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COMMENT

Disarray in the perinatal management of neonatal abstinence syndrome

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The incidence of neonatal abstinence syndrome (NAS), the withdrawal in the neonate secondary to prenatal opioid exposure, has increased dramatically due to the worldwide rise in opioid use.[1] The expression of NAS is highly variable and it is difficult to predict which neonates will require pharmacologic treatment and a prolonged hospital stay. This has highlighted the urgent need to improve diagnostic criteria and management of NAS. Serious questions have been raised about the tools used to diagnose NAS and the appropriate use of pharmacologic treatments. Complicating this issue is the fact that most pregnant women with maternal opioid use disorder (MOUD) often use other substances in addition to an opioid (e.g., nicotine, marijuana, etc.). The high rates of psychiatric co-morbidities in these women can also affect NAS.[2–4] Pregnant women with MOUD who have depression and/or anxiety disorders are often treated with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, which can on their own cause clinical signs that lead to a diagnosis of NAS.[5] Together, these two classes of drugs are known as SRIs. In a study of >200,000 pregnant women taking a prescription opioid, the concurrent use of antidepressants, gabapentin, benzodiazepines, and antipsychotics increased the frequency and severity of NAS.[6]

In this issue of *Pediatric Research*, Bakhireva et al. make a strong case for the role of SRIs in exacerbating NAS.[7] The authors compared NAS severity between neonates born to mothers with MOUD who also used SRIs (MOUD + SRI group) and those who did not use SRIs (MOUD group). They found that neonates in the MOUD + SRI group were >3 times more likely to need pharmacologic treatment than those in the MOUD group. The median length of hospital stay of neonates in the MOUD + SRI group was 11 days compared to the MOUD group (6 days). Although the total length of hospital stay in the MOUD + SRI group was approximately twice that of the MOUD group, the actual length of treatment did not differ between the two groups. However, length of hospital stay is complicated and can be due to factors such as unrelated medical conditions or social concerns (e.g., involvement of Child Protective Services), which does not appear to have been specifically addressed in this study. In addition, misuse of opioids and the use of heroin occurred more frequently in the MOUD + SRI group, which could also impact the severity of NAS.

The authors suggest that these differences in NAS severity associated with the use of SRIs could be due to drug–drug interactions between SRIs and opioid medications that inhibit the reuptake of serotonin. Although drug–drug interactions likely play an important role, other potential mechanisms should be considered. First, a serotonin toxicity syndrome has been described that includes signs similar to NAS, including irritability, hypertonia, and tremors.[5] Neurobehavioral assessment comparing SRI exposed with unexposed neonates shows worse performance in the SRI-exposed group across several domains of function that persist throughout the first month.[8] This assessment was performed with the NICU Network Neurobehavioral Scales (NNNS), which provides a standardized evaluation of the presence or absence of the motor and behavioral signs used in the assessment of NAS, as well as the severity and frequency of these signs.[9] Critically, neurobehavioral profiles using the NNNS predicted developmental outcomes in neonates with NAS and infant medical and behavioral outcomes through early childhood in children with cocaine and/or opioid exposure.[10,11] Thus, SRI exposure could have an additive rather than drug–drug interaction effect. This would mean that NAS severity scores that meet the criteria for pharmacological treatment in infants with SRI and opiate exposure could be artificially inflated resulting in neonates receiving pharmacologic treatment with an opioid when it is not warranted.

Second, biologic mechanisms associated with psychiatric disorders could similarly affect neonatal neurobehavior independent of prenatal SRI or opioid exposure (i.e., depressed women who are not treated with pharmacologic therapy). For example, maternal depression is associated with immune dysregulation, increased inflammation and stress-related alterations in the hypothalamic-pituitary axis (HPA), resulting in increasing cortisol levels.[12–14] Increased cortisol levels can be related to increased maternal and neonatal stress and influence the severity of NAS. In a study examining salivary cortisol levels and NAS severity, cortisol levels were higher in the first week of life and did not fall in neonates requiring pharmacologic treatment for NAS compared to those who did not require treatment.[15] The neurobehavioral assessment of neonates born to mothers with untreated depression as well as neonates of mothers who used SRIs during pregnancy showed a flatter trajectory and a widening gap in scores compared to unexposed controls.[8] Maternal depression could directly result in the programming of fetal/neonatal neurobehavior through epigenetic changes in placental genes implicated in perturbations of the HPA axis. Neonates of mothers with depression had greater methylation of placental *NR3C1* and showed worse neurobehavioral performance that could have resulted from chronically increased levels of corticosteroids in

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utero.[16] From a fetal programming perspective, these epigenetic changes could occur due to adjustments in neurobehavioral systems in response to maternal "signals" transmitted to the fetus.[17] From a prevention perspective, maternal mindfulness was related to neonatal neurobehavior in mothers with emotional dysregulation during pregnancy, likely due to the impact of stress reduction on the HPA axis.[18] Stress reduction techniques (e.g., non-pharmacologic care) could have similar effects on neonates with or without prenatal opioid exposure, thereby reducing NAS severity and the need for pharmacologic treatment.

