- Non-pharmacologic approaches like sleep promotion, good communication, and family engagement can go a long way

Crit Care Med 2017; 45:1562-1564

Key Takeaways

- Key Takeaway #1
  - PD occurs in up to 25% of our ICU patients
- Key Takeaway #2
  - Daily screening utilizing a validated tool (CAPD, p/psCAM-ICU) is essential for early detection
- Key Takeaway #3
  - When it comes to management – Less is More!
  - Optimize environment and minimize offending drug therapies before starting antipsychotics

Questions

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Evidence for the Use of Cannabidiol in Pediatric Epilepsy

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Director of Research Ascension Texas Hospital Systems

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Cannabinoids in History

- 1100-First mention of medical marijuana in the Middle East
- 1464- Treatment of “Inflammation of the Head”-*Pharmacopeia Londonesis*
- 19th Century-Introduction in Western Medicine
  - Marijuana extracts to control seizures including infantile convulsions
  - *“Noted to sometimes but not frequently be useful as an adjunct to bromides”*
- 1960’s-Δ^9-Tetrahydrocannabinol and cannabidiol purified
- 1970-DEA Cannabis and derivatives scheduled as C-I
- 1996-First law allowing medical use of cannabis
- 2001-Modern suggestion of cannabinoids usefulness in the treatment of epilepsy
- 2006-Charolette’s Web (Age 10 years)

Epilepsy and Behav. 2017:70:288-91., Epilepsy and Behav. 2017:70:319-27.

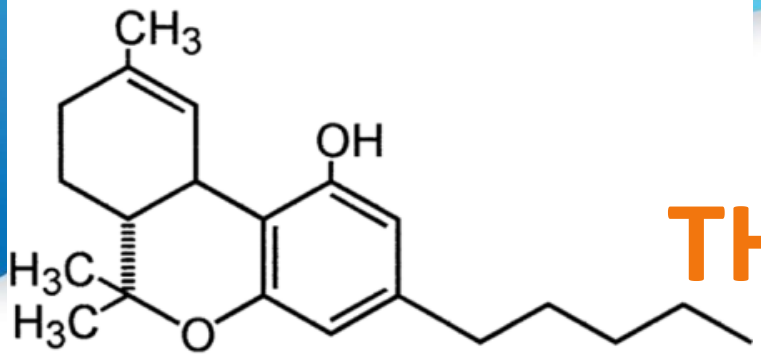
Definitions

- **Medical marijuana** -use of cannabis or its derivative products in the attempt to treat disease of alleviate symptoms by patient (Note: DEA classifies products as C-I)
- **Dietary supplement**- A product intended for the ingestion to add further nutritional value to supplement the diet. This includes vitamins, amino acids, minerals, herbs or botanicals, substance to increase dietary intake
- (Note: FDA *will not* permit CBD products to be marketed as dietary supplements, Nutraceuticals are not recognized by the FDA).

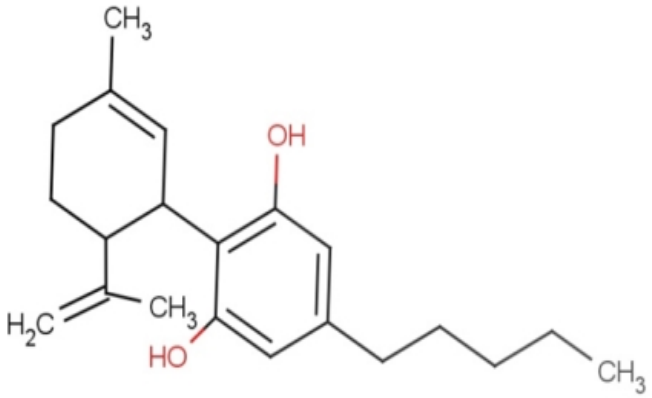
Definitions (2)

- **Cannabis**-generic name for products of *Cannabi sativa* L.
  - Subspecies *sativia* (<0.3% THC) vs *indica* (>0.3% THC)
- **Terpenoids**-substances in the cannabis plant giving scent/flavor
- **Cannabinoids** –molecules found in the cannabis plant (or their derivatives) that interact cannabinoid receptors
  - Endocannabinoids-physiologically made
  - Synthetic –made through chemical synthesis
  - Phytocannabinoids-those found in plant sources (>100)

Epilepsy and Behav. 2017:70:302-12. Epilepsy and Behav. 2017:70:313-8.



THC vs CBD

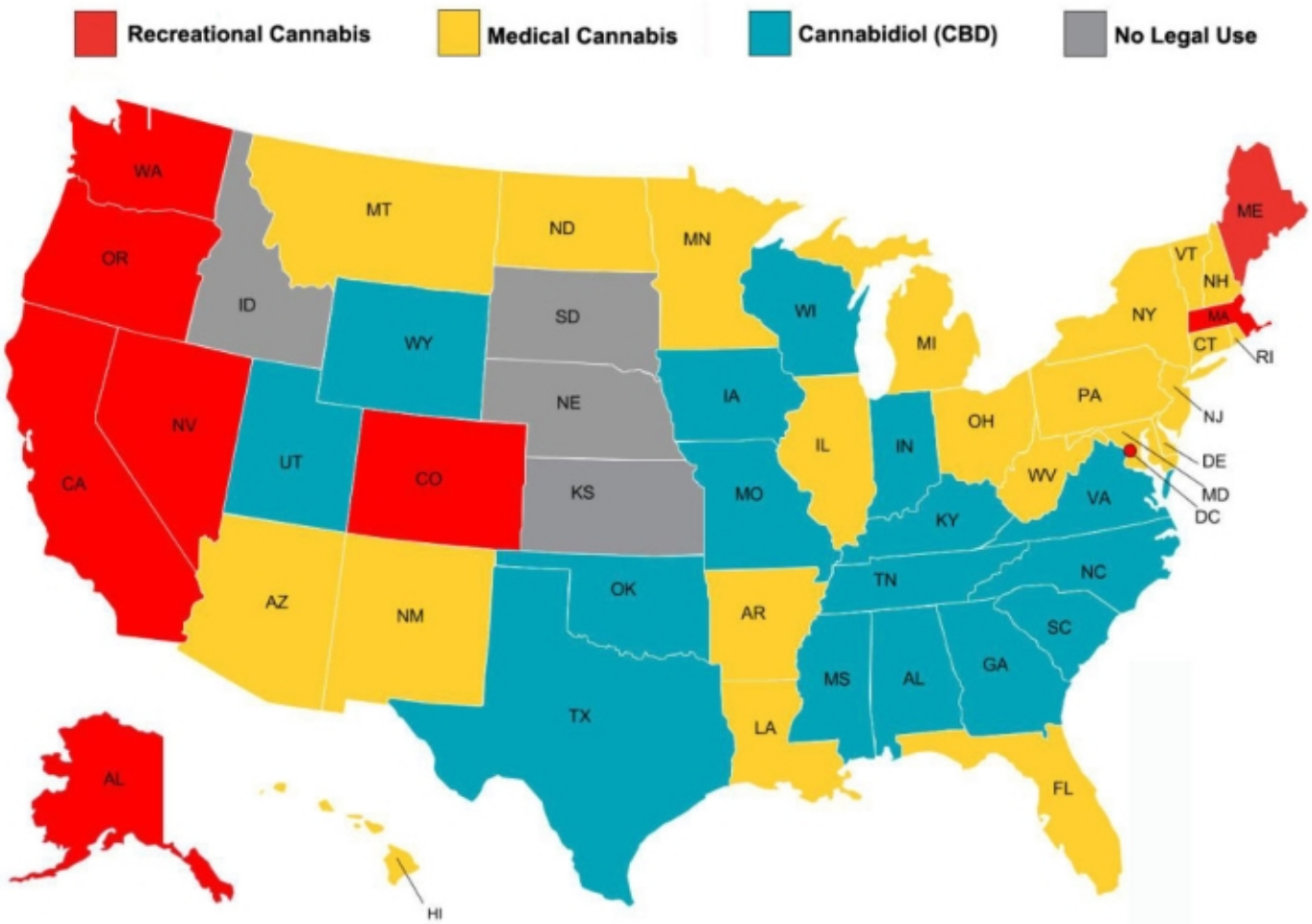


	THC	Cannabidiol
Mechanism of Action	**CB1 and CB2**	**TRPV1, T-VGCC, GPR55, 5-HT1a, 2b, adenosine**
Anticonvulsant	**+/- may be pro-convulsant**	**+**
Euphoria	**+**	**NA**

Epilepsy and Behav. 2017:70:313-8.

