WHAT'S HAPPENING NOW WITH NOWS/NAS AND NEONATAL IATROGENIC WITHDRAWAL?

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Disclosures

- I consult for Wolters Kluwer Clinical Drug Information, Inc. for Lexi-drug™ as a member of the Neonatal Advisory Panel.
- I will be discussing off-label use of medications.

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LEARNING OBJECTIVES

- Compare outcomes with Eat-Sleep-Console (ESC) with traditional neonatal opioid withdrawal (NOW)/neonatal abstinence syndrome (NAS) management.
- Discuss practical barriers to ESC implementation.
- Evaluate treatment options and considerations for non-opioid NAS.
- Discuss management of iatrogenic drug withdrawal in neonates, including scoring tools and conversions between agents.

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EAT-SLEEP-CONSOLE FOR NAS/NOWS

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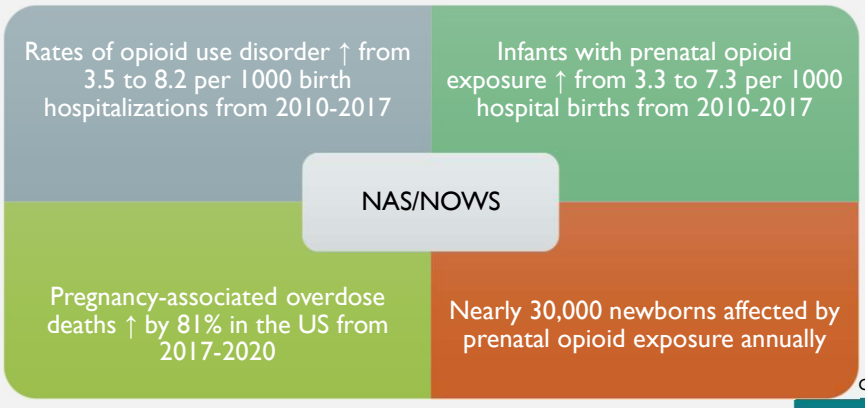
NEONATAL ABSTINENCE SYNDROME (NAS) AND NEONATAL OPIOID WITHDRAWAL SYNDROME (NOWS)



Gold C, et al. *Neoreviews*. 2025.

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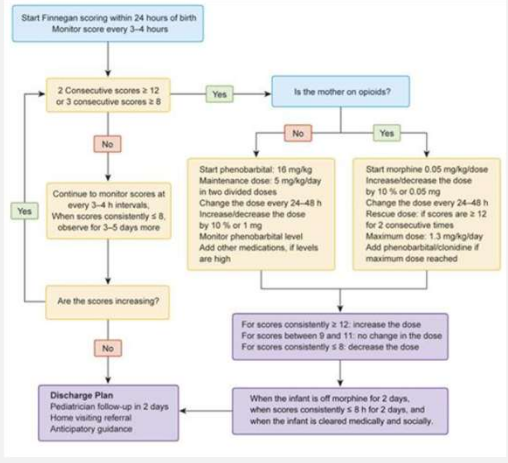
NAS/NOWS MANAGEMENT

- Traditional – Finnegan / modified Finnegan Tool (21 item assessment)

	SCORE
High pitched cry: inconsolable >15 sec. OR intermittently for <5 min.	2
High pitched cry: inconsolable >15 sec. AND intermittently for ≥5 min.	3
Sleeps <1 hour after feeding	3
Sleeps <2 hours after feeding	2
Sleeps <3 hours after feeding	1
Hyperactive Moro	1
Markedly hyperactive Moro	2
Mild tremors: disturbed	1
Moderate–severe tremors: disturbed	2
Mild tremors: undisturbed	1
Moderate–severe tremors: undisturbed	2
Increased muscle tone	1–2
Excoriation (indicate specific area):	1–2
Generalized seizure	8
Fever ≥37.2°C (99°F)	1
Frequent yawning (≥4 in an interval)	1
Sweating	1
Nasal stuffiness	1
Sneezing (≥4 in an interval)	1
Tachypnea (rate >60/min.)	2
Poor feeding	2
Vomiting (or regurgitation)	2
Loose stools	2
≤90% of birth weight	2
Excessive irritability	1–3
Total score	



Kocherlakota P, et al. *Pediatrics*. 2014.

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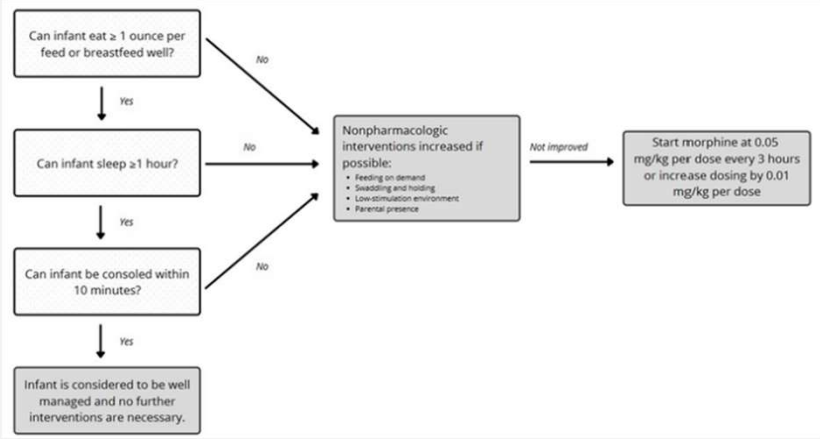
NAS/NOWS MANAGEMENT

- Eat-Sleep-Console (ESC) (3 item assessment)



Cortez J, et al. *Curr Treatment Pediatr.* 2023.

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NAS/NOWS MANAGEMENT

- Eat-Sleep-Console (ESC) (3 item assessment)
  - First-line emphasis on non-pharmacological management
    - Low stimulation environment (dark/quiet)
    - Swaddling to reduce auto-stimulation
    - Early response to infant signals/cues
    - Comforting techniques:
      - Rocking
      - Swaying
      - Pacifier
    - On-demand feeding (ideally breastfeeding)
  - Parents/caregiver ideally take primary role

Gold C, et al. *Neoreviews.* 2025.