Perinatal management of NAS is in disarray. The lack of biomarkers forces us to rely on clinical signs to diagnose NAS and to develop protocols for pharmacologic treatment. There is dissatisfaction with the clinical tools that are being used and there is no global standard of care.[19,20] Thus, it is not surprising that there is considerable site-to-site variation in the care of MOUD as well as neonates with NAS.[21] Although there is increasing interest in non-pharmacologic approaches to NAS, there is also concern with the potential for "undertreatment" and possible impact on longer-term neurodevelopmental outcomes.[22]

This article by Bakhireva et al. highlights a critically important and understudied issue in the perinatal management of MOUD and their neonates with NAS; the impact of polysubstance exposure on NAS severity.[7] Their findings have serious implications for the general approach and pharmacologic management of NAS. On the one hand, their findings could suggest that non-opioid drugs can "truly" increase NAS severity. On the other hand, there is the spectre that assessment tools and severity scores (designed specifically to assess opioid withdrawal) could be inflated by the presence of other substances potentially leading to the unwarranted use of pharmacologic treatment. While the authors present us with this conundrum in the case of SRIs, it is apparent that this phenomenon could be generalizable to other substances as well. This becomes even more important as we recognize that polypharmacy is becoming the "new norm" despite a lack of sufficient safety and efficacy data to support the approach. Clearly, there is an urgent need to better identify neonates at risk for NAS and develop novel approaches for prevention and treatment.

REFERENCES

1. Degenhardt, L. et al. Global burden of disease attributable to illicit drug use and dependence: findings from the global burden of disease study 2010. *Lancet* **382**, 1564–1574 (2013).
2. Faherty, L. J., Matone, M., Passarella, M. & Lorch, S. Mental health of mothers of infants with neonatal abstinence syndrome and prenatal opioid exposure. *Mat. Child Health J.* **22**, 841–848 (2018).
3. Benningfield, M. M. et al. Co-occurring psychiatric symptoms are associated with increased psychological, social, and medical impairment in opioid dependent pregnant women. *Am. J. Addict.* **19**, 416–421 (2010).
4. Wachman, E. M. et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. *J. Addict. Med.* **5**, 293–299 (2011).
5. Grigoriadis, S. et al. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. *J. Clin. Psychiatry* **74**, e309–e320 (2013).
6. Huybrechts, K. F. et al. Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: a cohort study. *BMJ* **358**, J33266 (2017).
7. Bakhireva, L. N. et al. Severity of neonatal opioid withdrawal syndrome with prenatal exposure to serotonin reuptake inhibitors. *Pediatr Res.* (2021). Epub ahead of print.
8. Salisbury, A. L. et al. The roles of maternal depression, serotonin reuptake inhibitor treatment, and concomitant benzodiazepine use on infant neurobehavioral functioning over the first postnatal month. *Am. J. Psychiatry* **173**, 147–157 (2016).
9. Lester, B. M. & Tronick, E. Z. History and description of the Neonatal Intensive Care Unit Network Neurobehavioral Scale. *Pediatrics* **113**, 634–640 (2004).
10. Flannery, T. et al. Neonatal Abstinence Syndrome Severity Index predicts 18-month neurodevelopmental outcome in neonates randomized to morphine or methadone. *J. Pediatr.* **227**, 101–107 (2020).
11. Liu, J. et al. Neonatal neurobehavior predicts medical and behavioral outcome. *Pediatrics* **125**, e90–e98 (2010).
12. Haapakoski, R., Mathieu, J., Ebmeier, K. P., Alenius, H. & Kivimaki, M. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behav. Immun.* **49**, 206–215 (2015).
13. Leff-Gelman, P. et al. The immune system and the role of inflammation in perinatal depression. *Neurosci. Bull.* **32**, 398–420 (2016).
14. Seth, S., Lewis, A. J. & Galbally, M. Perinatal maternal depression and cortisol function in pregnancy and the postpartum period: a systematic literature review. *BMC Pregnancy Childbirth* **16**, 124 (2016).
15. Rodriguez, N., Vining, M. & Bloch-Salisbury, E. Salivary cortisol levels as a biomarker for severity of withdrawal in opioid-exposed newborns. *Pediatr. Res.* **87**, 1033–1038 (2020).
16. Conradt, E., Lester, B. M., Appleton, A. A., Armstrong, D. A. & Marsit, C. J. The roles of DNA methylation of NR3C1 and 11b-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. *Epigenetics* **8**, 1321–1329 (2013).
17. Gluckman, P. D., Hanson, M. A., Cooper, C. & Thornburg, K. L. Effect of in utero and early-life conditions on adult health and disease. *N. Engl. J. Med.* **359**, 61–73 (2008).
18. Ostlund, B. D. et al. Maternal mindfulness during pregnancy predicts newborn neurobehavior. *Dev. Psychobiol.* **63**, e22131 (2021).
19. Chin Foo, C. A., Dansereau, L. M., Hawes, K., Oliveira, E. L. & Lester, B. M. Improving the assessment of neonatal abstinence syndrome. *Children* **8**, 685 (2021).
20. Patrick, S. W., Kaplan, H. C., Passarella, M., Davis, M. M. & Lorch, S. A. Variation in treatment of neonatal abstinence syndrome in US Children's Hospitals, 2004-2011. *J. Perinatol.* **34**, 867–872 (2014).
21. Young, W. et al. Site-level variation in the characteristics and care of infants with neonatal opioid withdrawal. *Pediatrics* **147**, e2020008839 (2021).
22. Jansson, L. M. & Velez, M. L. Optimal care for NAS: Are we moving in the wrong direction? *Hosp. Pediatr.* **9**, 655–658 (2019).

AUTHOR CONTRIBUTIONS

B.M.L. contributed to reviewing the manuscript cited in the Commentary, both authors contributed to the drafting of the Commentary, and final review and edits of the Commentary.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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