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Expanding Diagnostic Capabilities for Neonatal Opioid Withdrawal Syndrome: How LC-MS/MS Can Transform Clinical Outcomes

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Abstract

The opioid epidemic continues to be a public health crisis resulting in neonatal opioid exposure and Neonatal Opioid Withdrawal Syndrome (NOWS) with a growing prevalence and significant developmental, clinical and economic impacts. Current methods of diagnosis, such as the Finnegan Neonatal Abstinence Scoring System and Eat, Sleep, Console framework, focus mainly on subjective symptom-based evaluation, which fails to fully elucidate the biological diversity of opioid-exposed babies. This view suggests that NOWS management can be revolutionized with the use of liquid chromatography–tandem mass spectrometry (LC-MS/MS) for precision toxicology and mechanism-based neonatal care. Analysis of neonatal biospecimens using LC-MS/MS provides highly sensitive and multiplexed profiling of opioids, metabolites, inflammatory mediators, oxidative stress markers, neurotransmitter disruptions, mitochondrial dysfunction signatures, and profiling of microbiome-associated metabolites. The molecular characterization could enable identification of different biochemical endotypes linked to the severity of withdrawal and long-term neurodevelopmental outcomes. Combining metabolomic, exposomic and epigenomic data with clinical data and processes may help with objective risk stratification, personalized treatment, minimization of unnecessary opioid use and long-term monitoring. The article also emphasizes the implementation challenges like analytical standardization, ethical governance, clinical integration and equity of access. Precision neonatology guided by the LC-MS/MS technology can change the delivery of NOWS from a reactive approach to care of symptoms towards proactive approaches to individual and biologically informed intervention strategies.

Keywords: Neonatal Opioid Withdrawal Syndrome, public health, liquid chromatography–tandem mass spectrometry, toxicology.

1. Introduction

Opioid use disorder (OUD) is still a significant public health problem in the United States. Although there has been some stabilization among adults in overdose mortality in recent years, the effects of drug overdoses on the next generation have not abated much (Wenk et al., 2024). According to The Health Care Cost and Utilization Project (HCUP), approximately 6 out of every 1000 babies born in the United States are diagnosed with Neonatal Abstinence Syndrome (NAS) or Neonatal Opioid Withdrawal Syndrome (NOWS) (Pandya et al., 2023). This translates to 1 baby being diagnosed every 24 minutes. Nationwide rates increased 82% between 2010 and 2017, and there is extreme geographic variability in the incidence of NAS/NOWS, from less than 3 cases per 1,000 births in Hawaii to 40-68 cases in states such as West Virginia (Wenk et al., 2024). Since at least 2020, many regions have continued to report high rates of NAS/NOWS, demonstrating the ongoing impact of the opioid epidemic on the neonatal health of the current generation—rather than a fleeting phenomenon.

Newborns with NAS/NOWS are exposed to risks for prolonged hospitalizations, medication use (i.e., opioids) for treatment, feeding deficits, seizures, and other complications (Tobacyk et al., 2023). Long-term risks for infants exposed to NAS/NOWS include neurodevelopmental delay, behavioral issues, and increased health care utilization. Additionally, research has previously demonstrated significant costs associated with NAS/NOWS treatment, historically greater than $500-700 million per year. Despite decades of rising cases of NAS/NOWS, very little has changed regarding the way in which they are diagnosed (Therrell et al., 2024). Most diagnoses continue to rely on subjective clinical scoring systems that assess observable symptoms, for example, crying, irritability, as opposed to any underlying biological issues.

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2. Limitations of Current Diagnostic Paradigms

Clinical tools such as the Finnegan Neonatal Abstinence Scoring System and the Eat, Sleep, Console (ESC) offer valuable clinical guidance but are limited in some respects. These are subjective and can be affected by other factors apart from opioids, such as gestational age, polysubstance exposure, maternal medication, etc. and have limited value for individual pathophysiological trajectories (Kapur & Aleksa, 2020). As a result, treatment is largely trial-and-error and a jacked-up dosage approach. Many babies are given unnecessary opioids, and some babies who have high-risk molecular profiles are inadequately treated or have extended opioid withdrawal symptoms (Ververi et al., 2023). This non-precision, symptomatic strategy does not account for the incredible biological variability of neonates exposed to opioids.