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NAS/NOWS MANAGEMENT

- Eat-Sleep-Console (ESC) (3 item assessment)
  - Medication indicated if unable to eat, sleep, and/or console despite maximized non-pharmacological interventions

Morphine 0.05 mg/kg PO q3h PRN

Gold C, et al. *Neoreviews*. 2025.
Grossman MR, et al. *Pediatrics*. 2017.

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NAS/NOWS MANAGEMENT

- Eat-Sleep-Console (ESC) (3 item assessment)
  - Many studies do not provide exact descriptions on how they schedule, escalate, and wean morphine based on ESC tool
  - Original QI study:
    - Morphine 0.05 mg/kg PO q3h PRN – no mention of max number of PRN doses before scheduling
    - Morphine "initiated" or "increased" but not specified
    - Morphine weaned by 10% up to 3x daily but unclear how doses were decreased, remain unchanged, or re-escalated based on ESC tool

Gold C, et al. *Neoreviews*. 2025.
Grossman MR, et al. *Pediatrics*. 2017.

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NAS/NOWS MANAGEMENT

- Eat-Sleep-Console (ESC) (3 item assessment)
  - My center:
    - Morphine 0.04 mg/kg PO q3h PRN
    - Maximum of 3 doses in the "well-baby" postpartum area and then requires admission to NICU for scheduled morphine 0.04 mg/kg PO q3h
    - Escalation by 0.02 mg/kg/dose if still uncontrolled
    - Add clonidine when at morphine 0.12 mg/kg/dose as adjunctive therapy (but still escalate as needed)

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NAS/NOWS MANAGEMENT

- Eat-Sleep-Console (ESC) (3 item assessment)
  - My center:

f. Weaning of pharmacological therapy:
   i. When ESC scores are NO for 24 hours, may initiate morphine wean.
      1. Wean morphine by 10% of current dose.
      2. Continue ESC assessment every 3-4 hours.
         a. All NO – infant remains therapeutic, continue weaning by 10% of peak dose every 24 hours.
            i. Discontinue morphine at 0.02 mg/kg/DOSE PO/NG/OG q3h
         b. 50/50 YES/NO: Hold at current dose and reassess weaning in 24 hours.
         c. All YES – infant becomes symptomatic again.
            i. Consider rescue dose of morphine at 0.02mg/kg/DOSE PO/NG
            ii. AND/OR restart last effective dose of morphine for 24 hours and continue reassessments.
      3. If on clonidine adjunctive therapy:
         a. Decrease dose by 50% starting 24 hours after discontinuation of morphine.
         b. Discontinue clonidine 24 hours after dose reduction.

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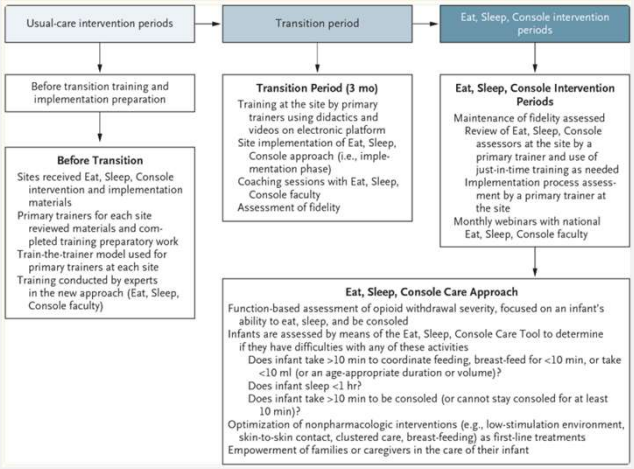
NAS/NOWS MANAGEMENT

- Traditional NAS/NOWS vs ESC – Study of 26 US hospitals (n=837)



Young LW, et al. *N Eng J Med.* 2023.

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NAS/NOWS MANAGEMENT

- Traditional NAS/NOWS vs ESC – Study of 26 US hospitals (n=837)

Characteristic	Usual Care (N = 702)	Eat, Sleep, Console Care Approach (N=603)
Maternal		
Median gravidity (IQR) — no.	3 (2–5)	4 (2–5)
Median parity (IQR) — no.	3 (2–4)	3 (2–4)
Race or ethnic group — no. (%)†		
Non-Hispanic White	462 (66)	447 (74)
Non-Hispanic Black	98 (14)	71(12)
Hispanic	107 (15)	33 (5)
Other	25 (4)	37 (6)
Missing data	10 (1)	15 (2)
Adequate prenatal care — no. (%)‡		
Yes	432 (62)	381 (63)
Missing data	21 (3)	9 (1)
Medication for opioid use disorder — no./total no. (%)		
Any	512/702 (73)	451/603 (75)
Buprenorphine	316/512 (62)	288/451 (64)
Methadone	191/512 (37)	154/451 (34)
Other	0	2/451 (<1)
Unknown	5/512 (1)	7/451 (2)
Missing data	15/702 (2)	20/603 (3)
Metropolitan residence — no. (%)§	586 (83)	547 (91)

Characteristic	Usual Care (N = 702)	Eat, Sleep, Console Care Approach (N=603)
Neonatal		
Female sex — no. (%)	336 (48)	314 (52)
Birth weight — g	3026.4+455.4	3012.8+490.4
Gestational age — wk	38.6+1.3	38.6+1.3
Polysubstance exposure — no. (%)¶	420 (60)	343 (57)

Young LW, et al. *N Eng J Med.* 2023.

