Editorial

Bringing attention to a need for a standardized treatment and weaning protocol for neonatal abstinence syndrome

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Neonatal abstinence syndrome (NAS) due to in-utero opioid exposure has increased 5-fold in the U.S. since 2000, with an incidence of 5.8 per 1,000 live births (1,2). NAS now accounts for 3% of all admissions to neonatal intensive care units (NICUs), with associated NICU hospitalization costs of approximately $53,000 per infant (2,3). Fifty percent to 80% of opioid-exposed infants require extensive pharmacologic treatment for withdrawal symptoms with an average length of hospitalization of three weeks, with a large range from one week to over a month (3,4). This variability is due to a variety of maternal-infant factors such as methadone versus buprenorphine exposure, infant feeding method, ability to room-in with the infant, genetic factors, and co-exposures to nicotine, illicit drugs, and psychiatric medications (4-8).

This variability in length of hospitalization and extent of pharmacotherapy received is due to not only individual patient factors, but also due to hospital factors, including institutional medication protocols and varying patient care models (9). Infants are monitored in level III NICUs, special care nurseries, mother-infant units, or pediatric wards depending on the hospital, with various requirements for length of inpatient monitoring (1,9). In 2006, only 54% of NICUs with accredited fellowships had a written protocol for NAS management (10). A more recent 2014 survey by Mehta *et al*. which included 179 U.S. NICUs found that an improved 72.5% of units had a written NAS protocol (11). Standardized approaches to NAS clinical assessments such as the Finnegan withdrawal scale with use of intra-observer reliability training programs are suggested as best practice but not universally utilized (4,12,13). Morphine and methadone are the two most commonly used first-line medications and are recommended by the American Academy of Pediatrics (AAP) as acceptable options for first-line treatment of opioid-exposed infants (13,14). However, there is lack of definitive evidence or high quality large randomized clinical trials for which agent is superior and neither medication has been approved by the Food and Drug Administration (FDA) for use in infants with NAS (4,13). Even when an agreed upon first-line medication is selected, many hospitals do not have a standardized approach to escalation and weaning which can lead to longer hospitalizations due to inconsistencies between providers (9).

In their recent article published in *Pediatrics*, Hall *et al*. present a multicenter cohort study from the Ohio NAS research collaborative that was focused on implementation of a standardized NAS weaning protocol to improve NAS outcomes (15). They present data from 981 infants cared for in 6 children's hospitals before and after implementation of a standardized multi-centered weaning approach. Their standardized approach included options for either methadone or morphine as first-line therapy, and strict weans were completed entirely in the inpatient setting (16). They found that the switch to stringent weaning guidelines for 3 of the centers who did not previously have a guideline was associated with shorter duration of opioid treatment (23.0 *vs*. 34.0 days, P<0.001), shorter inpatient hospitalizations (23.7 *vs*. 31.6 days, P<0.001), and less adjunctive drug therapy (5% *vs*. 21%, P=0.004) (15). This study is important as it indicates that that regardless of first-line medication or location of care, a standardized weaning protocol can result in shorter hospitalizations, and less exposure to opioid and adjunctive medications. In their control sites that already

had a pre-existing NAS protocol, adherence to the protocol increased during the intervention period with associated reduction in opioid treatment duration. This demonstrates that even in hospitals that do have a written NAS protocol, quality improvement initiatives aimed at protocol adherence can improve outcomes. The paper also highlights the importance of statewide collaboration across institutions that allows for local sites to share experiences and best practices with one another.

This study is limited by the relatively small group of infants in the protocol adopting site group (n=93), which included only 48% of the infants in the protocol-adopting sites were since once of the centers continued to discharge infants home on prescribed opioids (15). Additionally, there is limited objective data on the infants discharged home on opioids due to its retrospective nature. It is not clear if other standardized approaches to NAS care such as use of NAS scoring intra-rater reliability programs, regular provider education, or standardized breastfeeding guidelines influenced these improved outcomes over the study period at either the adopting sites or control sites. Seventy percent of the infants were cared for in level 3 NICUs, which can often make rooming-in models and optimization of non-pharmacologic care more challenging. Lastly, the inclusion of late preterm infants 34–37 weeks is sometimes challenging as these infants can be difficult to accurately score with the currently available NAS assessment tools designed for full-term infants.

