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Epidemic of Prescription Opiate Abuse and Neonatal Abstinence

Marie J. Hayes, PhD

Mark S. Brown, MD

In this issue of *JAMA*, Patrick et al[1] describe the effects on newborn infants of the widespread availability of prescription opiate medications. These medications provide superior pain control for cancer and chronic pain, but have been overprescribed, diverted, and sold illegally, creating a new opiate addiction pathway and a public health burden for maternal and child health.[2] Overdose mortality and dependence rates are highest among disadvantaged, young adults in rural areas (eg, Maine and Kentucky).[3]

Young women are nearly as likely as men to abuse opiate medications, leading to an increase in opiate-dependent newborns treated for withdrawal syndrome or neonatal abstinence syndrome (NAS). The standard of care for opiate addiction during pregnancy is methadone maintenance and psychiatric care.

Patrick et al[1] demonstrate that the increase in NAS (from an incidence of 1.20 [95% CI, 1.04-1.37] per 1000 hospital births per year in 2000 to 3.39 [95% CI, 3.12-3.67] per 1000 hospital births per year in 2009) has created a health care encumbrance primarily for state Medicaid budgets. In affected states, methadone treatment programs have expanded rapidly and voluntary prescription monitoring programs identify opiate medication use patterns (ie, opiate prescriptions are tracked and individuals who are "shopping" for physicians to prescribe opiates can be identified). However, the burden of addiction on state Medicaid budgets threatens retrenchment of recently established programs despite increased need. This poses a crisis of care for affected fetuses and newborns. However, without accessible treatment of both maternal opiate addiction and new methods of treating NAS, state and federal systems may pay in the future because many of these infants require special services for developmental and behavioral disorders.[4]

Patrick et al[1] also observed that over the last decade, there has been no improvement in NAS treatment efficiency as measured by length of stay (LOS). Furthermore, health care expenditures for NAS have increased during the same period. Even within the context of the status quo of medically managed prenatal methadone treatment, opiate-exposed infants risk adverse effects besides the specter of protracted withdrawal. In their analyses of hospital complications of infants with NAS, Patrick et al confirmed other data demonstrating increased rates of prematurity, respiratory disease, and seizures.[5,6] Opiate withdrawal is often compounded by comorbid polydrug exposure and maternal psychiatric medications, such as antidepressants and benzodiazepines, which have their own withdrawal syndromes.[7,8] Although the withdrawal from these agents is milder than opiates, such combinatorial withdrawal complicates neonatal care and often extends LOS. Neonatal abstinence syndrome withdrawal severity affects adaptation to postnatal life in critical regulatory areas of sleep, feeding, and autonomic function.[9,10]

Although 60% to 80% of infants exposed in utero to opiates develop NAS and require prolonged hospitalization, averaging 16 days in the study by Patrick et al,[1] there is still considerable uncertainty regarding optimal detoxification protocols and criteria for opiate withdrawal status typically based on symptoms assessed by the Finnegan score calculated every few hours from birth to day 5. Hospitals and clinicians burdened by the increase in NAS incidence can expend substantial efforts to develop treatment protocols to decrease LOS. As outlined by Patrick et al, most clinicians use oral opiate medication (eg, methadone or morphine) and, in difficult cases, a second-line nonopiate drug with γ-aminobutyric acid (eg, phenobarbital), benzodiazepine (eg, clonazapam), or anti-adrenergic (eg, clonidine) action. Novel pharmacotherapy research is needed to improve maternal opiate maintenance strategies to protect the fetus from in utero withdrawal, and to reduce the incidence and severity of NAS. These efforts have been frustrated by lack of controlled clinical trials.

Methadone maintenance therapy during pregnancy is currently idiosyncratic (eg, lack of standardization in maternal care related to dosing) and based on maternal withdrawal symptoms as gestation progresses. Research aimed at predicting which newborns are most at risk for a difficult withdrawal, or will require prompt treatment, has yielded few leads. In the adult pain management literature,[11] individual genetic differences have been found to predict opiate response and dose

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Author Affiliations: Department of Psychology, University of Maine, Orono, and Department of Pediatrics, Eastern Maine Medical Center and Psychiatry, Acadia Hospital, Bangor, Maine (Dr Hayes); and Department of Pediatrics, Eastern Maine Medical Center, Bangor (Dr Brown).
Corresponding Author: Marie J. Hayes, PhD, Department of Psychology, University of Maine, 5742 Little Hall, Orono, ME 04469 (marie.hayes@umit.maine.edu).

requirements. A pilot study of newborns with NAS found a relationship between withdrawal severity, replacement opiate dose requirements, need for a second drug, and LOS based on allelic variants of OPRM1 (opioid receptor, mu 1) and COMT (catechol-o-methyltransferase), which affect autonomic instability during withdrawal.[12]

Neonatal withdrawal status is monitored every few hours after birth by nursing personnel using the Finnegan scoring system, a clinical measure that rates sleep, movement, and feeding difficulty, as well as signs of opiate withdrawal similar to those established in withdrawing adults, such as yawning, tremors, and watery stools.[13] Standardization and interrater reliability of scoring is challenging and additional complementary tools are needed. Currently, this is the best method of diagnosing NAS, evaluating severity, and titrating dose change during neuropharmacological weaning, but it is inadequate.

