C-notes

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ARTICLE

Developmental Outcomes after Opioid Exposure in the Fetus and Neonate

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Educational gaps

- Opioid exposure (prenatally and post-natally) affects a neonate's brain and neurodevelopment
- What management strategies may help mitigate the neurodevelopmental delays and deficits associated with opioid exposures
- What do we tell parents?

Introduction

- 30.4 million people 15-44y used illicit opiates in 2018[1] (0.6% of global population[2])
- In the US: 333% increase in the number of infants exposed prenatally to opioids in the past 2 decades[3]
- 2019: CDC: 6.6% of surveyed pregnant women reported use of opioids, with 1 in 5 reporting misused[4]: 50-80% of infants will develop NOWS

[1]UN Office of Drugs and Crime. World Drug Report 2020: 2—Drug Use and Health Consequences. New York, NY: United Nations Publication; 2020

[2]Boardman JP, Mactier H, Devlin LA. Opioids and the developing brain: time to rethink perinatal care for infants of opioid-dependent mothers. Arch Dis Child Fetal Neonatal Ed. 2022;107(1):98–104

[3]Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization- United States, 1999-2014. MMWR Morb Mortal Wkly Rep. 2018;67(31):845–849

[4]Ko JY, D'Angelo DV, Haight SC, et al. Vital signs: prescription opioid pain reliever use during pregnancy- 34 U.S. Jurisdictions, 2019. MMWR Morb Mortal Wkly Rep. 2020;69(28):897–903

[5]Substance Abuse and Mental Health Services Administration (SAMHSA). Clinical guidance for treating pregnant and parenting women with opioid use disorder and their infants SAMHSA. 2018.

Introduction

- Another growing problem: frequent use of opioids for sedation and analgesia in NICU.
  - 5 to 15 painful procedures per day[6] : mechanical ventilation, invasive procedures, repeated heel sticks, venipunctures, postoperative pain, acute medical illness.
  - Wide variation in practice and management strategies for neonatal pain with limited options

[6]Simons SH, van Dijk M, Anand KS, Roofthooft D, van Lingen RA, Tibboel D. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. Arch Pediatr Adolesc Med. 2003;157(11):1058–1064

Immature pain pathways and opioid metabolism in neonates

- Insufficient data on neonatal developmental pharmacokinetics and opioid pharmacodynamics
- Pain pathways: μ, δ and κ : Rapid developmental changes during the first 3 weeks after birth[10,11]
- 24 weeks: ascending pain pathways are mature and functioning while the inhibitory descending spinothalamic fibers are still developing[8,9]
- Large extracellular and total body water compartments: higher volume of distribution, differences in metabolism and clearance of opioids.

[8]Simons SH, Tibboel D. Pain perception development and maturation. Semin Fetal Neonatal Med. 2006;11(4):227–231
[9]Mulla H. Understanding developmental pharmacodynamics: importance for drug development and clinical practice. Paediatr Drugs. 2010;12(4):223–233
[10]Nandi R, Beacham D, Middleton J, Koltzenburg M, Howard RF, Fitzgerald M. The functional expression of mu opioid receptors on sensory neurons is developmentally regulated: morphine analgesia is less selective in the neonate. Pain. 2004;111(1-2):38–50
[11]McClain BC, Kain ZN. Procedural pain in neonates: the new millennium. Pediatrics. 2005;115(4):1073–1075

Prenatal opioid exposure – Effects on brain

- μ-opioid receptors and endogenous opioid activity: allows proper fetal brain development, neuronal myelination and neuronal maturation
- Interruption of this process:
  - Improper fetal brain development[18]
  - Potential development of cognitive/behavioral deficits later in life
  - Affect critical phases of brain development
  - Effects on the development of special cognition, acquire/memorize and appropriate use spatial information to performed goal-directed tasks[22]

[18]Velasco B, Mohamed E, Sato-Bigbee C. Endogenous and exogenous opioid effects on oligodendrocyte biology and developmental brain myelination. Neurotoxicol Teratol. 2021;86:107002
[22]Retailleau A, Etienne S, Guthrie M, Boraud T. Where is my reward and how do I get it? Interaction between the hippocampus and the basal ganglia during spatial learning. J Physiol Paris. 2012;106(3-4):72–80