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NAS/NOWS MANAGEMENT

- Traditional NAS/NOWS vs ESC – Study of 26 US hospitals (n=837)

Outcome	Unadjusted Analysis (95% CI)*		Adjusted Analysis (95% CI)†			
	Usual Care	Eat, Sleep, Console	Usual Care	Eat, Sleep, Console	Absolute Difference	Estimated Effect
Primary outcome						
Mean time until medical readiness for discharge — days‡	15.3 (13.3 to 17.3)	8.0 (7.0 to 9.0)	14.9 (13.1 to 16.7)	8.2 (7.2 to 9.2)	6.7 (4.7 to 8.8)	Rate ratio, 0.55 (0.46 to 0.65)
Secondary outcomes						
Mean length of hospital stay — days§	13.9 (12.5 to 15.3)	7.8 (7.0 to 8.5)	14.0 (12.7 to 15.3)	7.8 (7.1 to 8.5)	6.2 (4.6 to 7.7)	Rate ratio, 0.56 (0.49 to 0.64)
Percent who received pharmacologic therapy§	53.6 (45.9 to 61.3)	19.2 (14.0 to 24.4)	52.0 (45.4 to 58.7)	19.5 (14.9 to 24.2)	32.5 (25.9 to 39.0)	Relative risk, 0.38 (0.30 to 0.47)
Mean time until initiation ofopioid replacement — hr¶	53.0 (49.1 to 56.8)	71.4 (61.5 to 81.3)	53.0 (48.7 to 57.3)	76.0 (63.0 to 89.0)	23.0 (8.1 to 37.9)	Rate ratio, 1.43 (1.16 to 1.77)
Percent who received adjuvant therapy ‖	21.6 (9.3 to 33.9)	15.6 (5.8 to 25.3)	19.4 (8.5 to 30.4)	15.7 (5.5 to 25.8)	3.7 (−9.8 to 17.3)	Relative risk, 0.81 (0.37 to 1.76)
Total opioid dose before discharge — mg/kg¶	6.9 (4.7 to 9.1)	5.2 (3.2 to 7.2)	7.5 (5.0 to 10.1)	5.3 (3.2 to 7.4)	2.3 (−0.4 to 4.9)	Rate ratio, 0.70 (0.46 to 1.06)
Maximum percentage weight loss — %§	7.5 (7.1 to 7.9)	8.0 (7.5 to 8.4)	7.6 (7.2 to 8.0)	8.0 (7.5 to 8.4)	0.4 (−0.3 to 1.0)	NA**
Feeding type at discharge —%††						
Exclusive maternal breast milk	6.6 (2.8 to 10.4)	13.9 (7.7 to 20.1)	6.3 (2.7 to 9.8)	12.1 (7.2 to 17.1)	5.9 (−0.4 to 12.1)	Relative risk, 1.94 (0.94 to 3.99)
Combination offormula and maternal breast milk	25.6 (18.4 to 32.9)	32.1 (23.6 to 40.5)	26.5 (18.7 to 34.2)	31.3 (23.6 to 39.0)	4.8 (−8.3 to 17.9)	Relative risk, 1.18 (0.75 to 1.87)
Exclusive formula	69.9 (61.4 to 78.4)	58.2 (50.6 to 65.8)	68.3 (62.2 to 74.4)	60.0 (53.7 to 66.8)	8.2 (−1.9 to 18.4)	Relative risk, 0.88 (0.75 to 1.03)
Any direct breast-feeding at discharge (%)††	19.1 (15.2 to 22.9)	35.3 (24.5 to 46.2)	19.5 (15.3 to 23.7)	32.7 (23.2 to 42.2)	13.2 (2.1 to 24.2)	Relative risk, 1.68 (1.13 to 2.48)
Safety outcome						
Composite safety outcome at 3-mo follow-up — %‡‡	15.5 (12.8 to 18.3)	15.0 (10.9 to 19.0)	15.8 (12.3 to 19.2)	16.1 (11.6 to 20.5)	0.3 (−6.2 to 5.5)	Relative risk, 1.02 (0.71 to 1.47)

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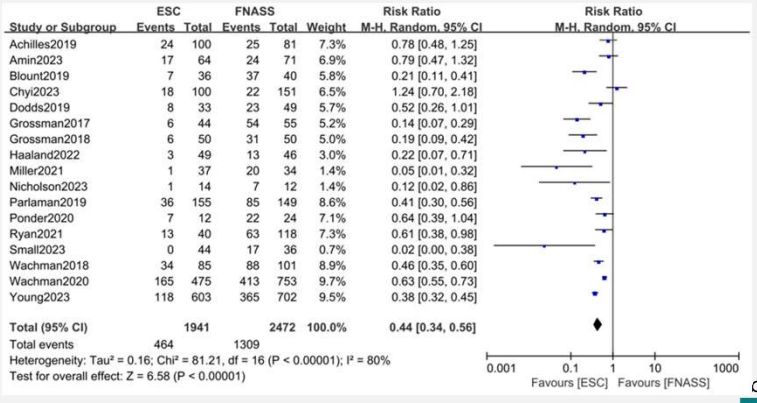
NAS/NOWS MANAGEMENT

- Traditional NAS/NOWS vs ESC – Meta-Analysis
  - Requirement for pharmacotherapy



Chu L, et al. *Frontiers Pediatr.* 2024.

