Mother & Baby Substance Exposure Toolkit Best Practices

Best Practice No. 21

A part of the California Medication Assisted Treatment Expansion Project

This version was published on 2020-07-17

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Consider methadone as first-line pharmacotherapy for the treatment of neonatal abstinence syndrome following evaluation of its benefits/risks

Best Practice No. 21

Nursery/NICU and Treatment

Overview

Methadone may be considered as first-line pharmacotherapy for the treatment of neonatal abstinence syndrome (NAS) following evaluation of its benefits/risks.

Why we are recommending this best practice

- Multiple studies have shown decreased length of treatment with methadone compared to morphine for the treatment of NAS. The decreased length of treatment varies from 2–7 days. One single site randomized controlled trial (RCT) reported a shorter length of treatment on methadone versus morphine with a median of 14 vs. 21 days.

- Multiple studies have also shown decreased length of stay with methadone compared to morphine treatment. The decreased length of stay varies from 2–5 days.
    - One multi-site RCT reported decreased mean length of stay by 2.7 days and decreased mean length of treatment by 2.3 days in NAS infants treated with methadone compared to morphine.
    - A multicenter, non-randomized, retrospective study (Pediatrix dataset) showed a decreased median length of stay of 18 days with methadone vs. 23 days with morphine.
    - An analysis of 14 children's hospitals showed NAS infants treated with methadone had shorter mean length of treatment (17.4 days with methadone vs. 22.2 days with morphine) and mean length of stay (21 days for methadone vs. 25 days for morphine) compared to those treated with morphine.

- Methadone's longer half-life allows for fewer swings in NAS symptoms and fewer drug administrations per day. The longer half-life, however, also makes it more complicated to titrate.

- Methadone is associated with prolonged QTc in adults and in newborns exposed to maternal methadone in the first two days of life, but it is unclear if this is clinically significant or an issue with doses used to treat newborns.

- Infants treated with morphine or methadone have similar short and long-term neurobehavioral outcomes.

- There are no studies to date comparing scheduled methadone to PRN morphine treatment strategies.

Strategies for Implementation

Develop a unit-specific guideline for initiation, escalation, and weaning of methadone to promote consistency and safety of practice.

Special Consideration

Buprenorphine pharmacologic treatment in newborns is not yet recommended until additional studies regarding safety and efficacy are available. A small phase one clinical trial in newborns has been conducted. There is currently minimal safety data on use in newborns and the phase one trial formulation contained 30% ethanol. However, breastfeeding for mothers on buprenorphine is recommended (refer to **Best Practice #30**).

References

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Deep Dive

Some centers have studied and adopted a practice of using methadone as first-line pharmacotherapy for the treatment of NAS. Methadone has a

longer half-life and provides a steadier exposure. However, the longer half-life may also make dose adjustment more complicated. Hospitals should develop a protocol that addresses all available options for pharmacotherapy for NAS within that institution, including information on initiation, monitoring with PRN dosing, when to escalate to scheduled dosing and strategies for using methadone. Developing such a protocol is likely to facilitate standardization of practice and reduce cumulative pharmacotherapy received.

While most newborns that require pharmacotherapy for NAS will need only one medication, some newborns with NAS whose symptoms are not controlled with first-line agents such as morphine and methadone may benefit from a second-line medication/adjunctive therapy. While phenobarbital has been a traditional second-line treatment, it is not an ideal therapy for opioid withdrawal. Therefore, clonidine is recommended as the second-line treatment of choice. Because of the theoretical risk of an effect on autonomic function, newborns receiving clonidine should have their heart rate and blood pressure closely monitored during the first two days of administration and also for 48 hours after discontinuation.

Regardless of which medication(s) are used, a pharmacotherapy weaning protocol should be established to guide practice. During the weaning process and for several days after completing pharmacotherapy, newborns should be monitored as an inpatient and assessed for rebound symptoms. Newborns that receive morphine or clonidine for NAS should receive inpatient monitoring for at least 48 hours and those receiving methadone for at least 72 hours after receiving the last dose of medication.

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Dr. Alexandra Iacob is a Neonatal-Perinatal Fellow at University of California, Irvine (UCI) based out of UCI Medical Center and Miller Children's and Women's Hospital Long Beach. While in fellowship, she is also pursuing a Master in Public Health at Johns Hopkins University. She is passionate about improving neonatal outcomes across all socioeconomic classes via both quality improvement projects and policy efforts. She is particularly interested in neonatal abstinence syndrome and the impact it has on the mother, the baby, and the family as a whole.

Angela Huang

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Angela Huang is a clinical nurse in the Neonatal Intensive Care Unit at Santa Clara Valley Medical Center, where she is also a nurse coordinator managing and leading quality improvement and research projects. She is actively involved in hospital-wide and county-wide opioid use reduction initiatives, specifically outcome improvement for mother/infant dyads with a history of substance use and exposure. Angela is also the co-chair for the CPQCC Maternal Substance Exposures Workgroup which is assessing the statewide scope of NAS and NAS management practices.

Kathryn Ponder

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Dr. Ponder is a neonatologist with East Bay Newborn Specialists, working in the neonatal intensive care units at the UCSF Benioff Children's Oakland, John Muir Walnut Creek, and Alta Bates hospitals. She is also the director of the John Muir High Risk Infant Follow-Up clinic. She has revised her practice's guidelines for the care of infants with Neonatal Abstinence Syndrome and is leading a quality improvement initiative at John Muir to implement these changes. She has previously conducted research and published in the fields of developmental/placental biology and maternal health. She continues to be interested in the developmental origins of disease and optimizing neurodevelopmental outcomes for infants.

Lisa Chyi

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Dr. Lisa Chyi is a practicing neonatologist at Kaiser Walnut Creek. She is co-chair for the CPQCC Maternal Substance Exposures Workgroup which is assessing the statewide scope of NAS and NAS management practices. She also helped develop the NAS management guideline and oversees NAS patient care for the Kaiser Northern California region.

Pamela Aron-Johnson

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Pamela has been at UCI Medical Center in Irvine, California for 35 years in several roles including staff nurse in the NICU for 17 years, Outpatient Nurse Manager for Primary and Specialty Services, and currently the Quality and Patient Safety Advisor for the NICU and OB departments. She is also a member of the Data Committee Advisory Group for CPQCC, and is the data nurse coordinator at UCI for both CPQCC and CMQCC.

Priya Jegatheesan

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Dr. Priya Jegatheesan is the Chief of Newborn Medicine and the Regional NICU Director for Santa Clara Valley Medical Center in San Jose, California, an institution committed to the medically underserved. Her main area of interest is outcomes and data-driven quality improvement. She established a comprehensive computerized database system in the SCVMC NICU that enables prospective data collection for quality improvement and research. She also actively participates in CPQCC's Perinatal Quality Improvement Panel and chaired the QI infrastructure sub-committee for 2 years. She became a member of the Society for Pediatric Research in 2014 and has actively participated in clinical research. She is currently the study site Principal Investigator for a NIH funded multi-center study evaluating ondansetron (5HT3 antagonist) for prevention of neonatal abstinence syndrome in newborns born to mothers who had chronic opioid use during pregnancy. She is a passionate champion for optimizing care of newborns exposed to substances during pregnancy to prevent neonatal abstinence syndrome by promoting mother-infant couplet care.