Prenatal opioid exposure - Neurodevelopmental effects

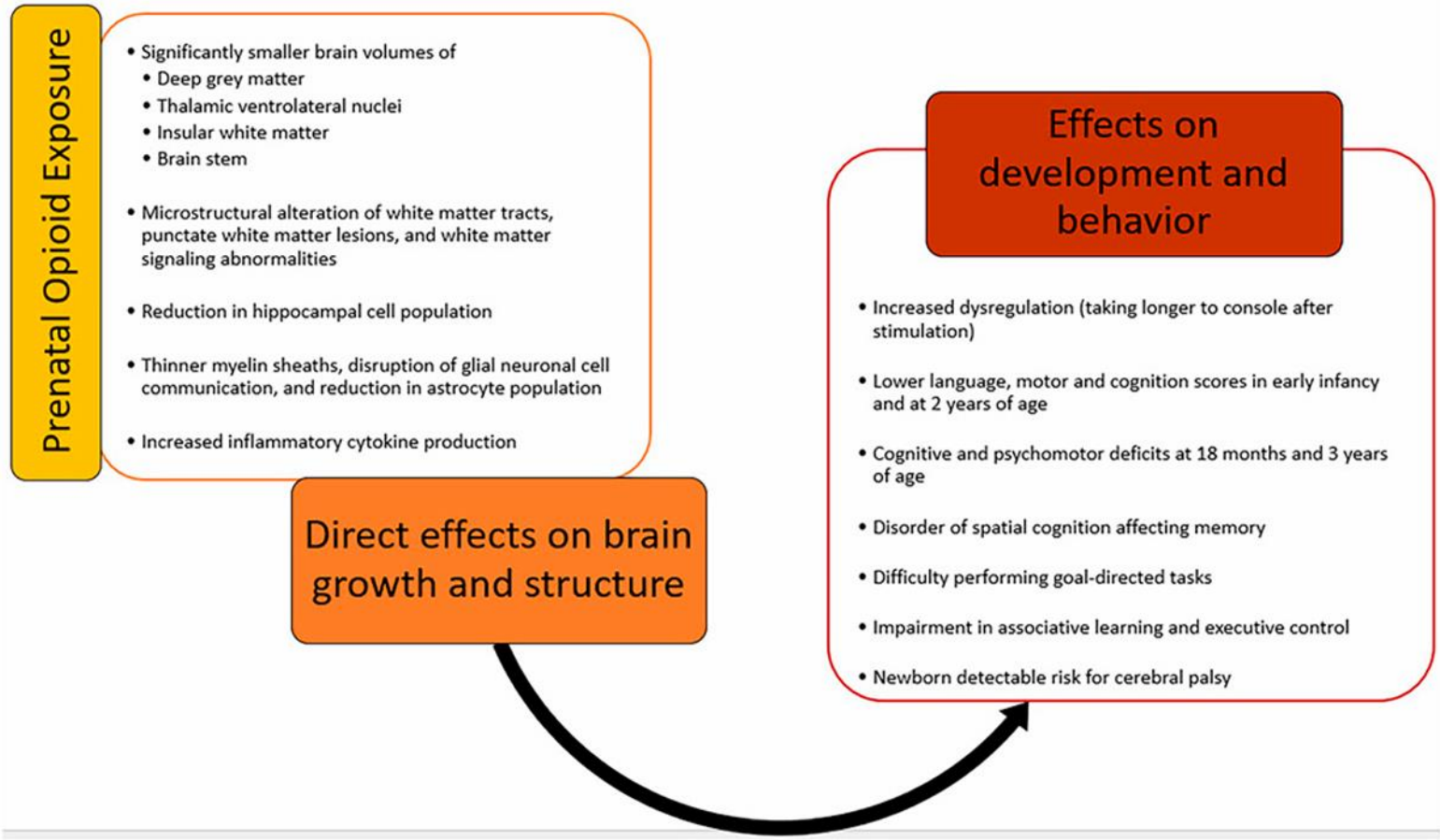

Figure 1. Prenatal exposure to opioids (morphine, fentanyl, methadone, buprenorphine, heroin) and their direct effects on brain growth and structure and effects on developmental outcomes (includes animal and human studies).