In the face of maternal addiction and psychiatric disease, characterizing the fetus' exposure to opiates and other drugs, and thereby inferring risk of NAS, is exceedingly complex. In many studies, comorbid nicotine, alcohol, and illicit drug use is not assessed because it is unknown or deemed too costly to conduct standard interview and bioassays of maternal urine and infant meconium. The lack of this information precludes the ability to isolate the effects of opiate withdrawal. Jones et al[14] assessed comorbid alcohol and drug use in a clinical trial comparing methadone vs buprenorphine, an opiate with less severe withdrawal in adults. Although buprenorphine reduced morphine requirements and duration of NAS, including LOS, there was no difference in the rate of NAS diagnosis.[15] The buprenorphine group demonstrated a higher dropout rate from the study, suggesting that this agent may not treat maternal addiction as effectively as methadone and may not be appropriate for all women with narcotic addiction.

A recent Substance Abuse and Mental Health Services Administration report[16] found that Maine was among the highest states in the nation in rates of prescription opiate abuse (45/100 000 vs 386/100 000 admissions per year). Low socioeconomic status is coupled with intergenerationally high alcohol, tobacco, and drug use.[17,18] During pregnancy and the periconceptional period, poverty associated malnutrition is only partially addressed by Women, Infants, and Children program and other assistance programs. Therefore, covariates related to deprivation in the environment, prenatal and postnatal psychiatric stress, and teratogenic effects of alcohol are critical to include in evaluation of long-term outcomes of NAS.[19]

Future directions in NAS research must address the need for clinical trials of new medications to establish optimal protocols for maternal opiate dependence with particular focus on methadone treatment induction of the mother early in pregnancy, maternal adherence to treatment, ancillary alcohol use monitoring, and psychiatric care. Postnatally, early identification and aggressive opiate replacement in infants with early signs of NAS may help to decrease severity and LOS. As suggested by Patrick et al[1] and other studies, breastfeeding may reduce treatment rate and LOS in opiate-exposed infants in all categories.[5,20] Clues to fetal-neonatal dependence and NAS risk are emerging from studies of placental transfer of opiates across gestation, relation to maternal dose change, infant pharmacogenomics, and meconium metabolites to determine other exposures. This additional information may lead to better postnatal care of infants with NAS.

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REFERENCES

1. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009 [published online April 30, 2012]. *JAMA*. doi:10.1001/jama.2012.3951.
2. Centers for Disease Control and Prevention. CDC Congressional Testimony, 2007. http://www.cdc.gov/washington/testimony/2007/t20071024.htm. Accessed April 16, 2012.
3. Paulozzi LJ, Xi Y. Recent changes in drug poisoning mortality in the United States by urban-rural status and by drug type. *Pharmacoepidemiol Drug Saf*. 2008;17(10):997-1005.
4. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Hum Dev*. 2007;84(1):29-35.
5. Brown MS, Hayes MJ, LaBrie S. Breastfeeding is associated with decreased risk and length of treatment for neonatal abstinence syndrome in methadone and buprenorphine exposed infants. Presented at: Pediatric Academic Societies; May 1-4, 2011; Vancouver, British Columbia, Canada. Abstract 2917.228.
6. Dryden C, Young D, Hepburn M, Mactier H. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *BJOG*. 2009;116(5):665-671.
7. Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *J Obstet Gynecol Neonatal Nurs*. 2012;41(2):180-190.
8. Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med*. 2006;160(2):173-176.
9. Jansson LM, Dipietro JA, Elko A, Velez M. Maternal vagal tone change in response to methadone is associated with neonatal abstinence syndrome severity in exposed neonates. *J Matern Fetal Neonatal Med*. 2007;20(9):677-685.
10. Wachman EM, Newby PK, Vreeland J, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. *J Addict Med*. 2011;5(4):293-299.
11. Lacroix-Fralish ML, Mogil JS. Progress in genetic studies of pain and analgesia. *Annu Rev Pharmacol Toxicol*. 2009;49:97-121.
12. Wachman EM, Brown MS, Paul JA, et al. Single nucleotide polymorphisms and variability in severity of neonatal abstinence syndrome. Presented at: Pediatric Academic Societies; April 28-May 1, 2012; Boston, MA.
13. Finnegan LP. Neonatal abstinence syndrome: assessment and pharmacotherapy. In: Rubatelli FF, Granati B, eds. *Neonatal Therapy: An Update*. New York, NY: Excerpta Medica; 1986:122-146.
14. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;363(24):2320-2331.
15. Salisbury AL, Ponder KL, Padbury JF, Lester BM. Fetal effects of psychoactive drugs. *Clinics in Perinatology*. 2009;36(3):595-619.
16. Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA). The Treatment Episode Data Set (TEDS). http://oas.samhsa.gov/dasis.htm#teds2. Accessed April 16, 2012.
17. Hayes MJ, Brown E, Hofmaster PA, Davare AA, Parker KG, Raczek JA. Prenatal alcohol intake in a rural, caucasian clinic. *Fam Med*. 2002;34(2):120-125.
18. Logan BA, Hayes MJ, Brown M, et al. Maine's high risk infants and maternal health and wellbeing. *Maine Policy Rev*. 2009;18:60-67.
19. Messinger DS, Bauer CR, Das A, et al. The maternal lifestyle study: cognitive, motor, and behavioral outcomes of cocaine-exposed and opiate-exposed infants through three years of age. *Pediatrics*. 2004;113(6):1677-1685.
20. Jansson LM, Choo R, Velez ML, et al. Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics*. 2008;121(1):106-114.