Cannabis-Based Products

	Hemp/Hemp Oil	CBD Oil	Cannabis Oil
Source	Stalks and seeds	Seeds, flowers	Seeds, flowers
Content	Minimal/No THC, CBD	CBD	THC, CBD Ratio varies
Use	Clothing, industrial products, soaps, food	Various, including epilepsy	Various
(-) Psychoactive	No	No	Yes
DEA Regulated	No	Yes	Yes



Legal status indicated here refers to the use of medical cannabis or cannabidiol for the treatment of epilepsy. For the use of these products to treat any other condition, laws may differ.

http://cqrcengage.com/efa/medical-cannabis/faq-access-and-advocacy.

EPILEPSY FOUNDATION

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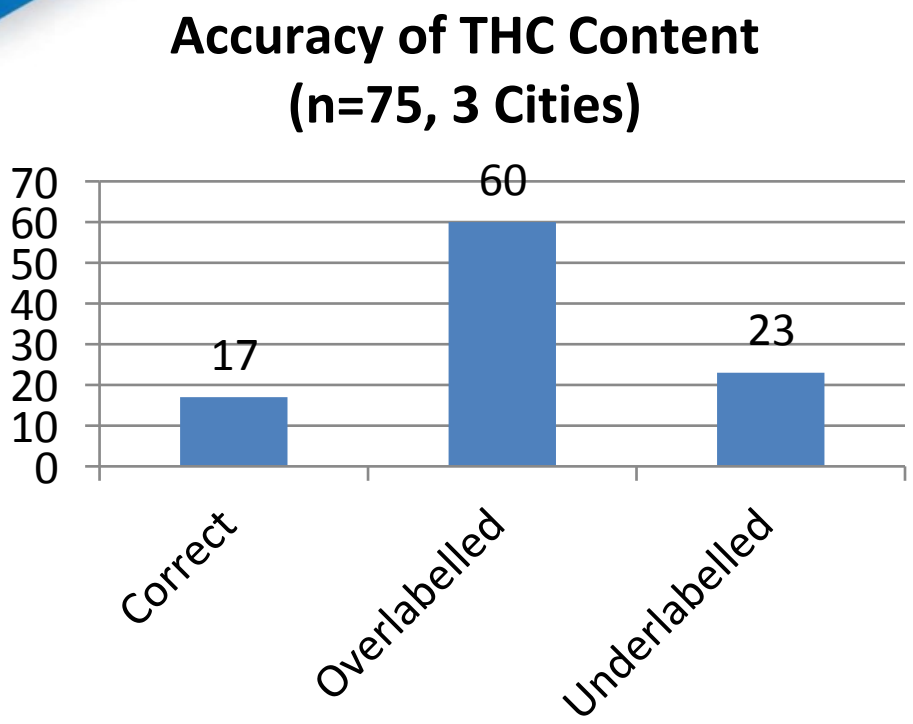
Pop Quiz (True or False)

- If medical marijuana is approved in a State an MD can prescribe it.
- A legal dispensary in one state can ship CBD extract to a house in another state where marijuana is legal.
- CBD products from one labeled at one dispensary will be the same as similarly labeled product at another dispensary
- Using CBD with THC improves the efficacy of medical marijuana.

Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products



Only 59% had CBD content but only 13% labeled as such

THC:CBD content 36:1

JAMA. 2015:313: 2491-3.,

Entourage Effect

- Idea that combining various cannabinoids that there is a synergy or bettering of response greater than that observed with a single cannabinoid.

- Currently there is no scientific evidence of this phenomenon.

“The anecdotal reports of positive effects of the marijuana derivative cannabidiol (CBD) for some individuals with treatment-resistant epilepsy give reason for hope. However, we must remember that anecdotal reports alone are not sufficient to support treatment decisions. Robust scientific evidence for the use of marijuana is limited. The lack of information does not mean that marijuana is ineffective for epilepsy. It merely means that we do not know if marijuana is a safe and effective treatment for epilepsy, which is why it should be studied using the well-founded research methods that all other effective treatments for epilepsy have undergone.”

– *-American Epilepsy Society Position Statement March 21, 2016*

https://www.aesnet.org/about_aes/position_statements/AES%20Position%20on%20Medical%20Marijuana

Cannabioids in Development with Epilepsy Indications

Company	Name	Cannabinoid	Dosage Form	Indication	Phase
Insys	NA	Synthetic CBD	Solution	CAE	I
				IS	II
				DS, LGS	III
Zynerba	ZYN002	Synthetic CBD	Topical Gel	Adult Focal Epilepsy	II
GW Pharmaceuticals	Epidiolex GWP42006	Plant derived CBD CBDV	Solution	TSC, DS, LGS	III
				IS	II
				CBDV-Focal Seizures Adults	II

https://www.insysrx.com/products/in-development, http://zynerba.com/in-development/cbd-gel-zyn002/, https://www.gwpharm.com/products-pipeline

Pediatric Epilepsy Syndromes

	Etiology	Onset Age	Seizures	EEG	Cognitive Impairment
Lennox Gastaut Syndrome (LGS)	Cryptogenic/Symptomatic	1-8 years	Atonic, atypical absence, absence, focal seizures	1.5-2.5 Hz spike and slow wave, slow background	Y
Dravet Syndrome (DS)*	SCNA1 Mutation	< 6-12 months (w Fever)	Myoclonic, focal	Slow then polyspikes	Y
Infantile Spasms (IS)	Cryptogenic/Symptomatic/ TSC	3-7 months	Spasms of limbs, trunk +/- focal seizures	hypsarrhythmia	Y>>N

*Severe Myoclonic Epilepsy of Infancy (SMEI)

Cannabidiol Parental Surveys

	Source	N (Ages)	Epilepsy Syndrome (%)					CBD Dose (mg/kg/d)	%Reduction in Seizures	% Seizure Free
			LGS	DS	IS	MAE	Other			
Porter [1] (2013)	Facebook	N=19 (2-16y)	5	68	-	21	6	0.5-28	84	11
Hussain[2] (2015)	Online Forum	N=117 (3-10y)	21	13	39	4	23	2.9-7.5	85	14
Press[3] (2015)	Emails/ Calls	N=75 (0.5-18y)	12	17	-	4	67	NA	57	0.3
Aguirre-Velazquez[4] (2017)	Emails/ Facebook	N=43 (0.8-18y)	47	0	19	2	32	1.6-9	81	16

1. Epilepsy Behav 2013;29:574-7, 2. Epilepsy Behav 2015;45:49-52.; 3. Epilepsy Behav 2015;47:138-41.; 4. Neurol Res. Int. 2017; 2017; 2017: 2985729.

Cannabidiol Parental Surveys Treatment Effects

Positive

- Improved Mood
- Improved Sleep
- Improved Alertness
- Decreased Self Stimulation
- Efficacy for most seizure types

Negative

- Drowsiness
- Fatigue
- Change in appetite
- GI Symptoms

1. Epilepsy Behav 2013;29:574-7, 2. Epilepsy Behav 2015;45:49-52.; 3. Epilepsy Behav 2015;47:138-41.; 4. Neurol Res. Int. 2017; 2017; 2017: 2985729.

CBD Prospective Studies-Design

	Study	Inclusion	CBD Dose (mg/kg/d)	Duration	Outcome
Devinsky[1] Mixed (2016)	OL	≥4 motor sz in 4 wks	Max 50	12 weeks	Change in motor sz
Devinsky[2] DS (2017)	DBPC	DS ≥1AED, >4 sz in 4 wks	20	2 week titration 12 weeks maint.	Change in convulsive sz
GW Pharma[3] LGS (2016)	DBPC	Uncontrolled LGS ≥1 AED	20	2 week titration 12 weeks maint.	% Change in Drop Attacks
GW Pharma[4] LGS (2016)	DBPC	Uncontrolled LGS >1 AED	10 or 20	2 week titration 12 weeks maint.	% Change in Drop Attacks
Hess[5] TSC (2016)	OL	Uncontrolled TSC >1 AED	Max 50	12 months	% Change in Sz %Responder