Postnatal exposure to opioids

- Clear evidence that neonates experience pain
- “Untreated” pain has potential negative consequences on the brain[47,48]
- Non-pharmacological: swaddling, non-nutritive sucking, skin-to-skin[49]
- Opioids to treat moderate to severe pain, prolonged pain, postsurgical pain

[47]Taddio A, Katz J. The effects of early pain experience in neonates on pain responses in infancy and childhood. Paediatr Drugs. 2005;7(4):245–257
[48]Attarian S, Tran LC, Moore A, Stanton G, Meyer E, Moore RP. The neurodevelopmental impact of neonatal morphine administration. Brain Sci. 2014;4(2):321–334
[49]McPherson C, Grunau RE. Pharmacologic analgesia and sedation in neonates. Clin Perinatol. 2022;49(1):243–265

Postnatal opioids exposure: Effects on brain and neurodevelopment

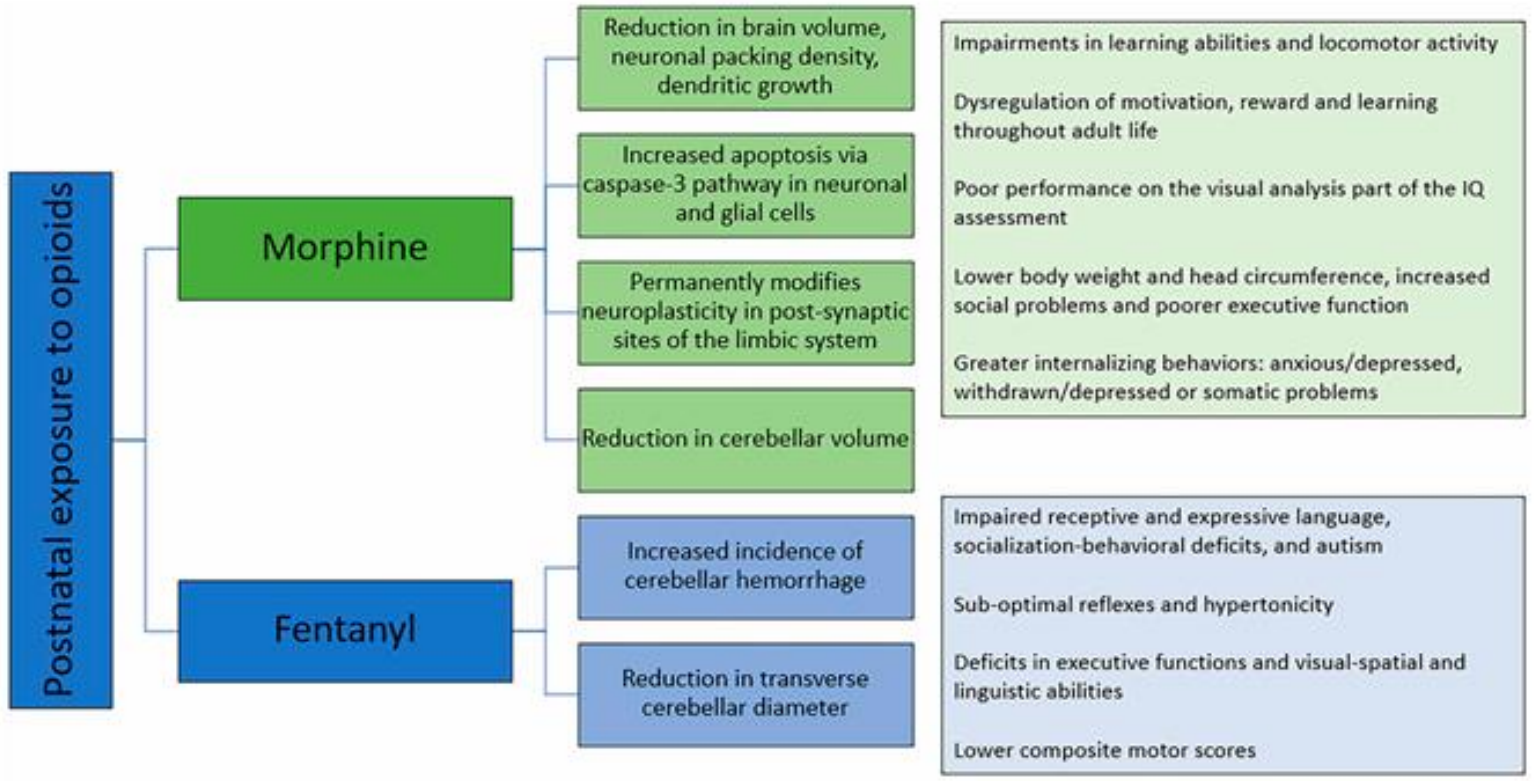

Figure 2. Postnatal exposure to opioids (morphine, fentanyl) and their direct effects on brain growth and structure and effects on developmental outcomes (includes animal and human studies).