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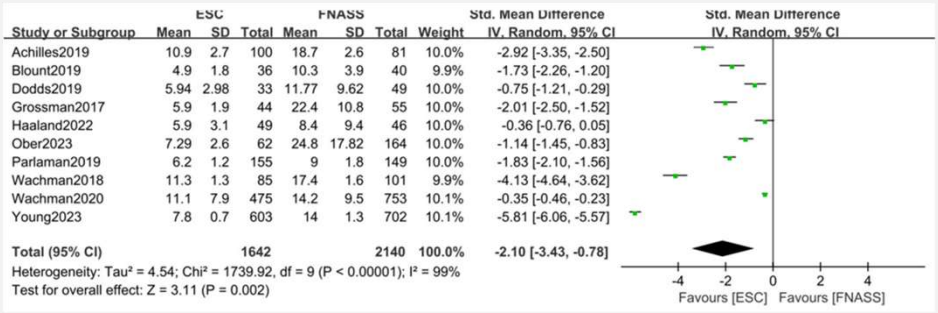
NAS/NOWS MANAGEMENT

- Traditional NAS/NOWS vs ESC – Meta-Analysis
  - Hospital length of stay



Study or Subgroup	ESC Mean	ESC SD	ESC Total	FNASS Mean	FNASS SD	FNASS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Achilles2019	10.9	2.7	100	18.7	2.6	81	10.0%	-2.92 [-3.35, -2.50]
Blount2019	4.9	1.8	36	10.3	3.9	40	9.9%	-1.73 [-2.26, -1.20]
Dodds2019	5.94	2.98	33	11.77	9.62	49	10.0%	-0.75 [-1.21, -0.29]
Grossman2017	5.9	1.9	44	22.4	10.8	55	10.0%	-2.01 [-2.50, -1.52]
Haaland2022	5.9	3.1	49	8.4	9.4	46	10.0%	-0.36 [-0.76, 0.05]
Ober2023	7.29	2.6	62	24.8	17.82	164	10.0%	-1.14 [-1.45, -0.83]
Parlaman2019	6.2	1.2	155	9	1.8	149	10.0%	-1.83 [-2.10, -1.56]
Wachman2018	11.3	1.3	85	17.4	1.6	101	9.9%	-4.13 [-4.64, -3.62]
Wachman2020	11.1	7.9	475	14.2	9.5	753	10.1%	-0.35 [-0.46, -0.23]
Young2023	7.8	0.7	603	14	1.3	702	10.1%	-5.81 [-6.06, -5.57]
Total (95% CI)			**1642**			**2140**	**100.0%**	**-2.10 [-3.43, -0.78]**

Heterogeneity: Tau² = 4.54; Chi² = 1739.92, df = 9 (P < 0.00001); I² = 99%
Test for overall effect: Z = 3.11 (P = 0.002)

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BARRIERS TO ESC IMPLEMENTATION

TABLE 1. Highlighting CFIR Reported Across Studies for Health Care Providers and Patients

Health Care Provider Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Innovation	Potential negative impacts of the ESC model (eg, decreased length of stay potentially leading to parents who are poorly equipped to care for an infant who is withdrawing)[50]	1 (5)	Ease and flexibility of the ESC tool[35,37]	2 (10)
	Nonnumerical value for assessment[43]	1 (5)		
Patient Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Innovation	Limited to only the English language[45]	1 (5)	Empowered by the ESC model philosophy and approach to care[37,49,53]	3 (15)
			ESC tool (eg, fewer interruptions)[49]	1 (5)

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BARRIERS TO ESC IMPLEMENTATION

TABLE 1. Highlighting CFIR Reported Across Studies for Health Care Providers and Patients

Health Care Provider Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Outer setting	COVID-19 pandemic[40,45]	2 (10)	Education to overcome personal biases[40]	1 (5)
	Systemic oppression (eg, racism, stigma, bias, etc)[31,37,45,47]	4 (20)		
	Small patient population[41]	1 (5)		
	Billing challenges[37]	1 (5)	Advocating for culture change[47]	1 (5)
	High turnover staffing rates[41]	1 (5)		
	Social challenges (eg, Child Protection Service involvement)[15]	1 (5)		

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BARRIERS TO ESC IMPLEMENTATION

Patient Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Outer setting	Competing priorities (eg, caregiving needs of other children or jobs)[42,47,48]	3 (15)	Resources to support childcare[37,42]	2 (10)
	Geographical location from the hospital[48]	1 (5)		
	Social factors (eg, systemic racism, segregation, discrimination, stigma, etc)[45]	1 (5)		
	Lack of community support (eg, lack of breastfeeding support)[49]	1 (5)		

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BARRIERS TO ESC IMPLEMENTATION

TABLE 1. Highlighting CFIR Reported Across Studies for Health Care Providers and Patients

Health Care Provider Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Inner setting	Resource limitations (eg, limited private rooms, high turnover rates, limitations in availability for training, limitations in diverse language abilities, time management)[31,38,40,41,43,45]	6 (30)	Education[40,51]	2 (10)
	Systemic oppression (eg, racism, stigma, bias, etc)[15,31,38,41,45]	5 (25)	Efficient communication[40]	1 (5)
	COVID-19 pandemic[40]	1 (5)	Financial support (eg, compensation for training on days off)[52]	1 (5)
	Billing challenges[37]	1 (5)	Cuddlers (additional support for parent relief)[41]	1 (5)
			Advocate for culture change (including strong regional leadership)[41,47]	2 (10)

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BARRIERS TO ESC IMPLEMENTATION

Patient Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Inner setting	Limited hospital supports (eg, availability of rooms, breastfeeding support, childcare)[42,48,49]	3 (15)	Resources to support childcare[42]	1 (5)
	Geographical distance from the hospital[48]	1 (5)		
	Social factors (eg, systemic racism, segregation, discrimination, stigma, etc)[45]	1 (5)	Rooming-in[49]	1 (5)
	Lack of communication (including language barriers and anticipatory guidance of the perinatal period)[49,54]	2 (10)		

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BARRIERS TO ESC IMPLEMENTATION

TABLE 1. Highlighting CFIR Reported Across Studies for Health Care Providers and Patients

Health Care Provider Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Individual	Resource limitations (eg, staff shortages, lack of time)[38,43]	2 (10)	Buy-in from nurses/medical staff[31,41,51]	3 (15)
	Steep learning curve (including lack of confidence and provider discomfort)[40,41]	2 (10)	Education to overcome personal biases[39]	1 (5)
	Bias/attitudes and culture (eg, ethnic variation in implementation)[31,38,41,47]	4 (20)	Interprofessional collaboration (including families)[12,40]	3 (15)
	Language barriers[45]	1 (5)	Holistic view and culture (including nonjudgmental care approach)[12,47]	2 (10)
	Lack of buy-in from Individuals (including staff, leadership, etc)[31,37,43]	3 (15)	Champions[41,46]	2 (10)
	Complexity of pregnant person[41]	1 (5)		