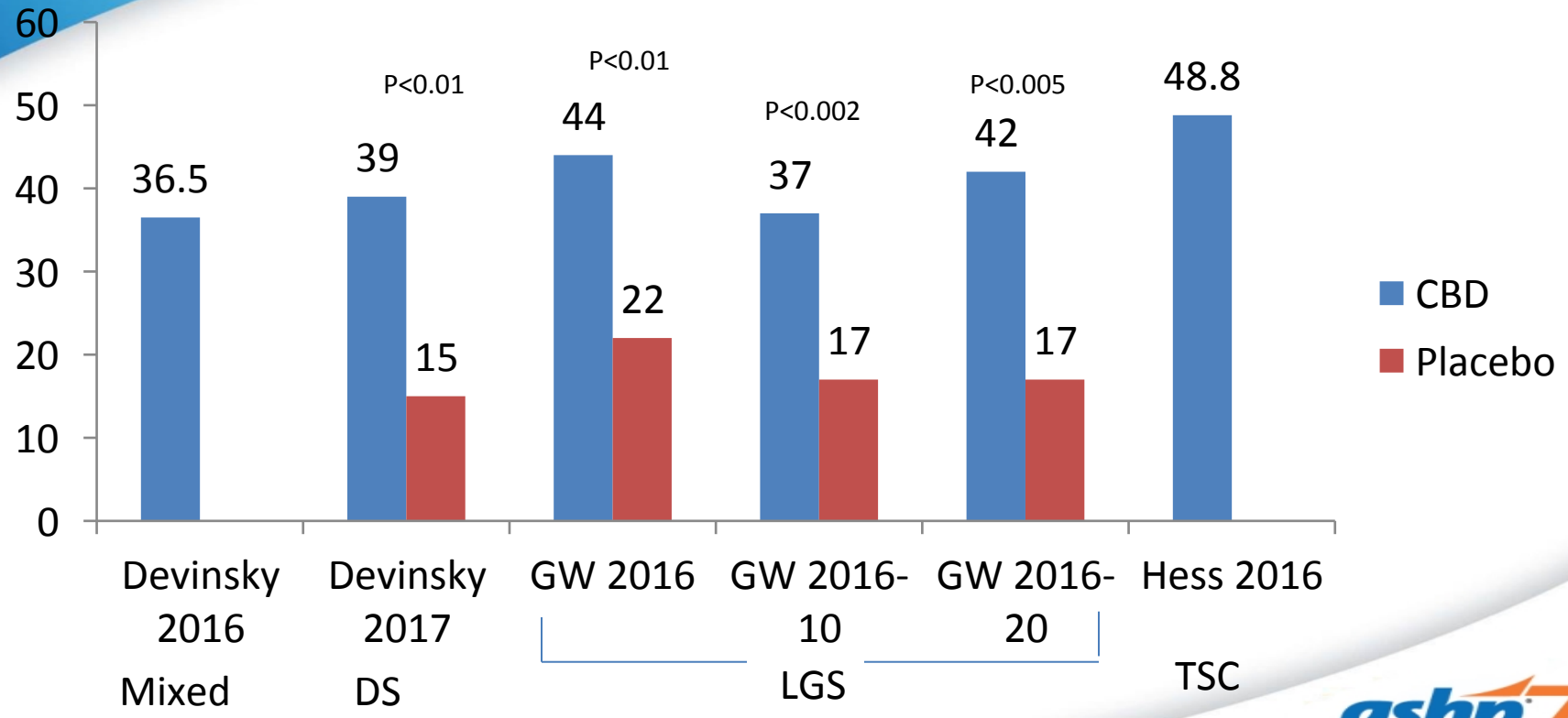
1. Lancet 2016; 15:270-8. ; 2. NEJM 2017; 376: 2011-20.; 3. ,4, GW Pharma /Epilepsy Behav 2017:70:341-8.; 5. Epilepsia 2016; 57:1617-24.

CBD Prospective Studies-Population

	N	Age ,yrs Median (R)	Median /Mean Concurrent AEDs	Mean CBD Dose (mg/kg/d)
Devinsky[1] (2016)	137	10.5 (0.9-20.2)	3 (0-7)	22.9 ±9.1 30% at 50 mg/kg/d
Devinsky[2] (2017)	120	9.1(2.5-18)	3 (1-5)	20 mg/kg/d
GW Pharma[3] (2016)	171	15 (2-55)	3	20 mg/kg/d
GW Pharma[4] (2016)	225	16 (2-55)	3	10 or 20 mg/kg/d
Hess[5] (2016)	18	14 (2-31)	3 (1-7)	36.2±12.5 28% at 50 mg/kg/d

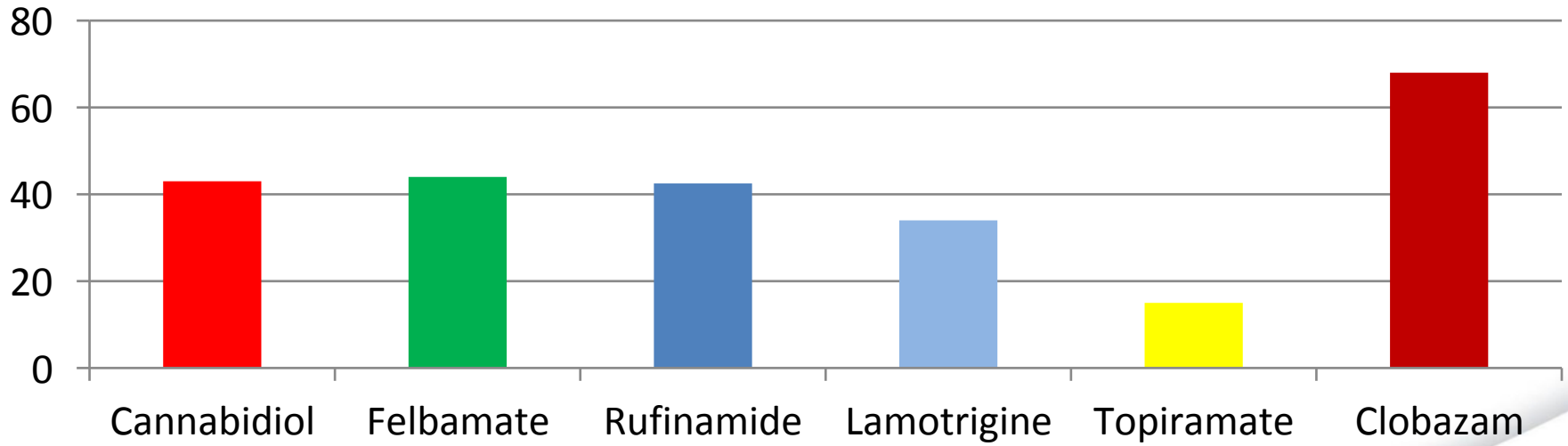
1. Lancet 2016; 15:270-8. ; 2. NEJM 2017; 376: 2011-20.; 3. ,4, GW Pharma /Epilepsy Behav 2017:70:341-8.; 5. Epilepsia 2016; 57:1617-24.

CBD Prospective Studies Seizure Reduction from Baseline



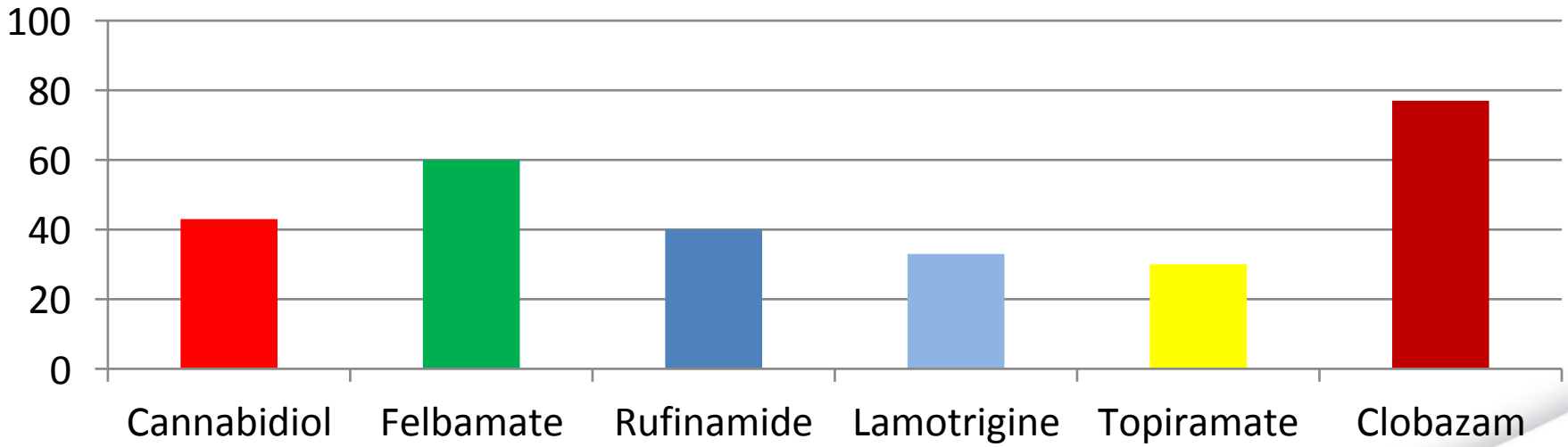
1. Lancet 2016; 15:270-8. ; 2. NEJM 2017; 376: 2011-20.; 3. ,4, GW Pharma /Epilepsy Behav 2017:70:341-8.; 5. Epilepsia 2016; 57:1617-24.

