EDITORIAL

Pharmacologic Treatment for Neonatal Abstinence Syndrome
Which Medication Is Best?

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Cases of neonatal abstinence syndrome (NAS) secondary to in utero opioid exposure have increased significantly over the past decade, with recent data from the US Pediatric Health Information System showing an incidence as high as 20 cases per 1000 live births.[1] An estimated 50% to 80% of infants with NAS are treated pharmacologically, with most of these infants cared for within newborn intensive care units. In 2012, these pharmacologically treated infants had a mean length of hospital stay (LOS) of 23.0 days, with an average hospitalization charge of $93 400 per infant.[2] There continues to be wide variation in care practices, including pharmacologic agents used to treat NAS, with no consensus as to which medication regimen is best.[3,4] To our knowledge, high-quality studies, such as randomized clinical trials (RCTs) and meta-analyses of management strategies for NAS, are very limited, providing little guidance to inform best practice recommendations.[3] Currently, the most common first-line medications used to treat NAS include morphine, methadone, and buprenorphine; phenobarbital and clonidine are the most commonly used adjunctive agents.[3,4]

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In this issue of *JAMA Pediatrics*, Disher et al[5] performed a systematic review and network meta-analysis of RCTs pertaining to the pharmacologic treatment of NAS, analyzing a total of 18 RCTs, including 10 published since 2000. The primary outcome measure for the meta-analysis was difference in average length of pharmacologic treatment (LOT), and secondary outcomes included differences in LOS, need for adjunctive treatment, and reported adverse events.[5] The authors concluded that buprenorphine was the optimal treatment for NAS, as it was associated with the largest reduction in LOT, which carries significant implications for care practices. Currently, buprenorphine is used by only a handful of institutions, while morphine is the most commonly used agent (more than 50% of US centers) followed by methadone.[3,6] The authors also concluded that morphine was the worst medication treatment option.

Network meta-analysis aims to synthesize results from RCTs with a variety of treatment comparisons in relation to a specific outcome.[7] Indeed, the network analysis approach has the potential to identify and quantify effectiveness of NAS treatment regimens given that at least 16 of 18 RCTs used different treatment protocols.[5] However, even sophisticated methods require careful consideration, particularly any underlying assumptions.[8] Two such assumptions in the study by Disher et al[5] are minimal bias and homogeneity of methods. However, some of the RCTs were not blinded and thus carry high risk of bias. Further, methods varied in multiple ways, including inclusion and exclusion criteria; assessment tools and protocols used to determine when to initiate, increase, and wean the study medications; and whether and what type of adjunctive medication treatment should be used.

Thus, the primary findings of this meta-analysis warrant further discussion. To our knowledge, 3 single-site RCTs of buprenorphine have been reported,[9-11] all by Kraft et al and all compared with morphine treatment. The first 2 studies[10,11] were small and not blinded and therefore at high risk of bias. The most recent report[9] was a blinded RCT of 63 infants comparing buprenorphine with morphine; buprenorphine was associated with both a shorter median LOT compared with morphine (15 vs 28 days) and a shorter median LOS (21 vs 33 days). The 2 prior smaller studies[7,8] also showed similar outcomes, with a mean LOT of 22 to 23 days in the buprenorphine group vs 32 to 38 days in the morphine group. While the difference in LOT between the 2 treatment groups is significant, it is important to note that the actual LOT for the morphine groups in all 3 studies (28 to 38 days) is substantially longer than the LOT reported in other recent RCTs of morphine-treated infants (15 to 21 days).[6,12] In addition, the total LOS in the Kraft studies[9-11] in the morphine group (33 to 42 days) is much longer than published national administrative data average (23 days) and those reported in other recent RCTs involving morphine.[2,3,6] The morphine treatment protocol used in the studies by Kraft et al[9-11] had a higher maximum daily dose, stricter weaning criteria, and lower dose for discontinuation compared with some of the other studies.[6,10,12] As Disher et al[5] mention in the Discussion section, the benefits seen with buprenorphine may have been more pronounced because of the optimized pharmacokinetic-informed buprenorphine titration and weaning protocol rather than solely the medication effect. Previous studies have demonstrated the association of pharmacokinetic-informed strict weaning protocols with reductions of LOT and LOS for NAS.[13]