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BARRIERS TO ESC IMPLEMENTATION

Patient Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Individual	Personal distress (including feelings of judgment)[31,47]	2 (10)	Feelings of empowerment[47,49]	2 (10)
	Lack of communication (including language barriers)[49,54]	2 (10)		
	Social factors (eg, individual experience of oppression)[45]	1 (5)		

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BARRIERS TO ESC IMPLEMENTATION

TABLE 1. Highlighting CFIR Reported Across Studies for Health Care Providers and Patients

Health Care Provider Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Implementation	Lack of education/training (including multidisciplinary training)[12,37,38,47]	4 (20)	Education[12,40,41,47,51,52]	6 (30)
	Schedules and education timing[37,40]	2 (10)	Compensation for training[52]	1 (5)
	Lack of support for change[47]	1 (5)	Systematic and collaborative approach to implementation (eg, a phased approach, quality improvement approach with feedback or pre/postreview, use of champions)[12,31,40,41,46]	5 (25)
	Integration into already existing structures[37,43]	2 (10)	Infrastructural and practice changes (eg, staffing, clinical practice updates/changes, structured handoffs, etc)[10,42]	2 (10)
	Lack of parental involvement[15,31,41,47]	4 (20)		
Patient Reported (N = 20)				
CFIR Domain	**Barriers Reported**	**n (%)**	**Facilitators Reported**	**n (%)**
Implementation	Lack of education/preparedness[42,47,49]	3 (15)	Education[42,47]	2 (10)
			Empowered parent engagement[47,49]	2 (10)

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BARRIERS TO ESC IMPLEMENTATION

- Despite barriers, studies demonstrated:
  - Reduced need for pharmacological treatment (n=22/23 studies)
  - Reduced length of stay (n=20/21 studies)

- One study with no change in pharmacological treatment or length of stay identified most likely barriers:
  - Limitations of rooming in
  - Lack of parental presence (rural setting with large geographical distance of parents from hospital)

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BARRIERS TO ESC IMPLEMENTATION

- Common barriers at my institution:
  - Rooming in:
    - Available in "well-baby" post-partum rooms
    - No individual rooms in ICU portion of NICU
    - Limited individual rooms in NICU step-down
  - Breastmilk:
    - Large portion of NAS/NOWS population positive for substance that limit ability to use breastmilk

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BARRIERS TO ESC IMPLEMENTATION

- Common barriers at my institution:
  - Parental involvement:
    - Large volume of NAS/NOWS cases with DCSF involvement and planned discharge of neonate not with parent
    - Difficulty of parent ability to be at hospital:
      - Other children at home with no help for childcare either at home and nothing offered by hospital
      - No free parking at the hospital
      - Distance from hospital (both to rural areas near Chicago or long travel distances by train/bus)

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BARRIERS TO ESC IMPLEMENTATION

- Common barriers at my institution:
  - Cuddlers:
    - Program halted during COVID-19 and slow to restart
    - Limited volunteers
  - Nursing ratios:
    - None guaranteed
    - Often initially a 2:1 but will stepdown to 3:1 or even 4:1 – difficult to provide non-pharmacological care without parental involvement

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BARRIERS TO ESC IMPLEMENTATION

- Successes at my institution:
  - Initial rooming in with parents who can has greatly reduced need for any pharmacological treatment and need for NICU admission
  - Highest dose of morphine needed and time to wean greatly reduced with strong parental involvement
- Areas of improvement:
  - Management for NAS/NOWS neonates with no parental involvement and requiring solely care from NICU staff
  - Use of ESC for non-opioid NAS? (e.g., cocaine)

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NON-OPIOID NAS

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NON-OPIOID NAS

- Many newborns with NAS have both NOWS and other concomitant drug withdrawal
- Some only have NAS from non-opioids → is ESC right for them?

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NON-OPIOID NAS

Drug	Timing of Withdrawal
Alcohol	3-12 hours
Benzodiazepines	3-7 days
Cocaine	Usually not "withdrawal" signs but sometimes neurobehavioral abnormalities/agitation (decreased arousal and physiologic stress) occur at 12 to 48 hours of life
Barbiturates	4-7 days but can range from 1-14 days
Marijuana	Usually no clinical withdrawal signs
Methamphetamines	Usually no withdrawal signs but sometimes neurobehavioral abnormalities (decreased arousal, increased physiologic stress, and poor quality of movement) occur at 48-60 hours
Nicotine	Few Hours
Phencyclidine (PCP)	1-8 days
Selective serotonin reuptake inhibitors (SSRI)	24-72 hours

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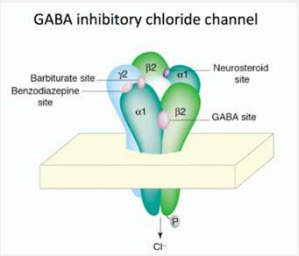
NON-OPIOID NAS



- **Benzodiazepines**
  - BZD use in pregnancy may be prescribed:
    - Alprazolam (Xanax) for anxiety
    - Clonazepam (Klonopin) for anxiety, seizures, myoclonus
    - Clobazam (Onfi) for seizures
  - Withdrawal from BZD can result in seizures – close monitoring and management
  - Treat BZD withdrawal by hitting similar receptors (GABA)
    - My practice: lorazepam 0.05 mg/kg PO q4-6 PRN and scheduled if needed
    - Other options: Phenobarbital (GABA)

Picture: *Trends Pharm Sci.* 2003.