LGS Reduction in Motor-Atonic Seizures



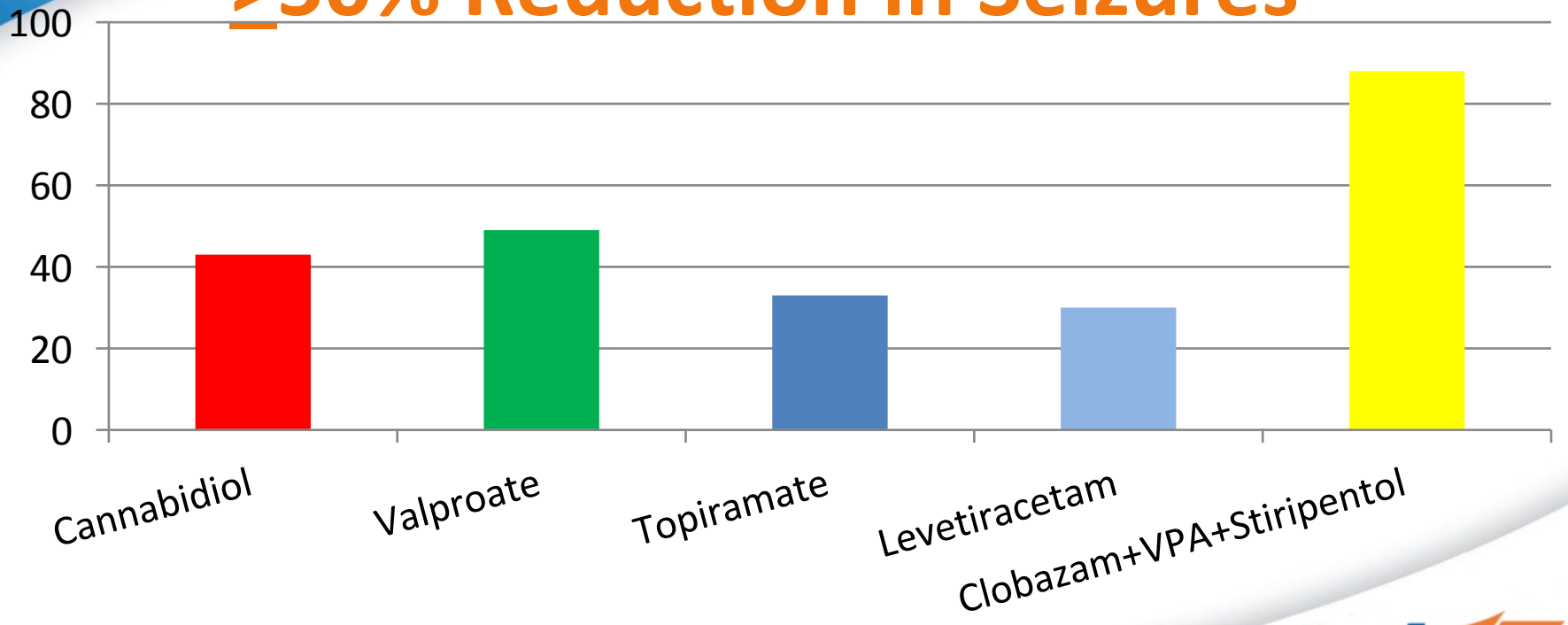
GW Pharma /Epilepsy Behav 2017:70:341-8.; NEJM 1993;328:29-33; Neurology. 2008; 20;70; 1950-8.; NEJM 1997;337:1807-17., Neurology 1999;52:1882-7., Neurology 2011;77:1473-51.

LGS Responder Rate
≥50% Reduction in Seizures



GW Pharma /Epilepsy Behav 2017:70:341-8.; NEJM 1993;328:29-33; Neurology. 2008; 20;70; 1950-8.; NEJM 1997;337:1807-17., Neurology 1999;52:1882-7., Neurology 2011;77:1473-51.

Dravet Syndrome
≥50% Reduction in Seizures



NEJM 2017; 376: 2011-20, Epilepsy Research. 2015; 109:81-89.

CBD Adverse Effects

>10% Difference vs Placebo

- Somnolence
- Drowsiness
- Fatigue
- Lethargy
- Diarrhea*
- Vomiting*
- Decreased Appetite*

>10% of CBD Treated Patients

- Upper respiratory tract infection
- Pyrexia
- Status Epilepticus

*May be related to the drug vehicle (oil based)

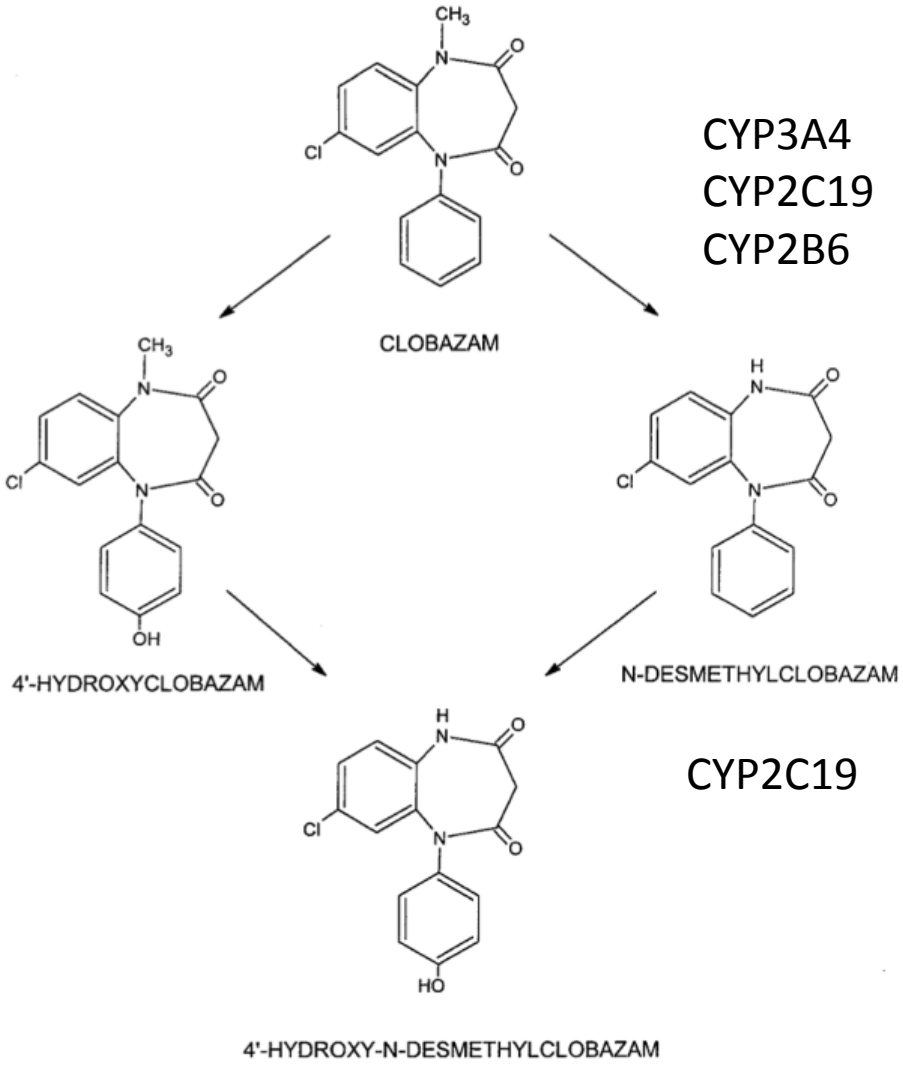
1. Lancet 2016; 15:270-8. ; 2. NEJM 2017; 376: 2011-20.; 3. ,4, GW Pharma /Epilepsy Behav 2017:70:341-8.; 5. Epilepsia 2016; 57:1617-24.