Postnatal Hydromorphone exposure: Effects on brain and neurodevelopment

- Pharmacokinetic data in children are sparse. No studies in children younger than 3y of age
- Rat models: protect hippocampal neurons and glial cells via a decrease in reactive oxygen especies[69,70]
- Similar effects to morphine due to structural and functional similarity of the 2 medications

[69]Xie W, Xie W, Kang Z, Jiang C, Liu N. Hydromorphone protects CA1 neurons by activating mTOR pathway. Neurosci Lett. 2018;687:49-54
[70]Kim YS, Kim WY, Kim Y-H, Yoo JW, Min TJ. The protective effect of hydromorphone to ischemia in rat glial cells. Springerplus. 2016;5:610

Postnatal Dexmedetomidine exposure: What is known?

- Selective alpha-2 receptor agonist. Its chemical structure is similar to clonidine, but more specific for alpha-2 than alpha-1 receptors.
- It produces anxiolysis, sedation and analgesia without causing respiratory depression
- Increased use significantly between 2010 and 2020, while overall opioid exposure decreased.
- Not approved by the FDA for use in neonatal patients
- Future studies are required to further examine dexmedetomidine's short- and long-term effects in premature and critically ill infants

Curtis S, Kilpatrick R, et al. Use of Dexmedetomidine and Opioids in Hospitalized Preterm Infants. *JAMA Netw Open*. 2023;6(11):e2341033. doi:10.1001/jamanetworkopen.2023.41033

Recommendations

- Clear negative consequences on the developing brain: neurodevelopmental deficits
- No standardized guidelines, center specific
- Frequently unintentionally excluded from routine state-mandated high-risk infants follow-up program