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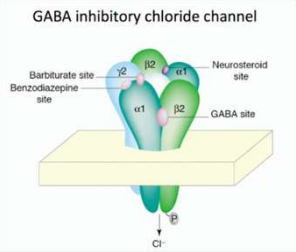
NON-OPIOID NAS



- **Barbiturates**
  - Barbiturate use in pregnancy may be prescribed:
    - Phenobarbital for seizures
    - Primidone for seizures or essential tremor
  - Withdrawal from barbiturates can result in seizures – close monitoring and management
  - Treat barbiturate withdrawal by hitting similar receptors (GABA)
    - My practice: phenobarbital 2.5 mg/kg PO q12h scheduled

Picture: *Trends Pharm Sci*. 2003.

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NON-OPIOID NAS

- **Cocaine**
  - CNS stimulant
  - Onset early in first 2-3 days of life
  - Signs/symptoms:
    - Irritability
    - Hyperactivity
    - Tremors
    - High-pitched cry
    - Excessive sucking
  - Likely drug EFFECT and not drug withdrawal…

Hudak ML, et al. *Pediatrics*. 2012.

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NON-OPIOID NAS

- **Cocaine**
  - Lack of data on pharmacological management
  - My practice:
    - Non-pharmacological first but often inadequate for high cocaine use in pregnancy near time of delivery
    - Manage/treat acute agitation/excitability with CNS depressants
      - Lorazepam 0.05 mg/kg PO q4-6h PRN
      - Clonidine 1 mcg/kg/dose PO q6h scheduled
    - Symptoms typically resolve after 3-5 days
      - If clonidine scheduled, can often wean over 2-3 days to off

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NON-OPIOID NAS

- **Phencyclidine (PCP)**
  - Drug of abuse popular in the 1980s – seeing resurgence of use
    - One study found 65% presented with NAS symptoms after prenatal exposure
  - Similar to cocaine – do symptoms represent drug EFFECT rather than withdrawal?
  - Adult management of PCP withdrawal: BZD PRN (GABA)
  - Treatment data in neonates limited:
    - Phenobarbital used published in two cases in the 1980s
  - My practice:
    - Phenobarbital 2.5 mg/kg PO q12h

Rahbar F, et al. *J Natl Med Assoc*. 1993.
Strauss AA, et al. *Pediatrics*. 1981.
Wachsman L, et al. *Am J Drug Alcoohol Abuse*. 1989.

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NON-OPIOID NAS

- **Selective Serotonin Reuptake Inhibitors (SSRI)**
  - Antidepressants (e.g., sertraline (Zoloft), escitalopram (Lexapro))
  - Drug effect (serotonin syndrome) vs drug withdrawal?
  - Rarely need pharmacological management
    - Consider CNS depressants for acute agitation or severe symptoms (e.g. clonidine, lorazepam, phenobarbital)

Hudak ML, et al. *Pediatrics*. 2012.

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NON-OPIOID NAS

- KEY TAKE-HOME POINT:
  - Treatment for non-opioid NAS is NOT OPIOIDS
    - Opioid + non-opioid: consider morphine + other treatment
    - Non-opioid only: other treatment only
  - Future directions: how do ESC algorithms incorporate this??

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IATROGENIC DRUG WITHDRAWAL

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IATROGENIC DRUG WITHDRAWAL

- AAP 2025 Update:
  - Withdrawal is a syndrome that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance.
  - Tolerance is signaled by requiring a markedly increased dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed.

Adler AA, et al. *Pediatrics*. 2025.

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IATROGENIC DRUG WITHDRAWAL

- AAP 2025 Update:
  - Scoring tools:
    - Sophia Observation Scale (SOS)
    - Withdrawal Symptoms Scale (Withdrawal Assessment Tool), Version 1 (WAT-1)
  - Scoring tools do not differentiate between different agents
    - Unclear which agent is causing withdrawal if weaning multiple

- NOTE: Finnegan is not appropriate for non-newborn withdrawal!!!

Adler AA, et al. *Pediatrics*. 2025.

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IATROGENIC DRUG WITHDRAWAL

- WAT-1 Score
  - Score ≥3 concerning for withdrawal
  - Obtain baseline WAT-1 prior to starting wean and consider alternative goal in patients with an altered baseline neurologic state
  - "State" uses SBS – can apply this to neonatal scores that correlate with "awake and distressed"

	DATE TIME
Information from patient record, previous 12 hours	
Any loose /watery stools	No = 0 Yes = 1
Any vomiting/wretching/gagging	No = 0 Yes = 1
Temperature > 37.8₀C	No = 0 Yes = 1
2 minute pre-stimulus observation	
State	SBS_1 < 0 or asleep/awake/calm = 0 SBS_1 > +1 or awake/distressed = 1
Tremor	None/mild = 0 Moderate/severe = 1
Any sweating	No = 0 Yes = 1
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1
Yawning or sneezing	None or 1 = 0 >2 = 1
1 minute stimulus observation	
Startle to touch	None/mild = 0 Moderate/severe = 1
Muscle tone	Normal = 0 Increased = 1
Post-stimulus recovery	
Time to gain calm state (SBS_1 < 0)	< 2min = 0 2 - 5min = 1 > 5 min = 2
Total Score (0-12)	

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IATROGENIC DRUG WITHDRAWAL

- Risk factors for withdrawal:
  - Drug exposure ≥ 5 days
  - Higher doses
  - May be more difficult to recognize withdrawal for younger patients and those with baseline neurocognitive impairments

- Medications common for withdrawal:
  - Opioids (e.g., fentanyl, morphine, methadone, hydromorphone)
  - BZD (e.g., midazolam, lorazepam, diazepam)
  - Alpha-2 agonists (e.g., dexmedetomidine, clonidine)

Adler AA, et al. *Pediatrics*. 2025.

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IATROGENIC DRUG WITHDRAWAL

- Tapering considerations:
  - Drug dose
  - Duration of drug exposure
  - Underlying efficacy need (e.g., still pain source?)