Drug-Drug Interactions
CBD inhibits CYP3A4 and CYP2C9/19

- Clobazam
  - Clobazam (↑60%)
  - n-CLB (↑500%)
- Valproate¶-Dynamic effected increased LFTs
- Warfarin
- Esclicarbazepine**
- Topiramate**
- Zonisamide**

¶Dynamic Effect Only. **Clinical significance is not yet defined

Epilepsia 2015;56:1246-51. Epilepsia. 2017, 58: 1586-92., AES Abst. 2016; 2.204



Drug Interaction Cannabidiol and Clobazam

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CBD Dosing Review*

Starting Dose	2.5-5 mg/kg/day
Weekly Increase	5 mg/kg
Target Dose	20 mg/kg/day
Maximum Dose	50 mg/kg/day

* May also titrate as rapidly to goal over 2 weeks

Available as 100 mg/mL oral solution-sesame seed and alcohol .

Which of the following is Cannabidiol demonstrated efficacy for?

- A. Doose Syndrome
- B. Infantile Spasms
- C. Lennox Gastaut Syndrome
- D. Dravet Syndrome

JB is a 6-year old with LGS (atonic seizures 10/day, Atypical Absence 75/day and complex partial seizures). Medications include clobazam, valproate, topiramate and is on the ketogenic diet. The parents ask about using medical marijuana in their child and prescribing it.

Which of the following statement(s) are correct?

- A. High THC: CBD ratio products are preferred for use in epilepsy.
- B. Currently, medical marijuana can only be recommended and not prescribed by MDs in most US.
- C. Medical Marijuana only is indicated for complex partial seizures in adults.
- D. THC and cannabidiol produce a synergistic anticonvulsant response.

You start JB on CBD and he becomes lethargic and his parents mention him sleeping all the time. What is the most likely way to ameliorate the symptoms?

- A. Decrease the cannabidol dose.
- B. Decrease the valproate dose.
- C. Decrease the clobazam dose.
- D. Decrease the topiramate dose.

You check JBs labs and notice his Liver Function Tests are 5-6-times upper normal limits, What is the most likely way to ameliorate the symptoms?

- A. Decrease the cannabidol dose.
- B. Decrease the valproate dose.
- C. Decrease the clobazam dose.
- D. Decrease the topiramate dose.
- E. Do not change anything.

Take Homes

- Cannabinoids represent a new class of antiepileptic medications.
- Cannabidiol is lacks the euphoria of THC containing products and demonstrates Class I, II, III level of evidence for treatment of Lennox Gastaut, Dravet Syndromes
- Common side effects include: Sedation, diarrhea, decreased appetite, nausea vomiting
- Cannabidiol and Clobazam-drug interaction can be significant

BREATHE!

Is everyone as dizzy as we are????

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ashp MIDYEAR 2017
Clinical Meeting & Exhibition

Evidence-Based Updates: Current Topics in Pediatrics

Eloise D. Woodruff, Pharm.D., BCPPS
Clinical Pharmacy Specialist, Neonatal Intensive Care Unit
Children's Hospital of The King's Daughters
Norfolk, Virginia

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Ductus Arteriosus (DA)

- Essential structure during fetal circulation
  - DA diverts blood from the pulmonary artery to the descending aorta
  - Blood flows from the aorta → pulmonary vein→ bypassing the lungs in utero
  - Patency is maintained *in utero* by low fetal P_aO_2 and high levels of circulating prostaglandins (PGE_2)
  - Creates a left-to-right shunt

Dice JE, Bhatia J. *J Pediatr Pharmacol Ther.* 2007; 12:138-146.
Scneider D, Moore J. *Circulation*. 2006; 114: 1873-1882.
De-Sanctis E, Clyman R. Patent Ductus Arteriosus: pathophysiology and management. *J Perinatol.* 2006; 26:14-18.

Ductus Arteriosus (DA)

Phase I of Spontaneous PDA Closure	**<u>Immediately after birth:</u>** 1. Systemic vascular resistance increases → constricts DA 2. Decrease in pulmonary vascular resistance 3. Right ventricle output enters the circulation → incr. P_aO_2 → PGs are metabolized in the lungs → circulating PGE_2 decrease 4. Cellular migration of the medial smooth muscle of the DA wall
	✓ Results in **"functional closure"** ✓ Commonly occurs within 12-72hr after birth
Phase II of Spontaneous PDA Closure	**<u>Usually completed by 2-3 weeks of life:</u>** 1. Infolding of the endothelium 2. Replacement of muscle fibers with fibrotic pieces
	✓ Results in **"structural closure"** ✓ Seals the DA closed permanently ✓ Commonly occurs within 12-72hr after birth

Clyman R. *Biol Neonate 2006; 89:330-335.*

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Patent Ductus Arteriosus (PDA)

- Occurs when the DA fails to close spontaneously shortly after birth
- Incidence: correlates inversely with gestational age (GA) and low birth weight (BW)
  - Term infants 1:2000 births (0.02-0.006%)
  - 10% (GA 30-37 weeks); 80% (GA 25-28 weeks); 90% born ≤ 24 weeks GA
  - Female to male ratio is 2:1
  - Symptomatic PDA (< 1000 g BW) at 72hrs: 48%
- PDA accounts for 5-10% of all congenital heart disease at birth

Dice JE, Bhatia J. *J Pediatr Pharmacol Ther.* 2007; 12:138-146.
Clyman RI. *New Engl J Med* 2000;343:728-739
Scneider D, Moore J. Patent Ductus Arteriosus. *Circulation*. 2006; 114: 1873-1882.
Overmeire B, Chemtob S. The pharmacologic closure of the patent ductus arteriosus. *Semin Fetal Neonat M.* 2005; 10:117-184.

Infants at Higher Risk with PDA

- Preterm infants with moderate to large left-to-right shunt
  - Higher mortality than those without PDA

Increased risk for complications including:	
Pulmonary edema	Abnormal cerebral blood flow
Intraventricular hemorrhage	Renal dysfunction
Bronchopulmonary dysplasia	Intolerance of enteral feeding
Necrotizing enterocolitis	Prolonged mechanical ventilation
Pulmonary Hypertension	Heart failure

Signs and Symptoms of PDA

Physical Exam and X-ray	Clinical Symptoms
Systolic murmur ✓ Size of PDA related to loudness; ✓ degree of shunting	Unexplained acidosis
Hyperdynamic precordium	Feeding intolerance, apnea/bradycardia with feeds
Bounding pulses with widened pulse pressure	Renal insufficiency / dysfunction
Pulmonary Edema	Increased ventilation support
Tachypnea, incr. WOB, tachycardia	Delayed hypotension
Enlarged cardiac silhouette	Irritability, fatigue

Dice JE, Bhatia J. *J Pediatr Pharmacol Ther.* 2007; 12:138-146.
Teixeira L, McNamara P. *Acta Paediatr.* 2006; 95:394-403.
Scneider D, Moore J. Patent Ductus Arteriosus. *Circulation*. 2006; 114: 1873-1882.
De-Sanctis E, Clyman R. *J Perinatol.* 2006; 26:14-18.

Diagnosis of PDA

- Signs and symptoms may be present
  - However, low sensitivity for diagnosis
  - Murmur and bounding pulses may or may not be present with a PDA
- **Echocardiogram** is the Gold Standard for diagnosing PDA
- Criteria for Symptomatic PDA:
  - Ductal diameter > 1.5 mm within the first 30hrs of life
  - Left atrial/aortic root ratio > 1.5
  - Pulsatile transductal flow < 1.8 m/sec
  - Reverse end-diastolic flow in the descending aorta/mesenteric artery

Reller M, Lorenz J, Kotagal U. *Pediatrr Cardiol.* 1985;6:17-24.
Madhulika K, Gokulakrishnan G, Price J et al. *Pediatr* 2015; 135: e510-525.

Who should we treat?

- Data published in the 1980s and 1990s previously led to aggressive pharmacologic and surgical treatment

Tiny/"silent" PDA	✓ Asymptomatic
Small PDA	• High resistance across the DA • Minimal increase in pulmonary blood flow • Typically asymptomatic • Murmur heard on routine physical exam
Moderate PDA	✓ Symptoms of heart failure ✓ Poor feeding, tachypnea, irritability
Large PDA	• Symptomatic • Irritable, poor feeding, failure to gain weight, incr. respiratory effort, tachypneic • Left ventricular failure with pulmonary edema

"…there is still uncertainty and controversy about the significance, evaluation, and management of patent ductus arteriosus in preterm infants."

