Advances in Management of Neonatal Abstinence Syndrome: What’s the score?

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Neonatal abstinence syndrome (NAS) is a constellation of symptoms and signs of withdrawal developing in infants following intrauterine exposure to opioids. In Ireland currently, this is typically methadone substitution for treatment of heroin addiction. In the United States, NAS has been declared an epidemic with a 5-fold increase in incidence between 2000 and 2012 and a current prevalence as high as 2% of live births.¹² In Ireland, data from the Hospital Inpatient Enquiry (HIPE) system indicates that between 2012 and 2016, 501 infants were treated for NAS; half of whom were in the three Dublin maternity hospitals. The most recent survey of practice within neonatal units in Ireland and the UK³ identified widespread variation in methods for assessment and treatment of NAS, reflecting the lack of quality evidence upon which current treatment regimens are based.

In a recent systematic review in *JAMA*, Wachman and colleagues assessed studies of approaches to diagnosis and treatment of NAS published in the last 10 years.⁴ Advances in four categories (evaluation, infant non-pharmacologic treatment and mother and infant pharmacologic treatment) are presented and areas lacking quality evidence are identified as a potential focus for future research. A total of 53 original research articles were included in the final analysis which incorporated a total of nine randomised trials.

The original (21-item) Finnegan scale is still the most widely used method of assessing the requirement for treatment of NAS and monitoring the effects thereof. Now in its fifth decade and despite reported poor inter-rater reliability it has yet to be widely superseded in clinical practice. Several modified versions have evolved, including a 7-item score which correlates highly with the original and a 5-item symptom-based prediction tool which has a positive predictive value of 100% for pharmacological treatment based on a score of 4 or more.⁴ Newer tools such as ‘Eat, Sleep, Console’,⁵ based on symptom prioritisation appear to reduce the need for pharmacologic therapy, however further studies including assessment of long-term outcomes are required for such an approach to become established.

The most substantial number of recent studies in NAS pertain to non-pharmacological interventions.⁴ Evidence, albeit retrospective, has demonstrated that rooming-in may be a preferential care model to mother-infant separation as occurs with neonatal unit admission. In situations where this approach is adopted, need for pharmacotherapy is reduced by 20-60%, duration of opioid treatment and length of
stay is shortened by 1-2 weeks, while breastfeeding rates are doubled. Breastfeeding itself may have similar beneficial effects however rooming-in is a potential confounding factor, not controlled for in any of the studies in the review. None of the non-pharmacologic treatments have been evaluated in a randomised trial but data from quality improvement studies focusing on function-based assessments such as ‘Eat, Sleep, Console’ and non-pharmacologic measures hint at substantial cost savings averaging $10,000 per infant.

Whether morphine, methadone or buprenorphine are the optimum first-line opioid treatment for NAS remains to be clarified. The most recent study of NAS management in Ireland and the UK found that morphine was the opioid most frequently prescribed, with widely variable dosing schedules. Studies comparing morphine and methadone, have failed to consistently reach the same conclusion. A recent randomised trial published in the New England Journal of Medicine demonstrated that treating infants with buprenorphine compared to morphine is associated with reduced length of stay (median 21 vs. 33 days) and shorter treatment duration (median 15 vs. 28 days). Furthermore, there is a lack of consensus regarding which therapeutic agent to add once maximal opioid dosing is achieved or polydrug use is present. Data regarding whether clonidine or phenobarbitone is a superior adjunctive treatment is at best equivocal and at worst conflicting.

There is evidence that the agent selected for maternal opioid substitution can also influence neonatal outcomes. A randomised trial, demonstrated that maternal substitution therapy with buprenorphine compared to methadone was associated with a reduction in neonatal length of stay and treatment duration. Currently, Ireland is one of only four EU member states where buprenorphine-based medications are not available on the same basis as methadone for opioid substitution therapy. Suboxone™ is a combination of the weak opioid agonist buprenorphine and the opioid antagonist naloxone in a 4:1 ratio; this lowers the potential for misuse. It was introduced to the Irish market in 2007, but an analysis by the National Centre for Pharmacoeconomics (NCPE) deemed it was not cost-effective. A Suboxone™ pilot access programme has been in existence for 10 years but accounts for just over 1% of the opioid substitution therapy cohort, considering there are 10,000 plus patients receiving methadone. A feasibility study of the Irish Suboxone™ cohort highlights several potential advantages over methadone. Current barriers to its more widespread introduction will include the need for legislative change to allow it take its place as an alternative to methadone as a part of opioid substitution therapy. Cost will undoubtedly remain a factor and the potential cost-benefits in reducing the number of neonatal unit bed-days due to treating selected pregnant women with buprenorphine rather than methadone merits consideration in this regard.

Significantly, while new developments in the NAS literature have emerged, historical issues persist. Old habits do indeed die hard. The preponderance of evidence is based on retrospective data and small sample sizes often without a comparator. Most non-randomised studies fail to account for maternal poly-
drug use, which is increasing in frequency and a major potential confounder. Due to emerging evidence regarding the potential utility of non-pharmacologic therapies, future randomised trials need to control for this. A reliable, reproducible validated assessment tool, which determines the need for pharmacologic therapy is paramount. Multicentre studies are preferable to generate adequate power. Opioid-exposed infants who are born preterm in significant numbers should no longer be excluded from studies when they too require a treatment that is not necessarily generalizable to their population. Long-term follow-up data from trials are also necessary as short-term outcomes such of length of stay and associated cost reductions are the only current barometers of success.

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**References**