- Tapering protocol:
  - No universally accepted protocol
  - AAP recommends weaning by 10-20% every 24-48 hours
  - Taper more slowly for medications with longer half-lives
  - Consider "rescue dose" for WAT-1 ≥ 3

Adler AA, et al. *Pediatrics*. 2025.

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IATROGENIC DRUG WITHDRAWAL

- Example taper protocols:

Robertson et al[149]
Conversion of continuous intravenous fentanyl of 7–14 d duration to enteral methadone: 1. By using the current hourly infusion rate, calculate the 24-h fentanyl dose. 2. Multiply the daily fentanyl dose by a factor of 100 to calculate the equipotent amount of methadone (ratio of potencies assumed to be fentanyl: methadone = 100:1). 3. Divide this amount of methadone by 6 (a correction for the longer half-life of methadone) to calculate an initial total daily dose of methadone, and on day 1 provide this amount orally in 4 divided doses every 6 h for 24 h. 4. Day 2: Provide 80% of original daily dose in 3 divided oral doses every 8 h for 24 h. 5. Day 3: Provide 60% of original daily dose in 3 divided oral doses every 8 h for 24 h. 6. Day 4: Provide 40% of original daily dose in 2 divided oral doses every 12 h for 24 h. 7. Day 5: Provide 20% of original daily dose × 1. 8. Day 6: Discontinue methadone. Conversion of continuous intravenous fentanyl greater than 14 d duration to enteral methadone: 1. Repeat steps 1–2 above. 2. Days 1–2: Divide the dose of methadone by 6 (a correction for the longer half-life of methadone) and on day 1 provide this amount orally in 4 divided doses every 6 h for 48 h. 3. Days 3–4: Provide 80% of original daily dose in 3 divided oral doses every 8 h for 48 h. 4. Days 5–6: Provide 60% of original daily dose in 3 divided oral doses every 8 h for 48 h. 5. Days 7–8: Provide 40% of original daily dose in 2 divided oral doses every 12 h for 48 h. 6. Days 9–10: Provide 20% of original daily dose once per day for 48 h. 7. Day 11: Discontinue methadone. For patients on continuous intravenous morphine, proceed as above but do not multiply the daily fentanyl dose by 100, because morphine and methadone are nearly equipotent.

Hudak ML, et al. *Pediatrics*. 2012.

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IATROGENIC DRUG WITHDRAWAL

- Example taper protocols:

Meyer and Berens[150]
Conversion of continuous intravenous fentanyl to intermittent intravenous morphine: 1. By using the target hourly infusion rate of fentanyl, calculate the 24-h fentanyl dose. 2. Multiply the daily fentanyl dose by a factor of 60 to calculate the equipotent dose of morphine (ratio of potencies assumed to be fentanyl: morphine = 60:1). 3. Divide the dose of morphine by 4 (correcting for the longer half-life of morphine) and on day 1 administer this amount intravenously in 6 divided doses every 4 h. 4. Titrate the morphine dose for adequate effect over 12 to 24 h. Conversion of intermittent intravenous morphine to enteral methadone: 1. Multiply the dose of morphine given every 4 h by 2 (ratio of potencies assumed to be morphine: methadone = 2:1) to determine an equipotent amount of methadone. 2. Provide this amount of methadone as an oral dose every 12 h for 3 doses. 3. Double this amount of methadone and provide as a single oral dose per day at bedtime. 4. Provide 90% of the initial dose on day 2, 80% on day 3, etc, so that the last dose of methadone (10% of the original dose) is given on day 10.

Hudak ML, et al. *Pediatrics*. 2012.

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IATROGENIC DRUG WITHDRAWAL

- Example taper protocols:

Protocols at Wolfson Children's Hospital, Jacksonville, Florida

Conversion of continuous intravenous fentanyl >7 d duration to enteral methadone:

1. By using the current hourly infusion rate, calculate the 24-h fentanyl dose.
2. Multiply the daily fentanyl dose by a factor of 100 to calculate the equipotent amount of methadone (ratio of potencies assumed to be fentanyl: methadone = 100:1).
3. Divide this amount of methadone by 8–12 (a correction for the longer half-life of methadone) to calculate an initial total daily dose of methadone (not to exceed 40 mg/day).
4. Days 1–2: Provide the total daily dose of methadone orally in 4 divided doses every 6 h for 48 h. At the time of the second methadone dose, reduce the fentanyl infusion rate to 50%; at the time of the third dose, reduce the fentanyl infusion rate to 25%; and after the fourth methadone dose, discontinue the fentanyl infusion.
5. Days 3–4: Provide 80% of original daily dose in 3 divided oral doses every 8 h for 48 h.
6. Days 5–6: Provide 60% of original daily dose in 3 divided oral doses every 8 h for 48 h.
7. Days 7–8: Provide 40% of original daily dose in 2 divided oral doses every 12 h for 48 h.
8. Days 9–10: Provide 20% of original daily dose once per day for 48 h.
9. Day 11: Discontinue methadone.

Conversion of continuous intravenous midazolam >7 d duration to enteral lorazepam:

1. By using the current hourly infusion rate, calculate the 24-h midazolam dose.
2. Because lorazepam is twice as potent as midazolam and has a sixfold longer half-life, divide the 24 h midazolam dose by 12 to determine the daily lorazepam dose.
3. Divide the calculated lorazepam dose by 4 and initiate every 6 h oral treatments with the intravenous product or an aliquot of a crushed tablet.
4. Wean lorazepam by 10% to 20% per day. The dosage interval can also be increased gradually to every 8 h, then every 12 h, then every 24 h, and then every other day before lorazepam is discontinued.

Hudak ML, et al. *Pediatrics*. 2012.

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IATROGENIC DRUG WITHDRAWAL

- But….They're all different?!