"… A large body of evidence now exists demonstrating that early, routine treatment to induce closure of the ductus in preterm infants, either medically or surgically, in the first 2 weeks after birth does not improve long-term outcomes (level of evidence: 1A). **AAP 2016**

Benitz WE and COMMITTEE ON FETUS AND NEWBORN. *Pediatrics. 2016; 137 (1): e20153730.*
Clyman R, Couto J, Murphy G. *Semin Perinatol.* 2012 April; 36(2): 123-129.

Is it a "hemodynamically significant" PDA (hsPDA)?

- ECHO confirmed; size of PDA determined; direction of shunting
  - Moderate-large PDA
- Hemodynamically significant PDA in preterm infants
  - Presence of systolic murmur, widened pulse pressures, prominent bounding pulses
- Asymptomatic patients with left heart enlargement or volume overload
- Deterioration in respiratory status
  - Increased ventilator support and oxygen demand
  - Difficulty to wean from ventilator
- Decreased organ perfusion leading to organ system dysfunction
- Prolonged symptom duration→ may lead to increased risk of BPD
- Serum biomarker (Brain Natiuretic Peptide-BNP)

Benitz WE and COMMITTEE ON FETUS AND NEWBORN. *Pediatrics. 2016; 137 (1): e20153730*
Dice JE, Bhatia J. *J Pediatr Pharmacol Ther.* 2007; 12:138-146.
Sanjeev S, Pettersen M, Lua J, et al. *J Perinatol* 2005; 25: 709-713.

To Treat or Not to Treat? That is the question…

- Is the patient hemodynamically unstable?
- Is it possible that the PDA will close on it's own?
  - 34% of ELBW infants demonstrated spontaneous PDA closure
- Does your patient meet criteria to use a pharmacologic agent?
- Is it safe to use medication to close the PDA in this patient?
- Are there risk factors or contraindications that may limit you from using a pharmacologic agent?
- Which medication(s) are available on your hospital formulary?
- Is the drug of choice on shortage or backorder?

Husted H, Raithel D. *PPAG Advocate Newsletter,* February 2016
Koch J, Hensley G, Roy L, et al. *Pediatrics 2006; 117: 1113-1121*

POLL #1: Which agent is used as the FIRST LINE treatment of PDA at your institution ?

A. Indomethacin
B. Ibuprofen
C. Acetaminophen
D. We don't treat many PDAs medically any more

Current Treatment Strategies

Conservative Approach --Watch, wait and monitor -- Supportive therapies alone	✓ Fluid restriction ✓ Diuretic use ✓ PDA may close spontaneously ✓ Minimized risk from intervention ✓ Con: decreased responsiveness to COX inhibitors if treatment needed
Pharmacologic Closure --Cyclooxygenase (COX_2) inhibitors	**Indomethacin or Ibuprofen:** ✓ COX_2 Inhibitors ✓ High success rate ✓ Con: side effects, renal dysfunction, oliguria, GI bleed/perforation, NEC, hyperbilirubinemia
--Prostaglandin synthesis inhibitor	**Acetaminophen** ✓ Competitive rate of closure ✓ Alternative if renal dysfunction present or contraindications ✓ Con: hepatotoxicity (<5%), elevated LFTs –often return to baseline post-Tx
Surgical Ligation	**Ligation with thoracotomy:** High success rate (90-95%) Option after pharmacologic failure or if medication is contraindicated Cons: Risk of bleeding, vocal cord paralysis, pneumothorax, death, poorer neurologic outcomes

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POLL #2: When is it appropriate to treat a hsPDA?

A. Moderate-large hsPDA with L→R shunt
B. Presence of systolic murmur, widened pulse pressures, prominent bounding pulses
C. Deterioration in respiratory status or end organ dysfunction present
D. Never treat hsPDAs medically or surgically
E. A, B, and C

Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates

El-Mashad A, El-Mahdy H, El Amrousy D, et al. *Eur J Pediatr 2017. 176: 233-240*

	Randomized prospective study: NICU at Tanta University Hospital
Number of patients	300 preterm infant ✓ All infants underwent ECHO within first 48hr of life to determine PDA and cranial u/s before and after treatment to detect IVH
Inclusion	• Preterm infants < 28 weeks GA • < 1500 g in first 2 weeks of life • Hemodynamically significant PDA diagnosed with ECHO and clinical exam ✓ Written informed consent ✓ Randomized into 1 of 3 groups (APAP, IBU or INDO)
Exclusion	• Preterm infants with major congenital anomalies, life threatening sepsis, NEC, IVH, oliguria (UOP < 1 ml/kg/hr x 24hr), SCr > 1.5 mg/dL, PLT < 100,000/ml, complex congenital heart or ductal dependent heart lesion

Randomization	• Random number list generated by QuickCalc GraphPad Software Inc. • Neonate enrolled by nonblinded MD not part of study
Blinding	• All treatment staff • Outcome assessors • Not completely blinded—different dosing/dose volume per group
Groups	**1.** **Paracetamol** (100 neonates): 15mg/kg IV x 1 over 30mins followed by 15mg/kg q6hr IV x 3 days. Dose diluted to 2mg/ml if subject < 1000 g **2.** **Ibuprofen** (100 neonates): 10 mg/kg IV x1 followed by 5 mg/kg x 2 days **3.** **Indomethacin** (100 neonates): 0.2 mg/kg IV over 30 mins q12hr x 3 doses

El-Mashad, El-Mahdy, El Amrousy, et al. *Eur J Pediatr. 2017; 176: 233-240*

Criteria of significant PDA	• ECHO: Left atrial dilation, diastolic turbulence on Doppler, duct diameter > 1.5 mm, reverse end diastolic flow • Clinical exam: Tachycardia, bounding pulse w/WPP, active precordium, continuous murmur, acidosis, failure for RDS to resolve in 2-7 days, CO_2 retention
Echocardiogram	• Reviewed by Pediatric Cardiologist: blinded to study and treatment group • Completed prior to treatment and 3 days after treatment • Closure = no flow through duct
Repeat Treatment Course	• No crossover treatment • If PDA didn't close with first course, same drug used for 2nd course

El-Mashad, El-Mahdy, El Amrousy, et al. *Eur J Pediatr. 2017; 176: 233-240*

Primary Outcome	• To compare the efficacy of each drug in closing a hsPDA in preterm infants with 1 or 2 courses of treatment
Secondary Outcome	• To compare side effects of medications used to treat hsPDA in preterm infants

Baseline demographics, statistics and ECHO results we similar among the groups and were not statistically different

	Group 1: APAP	Group 2: IBU	Group 3: INDO	ANOVA *P* value
Gestational Age	26 ± 1.9	25 ± 2.1	26 ± 2.1	0.969
Sex (m:f)	60:40	80:20	60:40	0.532
Weight (kg)	1.1 ± 0.13	1 ± 0.12	1.1 ± 0.14	0.682
Age at start of Tx (days)	2.7 ± 4.4	3.2 ± 4.2	3.1 ± 5.1	0.968
Size of PDA (diameter)	2.7 ± 0.6	2.8 ± 0.6	2.7 ± 0.7	0.907
SCr	0.56 ± 0.07	0.55 ± 0.07	0.52 ± 0.06	> 0.05
Daily UOP	2.25 ± 0.41	2.16 ± 0.44	2.28 ± .036	>0.05

El-Mashad, El-Mahdy, El Amrousy, et al. *Eur J Pediatr. 2017; 176: 233-240*

Results

Before Treatment: no difference in SCr, BUN, bilirubin, SGPT, SGOT, PLT, Hgb, or UOP ($P > 0.05$)

After Treatment: statistical significance in ALL groups comparing SCr, BUN, bilirubin, PLT, UOP ($P < 0.05$); No SS in SGPT, SGOT, Hgb

SCr & BUN: SS in Groups 2 & 3; INDO > IBU (P_{SCr}= <0.001, P_{BUN}= 0.000)

Hyperbilirubinemia: SS in Group 2 (IBU); (P= <0.012)

Decreased PLT & UOP: SS in Groups 2 & 3; INDO > IBU (P_{PLT}= <0.001, P_{UOP}= <0.001); no thrombocytopenia in Group 1 (APAP)