Infants with in utero exposure to opioids

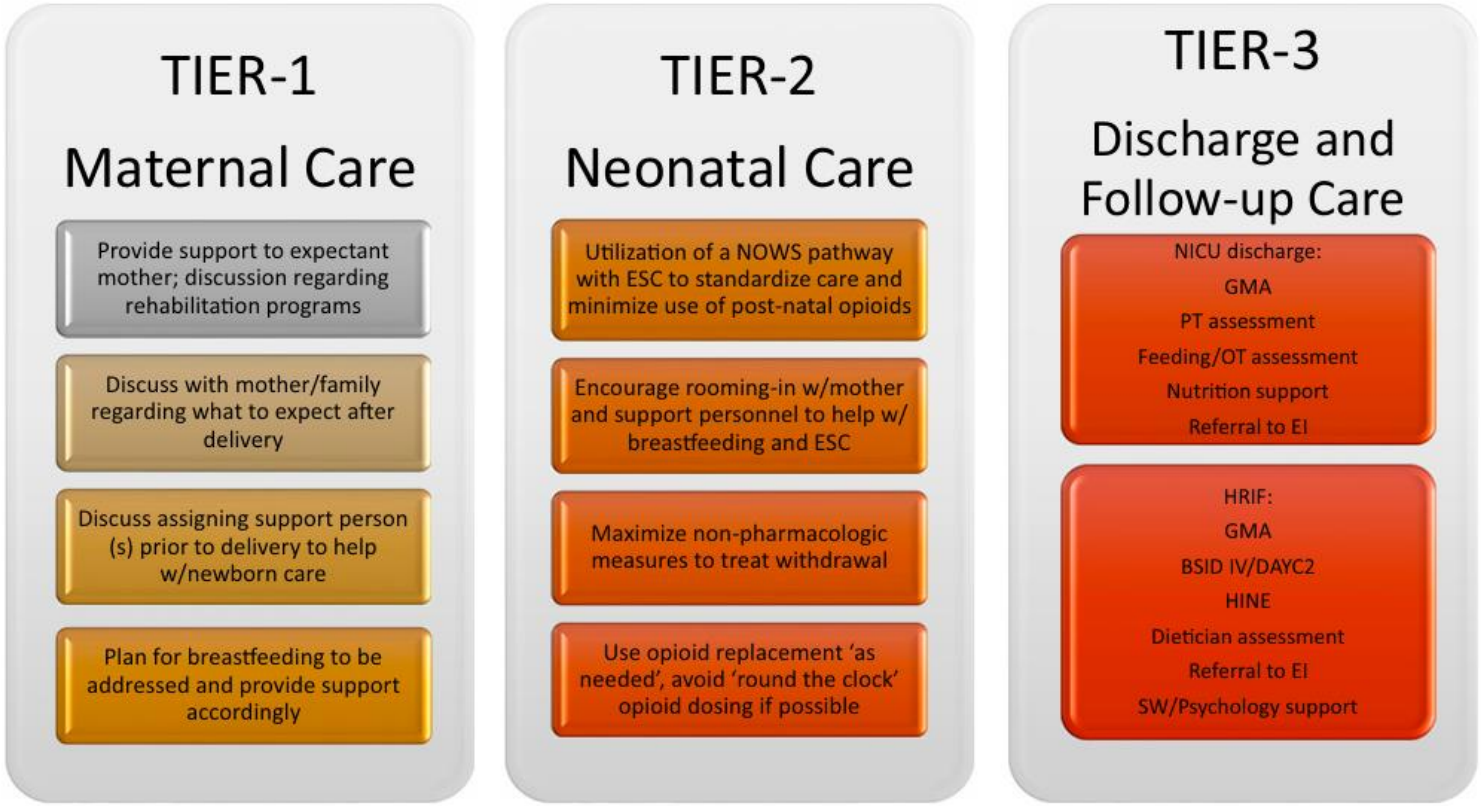

Figure 3. Possible algorithm of preventive/developmentally appropriate care after prenatal opioid exposure. BSID IV=Bayley Scales of Infant Development 4th edition, DAYC2=Developmental Assessment of Young Children 2nd edition, EI=early intervention, GMA=General Movement Assessment, HINE=Hammersmith Infant Neurologic Examination, OT=occupational therapy, PT=physical therapy.