It is also important to note that, to our knowledge, buprenorphine has never been compared with methadone in an RCT.[3] However, there have been 2 recent RCTs comparing methadone with morphine.[6,12] In the single-center blinded RCT by Brown et al,[12] 31 infants were randomized; methadone was associated with a shorter median LOT compared with morphine (14 vs 21 days). In a 2018 study by Davis et al,[6] a multicentered blinded RCT in 8 centers involving 117 infants, methadone-treated infants had

a shorter median LOT compared with morphine-treated infants (11.5 vs 15 days). As noted above, morphine-treated infants in both of these RCTs had a shorter absolute median LOT than those reported in all 3 studies by Kraft et al,[9-11] raising the possibility that the observed shorter LOT and LOS associated with buprenorphine may be overestimates.

In addition to the limitations of individual RCTs to date, there are many limitations of quantitative synthesis. First, some studies used means and others used medians to report LOT and LOS, making it difficult to compare study results. Second, as Disher et al[5] point out, no 2 studies used the same treatment protocol or scoring system, both of which are critical to how fast you escalate and wean the medications, therefore affecting the primary outcome of LOT. Third, study populations and maternal exposures differed, which can result in effect modification and violate aggregation assumptions. For example, premature infants were excluded from the 2 largest and blinded RCTs[6,9] but not the others, and maternal polypharmacy exposure was an exclusion criterion from 3 studies.[10,11,14] With so much variability across studies, including setting of care and exclusion criteria, the absolute LOT across different studies of the same medication is expected to also vary. Finally, the number of studies investigating NAS pharmacologic treatment is fewer than recommended for network meta-analysis.[15] Thus, results of the network meta-analysis by Disher et al[5] should be interpreted with caution, particularly their conclusion that buprenorphine reduces LOT and LOS by approximately 12 days.

Another major limitation of studies to date, which is highlighted by Disher et al[5] in Table 1, is the lack of reporting and adjustment for nonpharmacologic factors, such as breastfeeding and rooming-in.[5] In a 2018 meta-analysis by MacMillan et al,[16] rooming-in was associated with a relative risk of 0.37 for receiving pharmacologic treatment and a 10.4-day reduction in LOS. Some studies included breastfed infants and some did not, which can also alter LOS by an average of 3 to 7 days.[3] One might presume that nonpharmacologic variables were evenly distributed across randomization groups, but unblinded studies might have had imbalance; unfortunately, this was not systematically examined in all studies. There has been a shift over the past several years toward focusing on nonpharmacologic care as the primary treatment for infants with NAS, with significant improvement in outcomes despite use of the same medication treatment regimen.[3,16] Thus, these nonpharmacologic variables are particularly relevant to today's care practices.

One final point to keep in mind is that most studies did not examine long-term outcomes beyond the initial birth hospitalization. Is shorter LOT associated with improved long-term outcomes or does it put the infant at risk for re-admission and altered neurobehavior and development? One could argue that this matters more than the short-term hospitalization outcomes.

In conclusion, the systematic review and meta-analysis by Disher et al[5] presents evidence that buprenorphine is associated with a significantly shorter LOT for NAS compared with morphine. Two recent RCTs[6,12] also concluded that methadone is superior to morphine. To our knowledge, methadone and buprenorphine have yet to be compared head-to-head in an RCT; thus, it remains unknown at this time whether buprenorphine is superior to methadone. The evidence showing that morphine is an inferior treatment has significant implications for clinical practice because it is currently the most commonly used agent to treat NAS. However, results should be interpreted with caution given the small number of RCTs, small sample sizes, heterogeneous methods and study populations, and lack of long-term outcome data in many studies. Additional multicentered large-scale RCTs that compare methadone with buprenorphine and take into account nonpharmacologic factors are warranted before definitive recommendations on best practice can be made.

ARTICLE INFORMATION

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