El-Mashad, El-Mahdy, El Amrousy, et al. *Eur J Pediatr. 2017; 176: 233-240*

Results

Significant reduction > in closed PDAs: PIP, FiO_2, OI and duration of ventilation (P= <0.001)
No SS between groups regarding PDA closure success/failure
Closure $_{\text{course 1}}$: Group 1 (80%), Group 2 (77%), Group 3 (81%); ($P_{course\ 1}$ = 0.868)
Closure $_{\text{cumulative}}$: Group 1 (88%), Group 2 (83%), Group 3 (87%); ($P_{course\ 2}$ = 0.781)
Surgical Ligation: Group 1 (12%), Group 2 (17%), Group 3 (13%); (P = 0.674)
GI Bleed: SS in Groups 2 & 3; Group 1 (1%), Group 2 (7%), Group 3 (10%); (P=0.007)

El-Mashad, El-Mahdy, El Amrousy, et al. *Eur J Pediatr. 2017; 176: 233-240*

Study Summary

- It is better to close a hsPDA in preterm neonates to decr. complications
- Acetaminophen is an alternative treatment for hsPDA
- PDA closure: APAP = IBU = INDO
- APAP is equally effective as INDO, IBU
- Closure rate using APAP was similar to IBU and INDO
- Incr. SCr/BUN w/oliguria: INDO > IBU; unaffected in APAP
- Significant hyperbilirubinemia in IBU
- No significant difference in SGPT/SGOT elevation in all groups
- APAP appears to be safe to be considered as treatment for a hsPDA
- Limitation: Not completely blinded because of different doses and dose volume among groups

El-Mashad, El-Mahdy, El Amrousy, et al. *Eur J Pediatr. 2017; 176: 233-240*

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Comparison of Oral Paracetamol versus Ibuprofen in Premature Infants with Patent Ductus Arteriosus: A Randomized Controlled Trial

Dang D, Wang D, Zhang C, et al. PLoS ONE 8(11): e77888.

	Randomized, nonblinded, parallel-controlled, non-inferiority trial The First Hospital of Jilin University, China Between May 21, 2012 – March 30, 2013
Number of patients	249 preterm infants eligible; 160 patients randomized
Inclusion	• Preterm infants ≤ 34 weeks GA • Postnatal age ≤ 14 days • Hemodynamically significant PDA diagnosed with Echocardiogram ✓ Written informed consent ✓ Randomized into 1 of 2 groups; 1:1 ratio
Exclusion	• Infants with ductal dependent heart lesion, life threatening infection (within 24hr), Gr. 3-4 IVH, oliguria (UOP < 1 ml/kg/hr x 8hr), PLT < 50 x10^9/L, hyperbilirubinemia requiring exchange transfusion, active NEC +/- perforation, liver dysfunction

Primary Outcome	• To measure the rates of ductal closure of both paracetamol and ibuprofen after treatment
Secondary Outcome	• To compare side effects of both paracetamol and ibuprofen including oliguria, IVH, increased bleeding, NEC, hyperbilirubinemia, BPD, PVL, ROP, sepsis and death

Randomization	• Randomized 1:1 • Neonate enrolled by nonblinded MD not part of study
Blinding	• Physicians and Nurses were not blinded
Groups	1. **Oral Paracetamol** (80 neonates): 15 mg/kg q6hr x 3 days 2. **Oral Ibuprofen** (80 neonates): 10 mg/kg x 1 then 5 mg/kg after 24 and 48hr. This group also received same volume of D_5W as the paracetamol group (placebo doses)

Dang D, Wang D, Zhang C, et al. PLoS ONE 8(11): e77888.

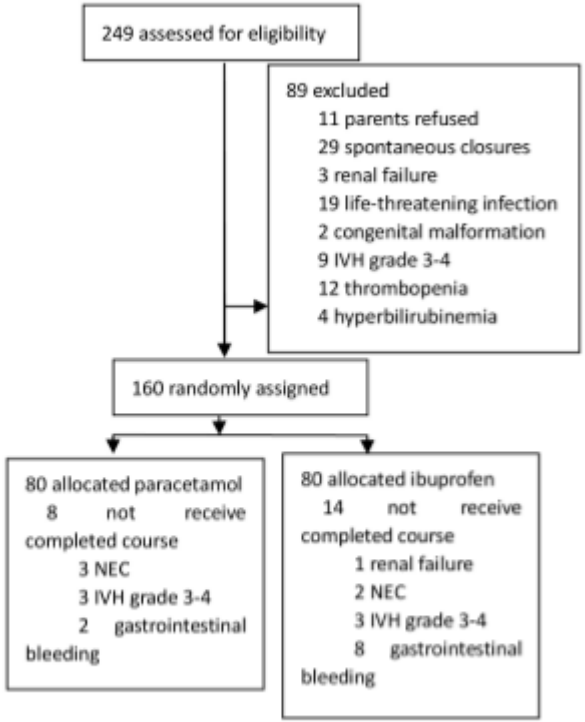

Figure 1. Flow diagram of study infants.
doi:10.1371/journal.pone.0077888.g001

Table 1. Baseline characteristics of study patients.

Characteristic	Ibuprofen group (n = 80)	Paracetamol group (n = 80)	*P* value
Gestational age (week)	30.9±2.2	31.2±1.8	0.474
Birth weight (g)	1531.0±453.5	1591.9±348.6 g	0.342
Gender			0.874
Male	42	41	
female	38	39	
Cesarean birth, n (%)	48(60%)	52(65%)	0.447
PIH, n (%)	33(41.2%)	34(42.5%)	0.873
Antenatal glucocorticoid n (%)	45(56.2%)	47(58.8%)	0.749
Perinatal asphyxia, n (%)	10(12.5%)	11(13.8%)	0.815
Early-onset infection, n (%)	11(13.8%)	10(12.5%)	0.815
Surfactant treatment, n (%)	38(47.5%)	39(48.8%)	0.874
NCPAP, n (%)	52(65.0%)	58(72.5%)	0.306
NSIMV, n (%)	31(38.8%)	29(36.2%)	0.744
SIMV, n (%)	10(12.5%)	12(15.0%)	0.646
IVH grade 1–2, n (%)	11(13.8%)	9(11.3%)	0.633
Mean ductal diameter (mm)	2.36±0.49	2.41±0.44	0.459
Mean max shunt velocity (mm/s)	191.9±30.0	190.8±27.5	0.805
LA/Ao	1.60±0.27	1.67±0.23	0.103

pregnancy induced hypertension syndrome(PIH).
doi:10.1371/journal.pone.0077888.t001

Dang D, Wang D, Zhang C, et al. PLoS ONE 8(11): e77888.

Efficacy

Table 2. Efficacy of paracetamol and ibuprofen treatments.

	Paracetamol group (n = 80)	Ibuprofen group (n = 80)	*P* value
Overall closure rate, n (%)	65(81.2%)	63(78.8%)	0.693
Primary closure rate	45(56.3%)	38(47.5%)	0.268
Secondary closure rate	20 (25%)	25(31.3%)	0.379
Reopening after closure	5(7.7%)	6(9.5%)	0.712
Reclosure rate [a]	4 (80%)	4(66.7%)	0.621
Mean days needed for closure	3.22±0.14	3.71±0.16	0.020

[a]Ductal closure rate after continuing drug treatment among infants with ductal reopening.
doi:10.1371/journal.pone.0077888.t002

The Paracetamol group was non-inferior to the Ibuprofen group

Dang D, Wang D, Zhang C, et al. PLoS ONE 8(11): e77888.

Safety Data

No difference in the incidence of oliguria, renal failure, NEC, IVH, or SCr.
SS seen in the incidence of GI bleeds and hyperbilirubinemia ($P < 0.05$)

Table 3. Safety profiles of paracetamol and ibuprofen treatments.

	Paracetamol group (n = 80)	Ibuprofen group (n = 80)	*P* value
Early outcomes			
Oliguria	6	9	0.42
Renal failure	0	1	0.32
NEC	3	2	0.65
IVH 1–2	6	7	0.77
IVH 3–4	3	3	1
Hyperbilirubinemia	16	28	0.03
Gastrointestinal bleeding	2	8	0.03
Serum creatinine (mg/dl)	61.62±14.53	62.40±15.24	0.74
Late outcomes			
BPD	4	5	0.73
PVL	6	5	0.59
NEC	3	2	0.65
ROP	7	9	0.60
Sepsis	18	23	0.37
Death	10	12	0.65

doi:10.1371/journal.pone.0077888.t003

Study Summary

- Paracetamol has good efficacy and is comparable to Ibuprofen
- PDA closure rate by Paracetamol is comparable to oral Ibuprofen
- Number of days to close hsPDA was shorter in the Paracetamol group (3.22 + 0.14 days vs. 3.71 + 0.16)
- Paracetamol is effective after ductal reopening
- GI bleed and hyperbilirubinemia was significantly lower in the Paracetamol group
- Paracetamol may become the drug of choice for PDA closure due to exhibiting few side effects
- Paracetamol should be considered in patients with hyperbilirubinemia

Dang D, Wang D, Zhang C, et al. PLoS ONE 8(11): e77888.