Infants with potential postnatal exposure to opioids

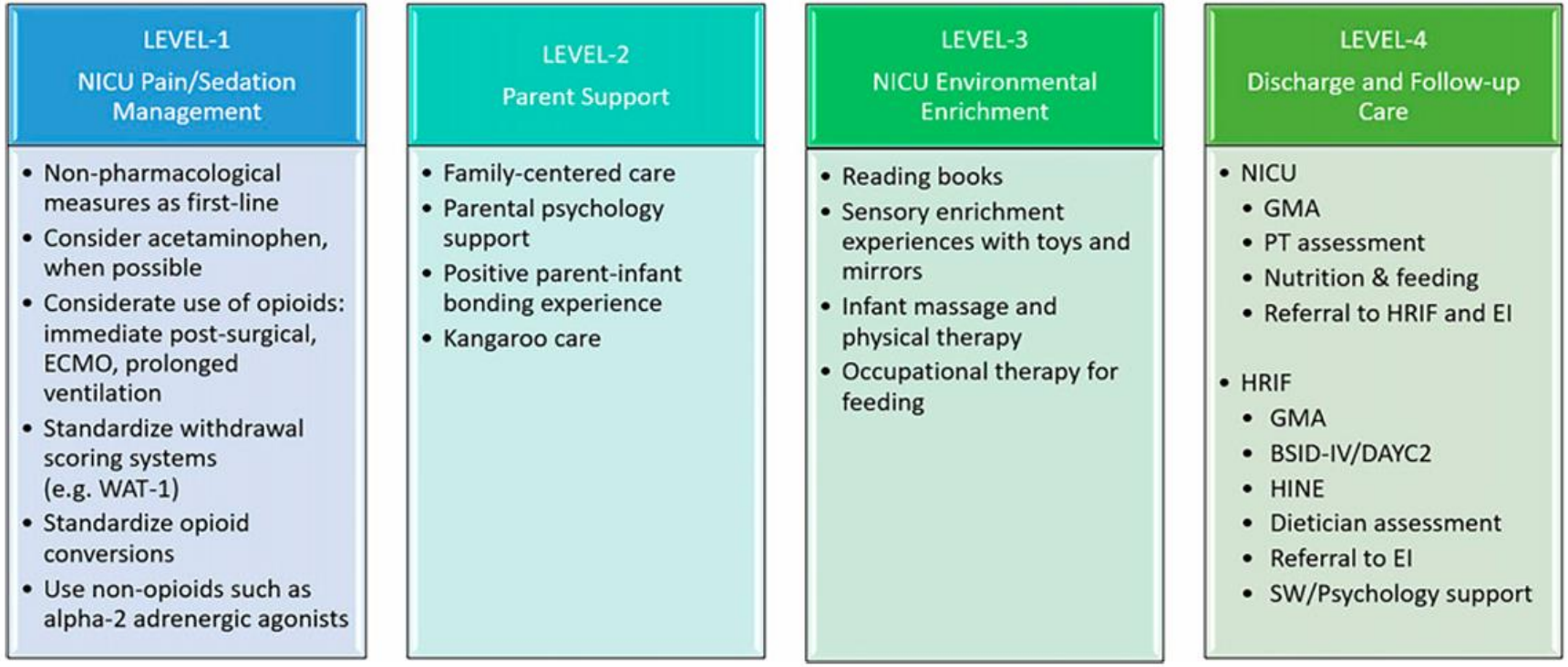

Figure 4. Possible algorithm of preventive and developmentally appropriate care after postnatal opioid exposure. BSID IV=Bayley Scales of Infant Development 4th edition, DAYC2=Developmental Assessment of Young Children 2nd Edition, ECMO=extracorporeal membrane oxygenation, EI=early intervention, GMA=General Movement Assessment, HINE=Hammersmith Infant Neurologic Examination, HRIF= high-risk infant follow-up, PT=physical therapy, SW=social work, WAT-1=Withdrawal Assessment Tool 1.