In the protocol-adopting sites, there was a statistically significant increase in the use of methadone compared with morphine following adoption of the protocol, despite neither medication being chosen as the standard of care in this study which may have contributed to the improvement in length of stay and length of treatment on top of adherence to the protocol. This emphasizes the need for higher quality data from randomized clinical trials to determine if morphine or methadone is a superior-choice for first line pharmacologic therapy. Morphine is the most commonly used medication, chosen by approximately 50–70% of hospitals in the U.S. (9,11). Morphine is typically dosed every 3–4 hours with dose ranges of 0.3–1.0 mg/kg/day and most commonly weaned in the inpatient setting. Methadone is used by 20–25% of hospitals with dose ranges of 0.2–0.9 mg/kg, typically with less frequent dosing every 6–12 hours, with recent pharmacokinetic data suggesting every 6 hour dosing may be optimal (17). A previous study by Hall *et al*. indicated no differences in length of hospitalization with methadone versus morphine treatment in the Ohio collaborative (18). A 2014 retrospective cohort study by Patrick *et al*. which included data from 14 Children's Hospitals in the U.S. found that methadone was associated with shorter length of opioid therapy and shorter hospitalizations (9). A single center randomized control trial of 31 methadone or buprenorphine exposed infants found that methadone had the advantage with 7 fewer days of opioid treatment in comparison with morphine (14). One benefit of morphine is its short half-life, with frequent dosing making tailoring of dose to symptoms potentially easier. The advantages of methadone are that is can be dosed less frequently with a longer half-life which may be better for cases of more severe withdrawal. Less frequent dosing also makes methadone a more feasible option for outpatient dosing. Methadone comes with potential downsides however, including potential risk for QTc prolongation and less frequent dosing which could potentially make titration more challenging. The long-term outcomes of methadone versus morphine treatment are currently unknown (13).

Less preferred first-line agents such as diluted tincture of opium (DTO) and phenobarbital are still used by 10–15% of institutions (11). The newest treatment modality is sublingual buprenorphine, which may be particularly useful in the treatment of buprenorphine-exposed infants. Preliminary studies have indicated that buprenorphine, in comparison with DTO or oral morphine, is associated with reduction in length of therapy and lengths of hospitalization by 25–50% (19,20). However, data and experience is limited. The concern with many of these neonatal opioid preparations, including neonatal methadone, DTO, and buprenorphine preparations, is the inclusion of preservatives such as ethanol which may also affect long-term infant neurodevelopment (21). On the horizon is use of non-opioid medications such as ondansetron for mothers during delivery and neonates shortly after birth in an attempt to prevent withdrawal (22).

There are numerous health services delivery challenges, differences in provider attitudes and knowledge bases, and systems issues that are barriers to a standardized approach to NAS care. Rooming-in models of care, which are often possible on pediatric inpatient units as opposed to special care nurseries and NICUs, have been shown to decrease need for pharmacologic treatment lengths of stay (6,12). However, some hospitals are not able to offer rooming-in due to space limitations and staffing issues, particularly with infant hospitalizations that may last for weeks. According to a 2014 survey of U.S. NICUs, 30% of units have started

to transition infants to outpatient opioid therapy, primarily with methadone (11,23). This can lead to up to a 50% reduction in hospital days and associated cost savings, and better promotion of non-pharmacologic interventions such as breastfeeding (23,24). While this is associated with shorter time in the hospital, it is often linked with longer total opioid days. Outpatient opioid tapering requires significant infrastructure with a dedicated physician to monitor signs of withdrawal and guide tapers, monitoring of dispensed medication, multiple outpatient visits per week, more intensive visiting nurses and social work services, and a dependable and committed family. The outpatient weaning without constant clinical supervision means that the infants are not being objectively scored for withdrawal symptoms by a trained professional every 3–4 hours, and may experience complications that could be more easily picked up in the inpatient setting. In programs that have high volumes of patients coming from many locations across the state, this may not be a feasible option. The safety and efficacy, optimal dosing regimens and weaning schedule, as well as long-term neurodevelopmental outcomes of treating infants in the outpatient setting has yet to be determined.

Response to therapy is going to vary depending on the infant and is contributed to by a number of factors. Prenatal exposure to methadone may be more appropriately treated with methadone, while exposure to buprenorphine may be better treated by morphine or buprenorphine (14). Infants with exposure to polypharmacy, particularly benzodiazepines, have a much higher risk of requiring higher doses of replacement opioids and adjunctive therapy thus may warrant a more aggressive medication regimen (5). In addition, genetic factors may affect an infant's response to a particular medication regimen (7,8). A "one regimen fits all" may not be the best approach to ensure success in all infants. Algorithms that incorporate several evidenced-based options for therapy based on infant risk factors may be the best approach.

In conclusion, this well-written manuscript is a significant contribution to the NAS literature. It emphasizes the importance of developing a standardized approach across care settings and providers for NAS medication weaning as a way to decrease exposure to opioid medications and shorten length of stay. It also highlights that there are various ways to accomplish the goal of decreasing length of stay, and that not one medication regimen is currently recommended for all patients and inpatient settings. It emphasizes that more evidence if needed to establish the most effective treatments for infants with opioid exposure. In addition, the feasibility and safety of outpatient therapy warrants further investigation. Lastly, large NAS collaborations between local hospitals can result in significantly improved NAS outcomes in a short period of time.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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