Case Study

- Baby MCM is a 540 gram product of a 23 and 3/7 week female, born by spontaneous vaginal delivery at an outside hospital to a 22 year-old G2 P0-0-1-0 mother. Pregnancy was complicated with morbid obesity, PCOS, and chronic hypertension. Serologies were all negative. GBS was unknown. She received ampicillin, azithromycin and betamethasone prior to delivery. Rupture of membranes occurred at time of delivery.
- At delivery, the infant had a weak cry. She was pink but apneic. We began PPV with a rate of 40, pressures of 20/5, and initially 21%, which increased to 50%. The infant continued to have irregular respiratory effort, so she was intubated by the resident at 7 minutes of life. She was given 1.35ml of Curosurf via the ETT before 10 minutes of life. The FiO_2 was weaned to 21% and the infant was then transferred on these settings. APGAR score was 3 and 7 at 1 and 5 minutes of age.
- On admission, the infant was placed on volume control with a rate of 40, a tidal volume of 5.5 ml/kg, a PEEP of 5, and 21%. Initial capillary blood gas showed a pH of 7.33, pCo_2 of 43, base deficit of -3 and a blood glucose of 51.
- Physical exam: weight 540 grams, length 31 cm, FOC 21 cm, heart rate 171, oxygen sats 94%, respiratory rate 57, blood pressure 34/22 with a mean of 28.

Case Study

- Over the course of the last 2 weeks, Baby MCM received a repeat dose of Curosurf (0.72ml) for RDS. The infant remains on the ventilator requiring significant support.
- Baby MCM has become progressively hypotensive and acidotic requiring Dopamine @ 10 mcg/kg/hr and stress hydrocortisone at 1 mg/kg q8hr. The nurses have noticed that Baby MCM has tachypnea, tachycardia, a systolic murmur, widened pulse pressure, and a hyperactive precordium. She has been receiving TPN and Intralipids for total fluids of 120 ml/kg/day.
- Current vital signs include: HR 93 bpm, RR 57 bpm, BP 43/11, MAP 23, and capillary blood gas of 7.13, 54, -10. Her BMP today is: Na 136, K 4.3, CL 113, CO2 16, BUN 85, SCr 1.4, GLU 185, TB 9, DB 2.6, TG 84, AST 68, ALT 21. UOP has been < 1 ml/kg/hr x the last 10 hrs.
- Today the Neonatologist ordered an echocardiogram in which it showed a moderate-large PDA with left-to-right shunt.

POLL #3:
Would you choose to medically close this PDA?

A. Medical treatment is not necessary. Continue to “watch” and fluid restrict.
B. Yes, treat this hsPDA with a pharmacologic agent
C. Yes, surgically ligate this hsPDA

POLL #4:
If you chose to treat this PDA, which agent would you recommend?

A. Indomethacin
B. Ibuprofen
C. Acetaminophen
D. Medical treatment is not necessary. Continue to “watch”.

PDA Closure Practice at Children's Hospital of The King's Daughters (CHKD)

- ✓ **Echocardiogram** is obtained when clinical signs & symptoms are present in preterm infant
- ✓ Pharmacologic treatment will be the initial approach if the PDA is "hemodynamically significant"
- ✓ **Intravenous Indomethacin** is our first-line therapy for hemodynamically significant PDAs
- ✓ If an infant presents with renal dysfunction, either **IV Ibuprofen** or **IV Acetaminophen** will be considered

--- decision of agent will be dependent upon the degree of renal insufficiency (SCr, urine output, perfusion)

- ✓ If an infant has failed Indomethacin/Ibuprofen, Attending may consider Acetaminophen course prior to pursuing ligation
- ✓ Oral Acetaminophen may be considered if patient has achieved enteral feeds of 80-100ml/kg/day
- ✓ A repeat ECHO will be obtained after the first course of pharmacologic treatment to determine if an additional course or agent should be used. A repeat ECHO after a second course is not necessary if symptoms have resolved.

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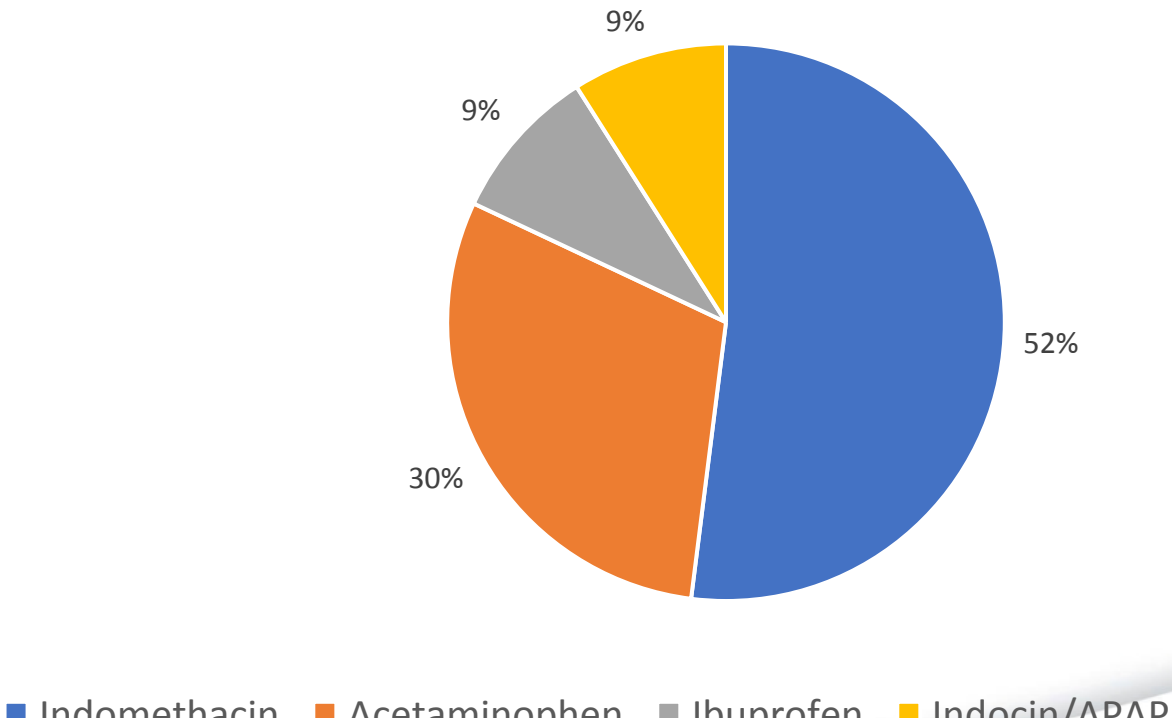
Pharmacologic Treatment of hsPDA at CHKD

January 2016 - June 2017



Medication Use at a Free Standing Children's Hospital

21 patients between January 1, 2016 through June 30, 2017

19 courses were give intravenously; 2 courses of oral Acetaminophen were administered

Agent Used	# of Patients	Percentage of overall use	Gestational Age	Age at Intervention	Success rate: decr. to Small PDA or Full closure
Indomethacin	11	52%	22 - 29 weeks	5 days – 3 weeks/2 days	73% (8)
Acetaminophen	7	30%	23 - 28 weeks	6 days – 14 weeks	71% (5)
Ibuprofen	2	9%	24 weeks, 26 weeks	6 days, 2 weeks/1 day	50% (1)
Indomethacin / APAP*	2	9%	25 weeks 26 weeks	3 week/4 days, 5 weeks/6 days	100% (2)

*Patient given 1-2 courses of Indomethacin prior to administering IV Acetaminophen

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Key Takeaways

- **Key Takeaway #1**
  - Spontaneous closure of the DA occurs in 30-35% of ELBW infants (< 1000g) and 70% VLBW (<1500g) by 1 week of life
  - Treatment should be reserved for those with hemodynamically significant PDAs
- **Key Takeaway #2**
  - Use of a conservative approach or treatment should be made on a case-by-case basis (watch vs. pharmacologic treatment vs. surgery)
- **Key Takeaway #3**
  - Indomethacin and Ibuprofen remain as first-line therapies
  - However, more data have become available showing that Acetaminophen is equally effective without the concerning side effect profile
  - Premature infants with contraindications to NSAIDs may benefit from Acetaminophen as a treatment option for PDA closure or be considered before pursuing surgical ligation

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