Recommendation for HRIF Follow up

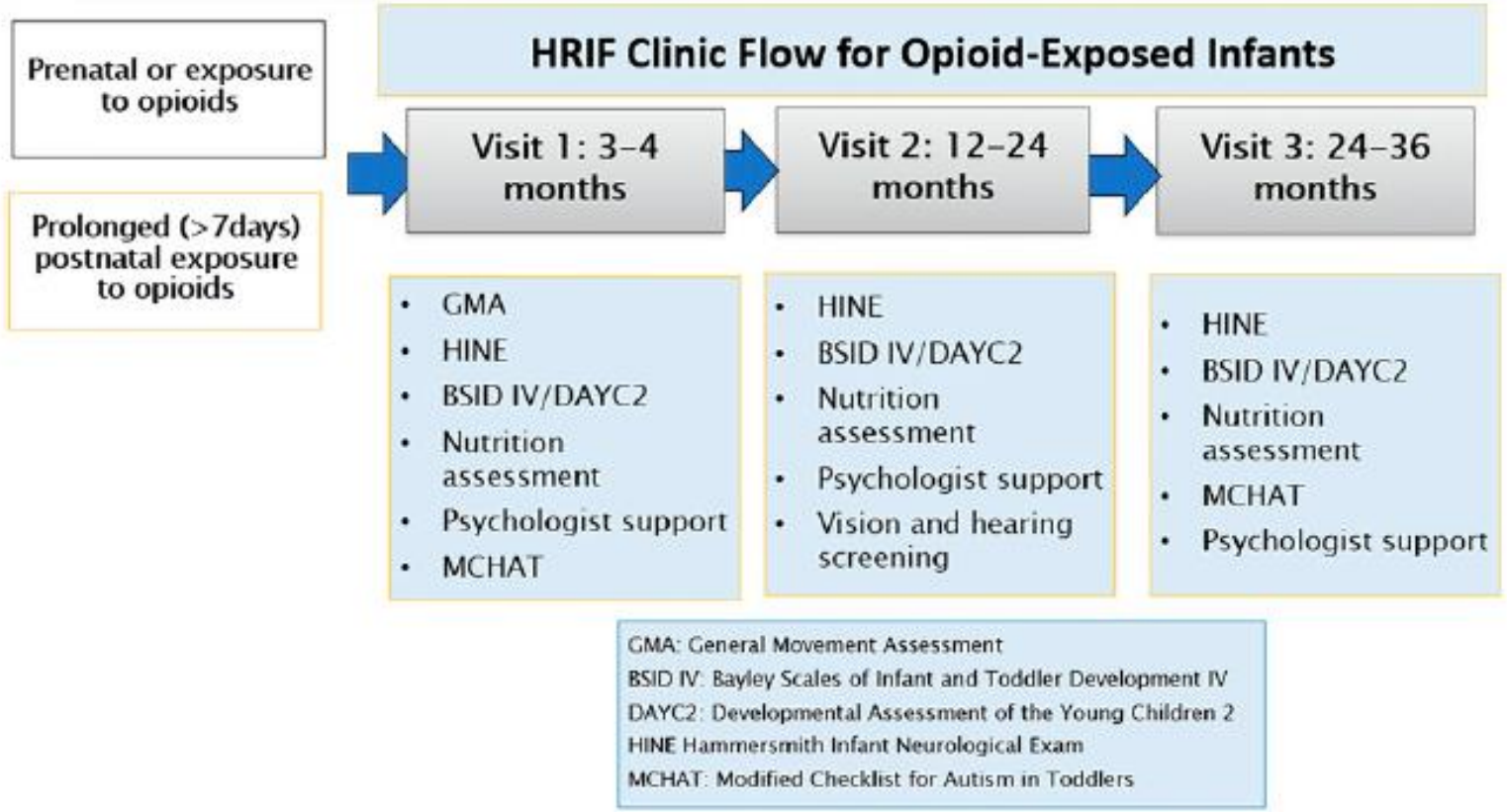

Figure 5. Recommendations for high-risk infant follow-up (HRIF) clinic schedule and recommended assessments. Earlier or more frequent visits (in addition to the 3 standard visits) may be determined to be medically necessary by the HRIF team. Social services referral and support are recommended at every visit.

What do we do?

Neonatal Abstinence Syndrome Treatment Guideline

TEST PATIENT
(NAME)

Enter birth weight (grams) ..... 3,480 grams

1. Capture phase: Objective is to "capture" the dose using first line (oral morphine) and potentially second line agents (oral phenobarbital, clonidine) at which withdrawal symptoms are brought under control (Finnegan scores averaging ≤8).
   - Please initiate non-pharmocologic interventions on any infant at risk for opioid withdrawal and in which Finnegan scoring is initiated.
   - Start oral morphine if Finnegan scores average >8 for three consecutive scores or >12 for two consecutive scores.
   - Continue to increase dose per guideline if Finnegan scores remain >8 for three consecutive scores or >12 for two consecutive scores.

		Date	Initial
Starting dose of morphine (oral)	0.17 mg Q3H	_____	____
2nd dose of morphine	0.27 mg Q3H	_____	____
3rd dose of morphine	0.38 mg Q3H	_____	____
4th dose of morphine	0.48 mg Q3H	_____	____
5th dose of morphine	0.59 mg Q3H	_____	____
6th dose of morphine	0.69 mg Q3H	_____	____

If dose of oral morphine is at 0.69 mg Q3H (~0.2 mg/kg/dose), consider adding second line agent (see guideline for use of phenobarbital as second line agent).

Please enter dose at which scores captured ..... 0.70 mg Q3H _____ ____

** Hold at "capture" dose and do not begin weaning phase until scores stable (Finnegan scores averaging <8) for at least 24 hours.

2. Weaning phase: Once average of scores <8 over a 24-hour period, begin weaning dose. Continue to wean dose by ~10% of "capture" dose every 24 hrs if average of scores <8. Increase back to previous effective dose if obtain Finnegan scores >8 for three consecutive scores or >12 for two consecutive scores.

		Date	Initial
Dose of morphine after 1st wean	0.63 mg Q3H	_____	____
Dose of morphine after 2nd wean	0.56 mg Q3H	_____	____
Dose of morphine after 3rd wean	0.49 mg Q3H	_____	____
Dose of morphine after 4th wean	0.42 mg Q3H	_____	____
Dose of morphine after 5th wean	0.35 mg Q3H	_____	____
Dose of morphine after 6th wean	0.28 mg Q3H	_____	____
Dose of morphine after 7th wean	0.21 mg Q3H	_____	____
Dose of morphine after 8th wean	0.14 mg Q3H	_____	____
Dose of morphine after 9th wean	0.07 mg Q3H	_____	____

**Hold weaning further if at or below final dose of 0.07 mg Q3H (~0.02 mg/kg/dose).

***Once scores stable at final dose for 24 hours (~0.02 mg/kg/dose), may attempt to trial off dose. Monitor for 48-72 hours off medications prior to discharge to ensure scores remain stable.

Thank you!