Opioid exposure during early development impairs functioning across several interrelated systems, including oxidative stress, proinflammatory, protransmitter, and mitochondrial pathways in the brain axis (Mussap et al., 2020). These disruptions are not all alike, however, and result in unique biochemical endotypes that contribute to differences in withdrawal severity and long-term outcomes. Without a molecular-level interrogation tool, clinicians are using blunt instruments to treat a complicated syndrome.

3. LC-MS/MS is a Precision Toxicology Platform

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is an ideally suited technique to bridge this gap. LC-MS/MS is already a highly sensitive, specific and multiplexing tool for drug detection and has the potential to become a comprehensive precision diagnostic tool for NOWS (Fariha et al., 2025). It enables high-throughput exposome profiling, simultaneously quantifying opioids and their metabolites, as well as hundreds of downstream small-molecule biomarkers, from umbilical cord blood, meconium, plasma, or dried blood spots.

LC-MS/MS can identify children into proposed biochemical endotypes by targeted and untargeted metabolomics. Oxidative stress endotypes are characterized by the increase of malondialdehyde (MDA), 4-hydroxynonenal (4-HNE) and oxidative glutathione. Increased metabolites of the kynurenine pathway, including kynurenic acid and its metabolites, are present in the neuroinflammatory signatures (Fariha et al., 2025). The mitochondrial dysfunction is manifested by the change in lactate/pyruvate ratios and loss of tricarboxylic acid (TCA) cycle intermediates. Other factors, such as neurotransmitter dysregulations and microbial metabolites (e.g., short-chain fatty acids), highlight gut-brain axis disruption. These profiles, combined with epigenomic markers, for instance, DNA methylation at OPRM1, BDNF, and HPA-axis genes and microbiome data, create potent and personalized risk signatures.

4. Clinical transformation and improved outcomes

Precise LC-MS/MS analysis could dramatically change the way NOWS is managed. Rapid exposome and metabolomic profiling at birth would allow objective risk stratification, which would include identification of infants who were at risk of severe withdrawal who could be treated with pharmacologic agents versus infants who were not at risk of severe withdrawal who were appropriate for rooming-in and non-pharmacologic treatment (Delaney et al., 2022). This would minimize exposure to such drugs as morphine or methadone, which is very important because of the fear of iatrogenic effects of opioids on the developing brain.

Specific endotypes would also be helpful to inform the development of mechanism-based adjunctive treatments. Infants who have a strong oxidative stress signature, for example, could be given N-acetylcysteine (NAC); babies with gut-brain axis disruption, targeted microbiome support (Adav & Ng, 2025; Albano et al., 2023). Dynamic care plans would be possible with real-time monitoring of biomarker trends, reducing family separation and costs, and shortening hospital stays. Linking neonatal molecular profiles with longitudinal neurodevelopmental cohorts would allow for ‘precision surveillance protocols’ instead of ‘generic referrals’ over the longer term.

5. Implementing ethics and equity

To make this vision a reality, there are some challenges to overcome. Analytical standardization, reference ranges for neonates, and cross-laboratory harmonization are key. Seamless integration requires user-friendly clinical decision support systems, preferably based on artificial intelligence, that integrate LC-MS/MS data with EHRs (Hubbard et al., 2020). Ethics are of primary importance. Clear policies must be established to ensure maternal consent, data privacy, and the prevention of punitive action based on toxicology results. Equity is perhaps most important, as its foundation (Adav & Ng, 2025). Advanced diagnostics should not increase racial and socioeconomic or high and low-resource disparities. There is a need to develop cost-effective, scalable protocols and

"equity-aware precision neonatology" platforms to secure general benefit.

6. Conclusion

The opioid crisis has brought to light very important gaps in maternal-child health. Advanced diagnostics are a rare chance to shift an upstream problem into an upstream solution. LC-MS/MS technology is well developed and accessible to most clinical laboratories, and it is ready for use in neonatal care (de Campos et al., 2022). The paradigm shift in toxicology is from reactive symptom management to proactive, mechanism-based, personalized care, which can be achieved by changing the perspective to that of precision toxicology. Advances are going quickly in science. Now the need is for investment by funding agencies, professional societies and health systems to validate, standardize and implement these tools (Crews & Pesce, 2024). So the kids born now in this opioid crisis are not being entitled to whatever we're doing right now; they're entitled to something better, that is, something more precise.

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