Summary of Conversion Of Intravenous Opioids to Enteral Methadone

1. Tobias et al[147]: Converted 2 patients on morphine (0.1–0.15 mg/kg q3h) and 1 patient on fentanyl (1–2 µg/kg every 1–2 h) to methadone at a starting dose of 0.2 mg/kg per day.
2. Robertson et al[149]: 1 µg/kg per h fentanyl = 0.4 mg/kg per day methadone.
3. Meyer and Berens[150]: 1 µg/kg per h fentanyl = 0.24 mg/kg per day methadone.
4. Wolfson Children's Hospital: 1 µg/kg per h fentanyl = 0.2–0.3 mg/kg per day methadone.

- Data shows ANY protocol is better than no protocol
- My practice:
  - More aggressive dose reduction as reported by Tobias, et al

Hudak ML, et al. *Pediatrics*. 2012.

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IATROGENIC DRUG WITHDRAWAL

- My practice:
  - Wean continuous infusions without conversion to enteral options in those who need to maintain lines for other reasons
    - Avoids potential for withdrawal during dose conversion
  - If switching to enteral agents, I use the more aggressive dose reduction as reported by Tobias which takes into account:
    - Drug potency
    - Drug half-life
    - Drug bioavailability
    - Cross-tolerance

Tobias JD. *Crit Care Med.* 2000.

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IATROGENIC DRUG WITHDRAWAL

- My practice (similar to Tobias, et al):
  - Example conversion:
    - Fentanyl 3 mcg/kg/hr (weight 2 kg) = 144 mcg/day
    - Fentanyl IV : morphine IV potency = 100 mcg:10mg
      - 144 mcg/day IV fentanyl = 14.4 mg/day morphine
    - Fentanyl IV : morphine IV half-life = ~1 hour:~4 hours
      - 14.4 mg/day morphine → 3.6 mg/day morphine
    - Morphine IV : morphine PO bioavailability = 1:3 to 1:2
      - I use 1:2 in neonates (different gastric pH) and 1:3 in older children
      - 3.6 mg/day morphine → 7.2 mg/day morphine in neonates
    - Cross-tolerance reduction by ~25-50% (I typically do ~30%)
      - Final dose: morphine 0.6 mg PO q3h (4.8 mg/day)

Tobias JD. *Crit Care Med.* 2000.

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IATROGENIC DRUG WITHDRAWAL

- Dexmedetomidine to clonidine conversion
  - Recent retrospective NICU study (n=43)
    - Dex 17.4 mcg/kg/day = 0.725 mcg/kg/hr
    - Clonidine 7.8 mcg/kg/day = 1.95 mcg/kg q6h
    - For every dex 0.5 mcg/kg/hr = clonidine 1.3 mg/kg q6h

Table 2. Conversion Results*

Variable	Median (IQR)
Duration of dexmedetomidine, days	18 (11–38)
Dose of dexmedetomidine prior to conversion, mcg/kg/day	17.4 (11.3–24.0)
Initial dose of clonidine, mcg/kg/day	7.5 (4.0–8.5)
Initial conversion factor	0.37 (0.26–0.58)
Post-titration dose of clonidine, mcg/kg/day	7.8 (4.7–9.3)
Post-titration conversion factor	0.42 (0.30–0.62)

Stroder J, et al. *J Pediatr Pharmacol Ther*. 2024.

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IATROGENIC DRUG WITHDRAWAL

- Dexmedetomidine to clonidine conversion - older pediatric literature:
  - Lee 2020 (n=38):
    - dex 1 mcg/kg/hr ~ clonidine 1-2 mcg/kg q6h
  - Liu 2020 (n=22):
    - dex 1.2 mcg/kg/hr ~ clonidine 1-2 mcg/kg q6h
  - Beitz 2019 (n=115):
    - dex 0.9 mcg/kg/hr ~ clonidine 1.1 mcg/kg q6h

Lee MM, et al. *J Pediatr Pharmacol Ther*. 2020.
Liu J, et al. *J Pediatr Pharmacol Ther*. 2020.
Beitz ER, et al. *J Pediatr Pharmacol Ther*. 2019.

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IATROGENIC DRUG WITHDRAWAL

- My practice:

Initial Drug	Converts To:
Fentanyl 1 mcg/kg/hr	Morphine 0.06 mg/kg IV q4h Morphine 0.6 mg/kg PO q3h with feeds Methadone 0.12 mg/kg IV daily divided Methadone 0.24 mg/kg PO daily divided
Morphine 0.01 mg/kg/hr	Morphine 0.04 mg/kg IV q4h Morphine 0.05 mg/kg PO q3h with feeds Methadone 0.08 mg/kg IV daily divided Methadone 0.16 mg/kg IV daily divided
Midazolam 0.1 mg/kg/hr	Lorazepam 0.1 mg/kg IV/PO q6h
Dexmedetomidine 0.5 mcg/kg/hr	Clonidine 1 mcg/kg/dose PO q6h

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IATROGENIC DRUG WITHDRAWAL

- My practice:

Initial Drug	Converts To:
Fentanyl 1 mcg/kg/hr	Morphine 0.015 mg/kg/hr Hydromorphone 0.004 mg/kg/hr
Morphine 0.01 mg/kg/hr	Fentanyl 0.4 mcg/kg/hr Hydromorphone 0.002 mg/kg/hr

- NOTE: Fentanyl → morphine is not the same as morphine → fentanyl!
  - Cross-tolerance reduction in both directions

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KEY TAKEAWAYS

- ESC has demonstrated improvement in reducing pharmacological treatment and length of stay for NOW compared to traditional management.
- Several barriers still need to be addressed for ESC, including management of newborns where parental involvement is limited.
- ESC does not adequately address non-opioid NAS, and the treatment of choice for non-opioid NAS is not opioids.
- Iatrogenic withdrawal should be assessed using appropriate scoring tools, even in neonates.
- Conversion between agents requires additional considerations beyond potency.

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WHAT'S HAPPENING NOW WITH NOWS/NAS AND NEONATAL IATROGENIC WITHDRAWAL?

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