Minireview

Developmental opioid exposures: Neurobiological underpinnings, behavioral impacts, and policy implications

Samantha S Goldfarb[1], Gregg D Stanwood[2,3], Heather A Flynn[1,3] and Devon L Graham[2,3]

[1]Department of Behavioral Sciences and Social Medicine, Florida State University College of Medicine, Tallahassee, FL 32306, USA; [2]Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, FL 32306, USA; [3]Center for Brain Repair, Florida State University College of Medicine, Tallahassee, FL 32306, USA
Corresponding author: Gregg D Stanwood. Email: gregg.stanwood@med.fsu.edu

Impact statement

Opioid abuse is a critical epidemic affecting individuals, families, and communities. This mini-review summarizes current literature on the impact of opioid drugs—including prescription pain relievers and illicit opioids—on neurobiological and neurobehavioral development. Using concepts related to the medical model of addiction as a brain disease, we review the public policy implications of these data and identify needs for future investigations.

Abstract

The devastating impact of opioid abuse and dependence on the individual, family, and society are well known but extremely difficult to combat. During pregnancy, opioid drugs and withdrawal also affect fetal brain development and newborn neural functions, in addition to maternal effects. Neonatal Abstinence Syndrome/Neonatal Opioid Withdrawal Syndrome (NAS/NOWS) rates have drastically increased in the US in the past decade. Solutions to this complex problem must be multi-faceted, which would be greatly enhanced by a translational, multidisciplinary understanding. Therefore, this mini-review incorporates biomedical, clinical, and policy aspects of opioid use during pregnancy. We review the known roles for endogenous opioids in mediating circuit formation and function in the developing brain, discuss how exogenous opioid drug use and addiction impact these processes in animal models and humans, and discuss the implications of these data on public policy. We suggest that some current policy initiatives produce unintended harm on both mothers and their children and delineate recommendations for how legislation could better contribute to addiction recovery and increase neural resilience in affected children.

Keywords: Opiate, prenatal, perinatal, brain, addiction, neuropharmacology

***Experimental Biology and Medicine* 2020; 245: 131–137. DOI: 10.1177/1535370219883601**

Overview

The use and abuse of opioid drugs have recently reached historic levels, despite some of these compounds being known about and used for over two centuries. This is likely due to the position of opioid drugs at the intersection of two undertreated and inter-related medical problems—drug addiction and chronic pain.[1] The creation of synthetic analogs exhibiting 100–1,000-fold higher potency has also contributed substantially to this public health crisis.[2] Several recent reviews have focused on the uniquely powerful current role for opioid drugs—both legal and illegal—in producing overdose deaths, physical dependence, and long-term health and societal impacts. The developmental impact of opioid use during pregnancy has received less research attention, despite data demonstrating early expression and function of opioid drug targets during neural development. There has been a steady increase in opioid use in people aged 18–25; this obviously includes women of child-bearing age.[3] There has been a drastic rise in Neonatal Abstinence Syndrome/Neonatal Opioid Withdrawal Syndrome (NAS/NOWS) in the US since 2004.[4] Moreover, pregnant women with opioid use disorder often struggle with other co-occurring antenatal medical and neuropsychiatric conditions—particularly anxiety, major depression, and post-traumatic stress disorder—and are at increased risk for postpartum depression.[5] They are also at increased risk for using other substances with abuse liability, including marijuana, nicotine, and cocaine.[6] Solutions to this complex problem must be multi-faceted, which would be greatly enhanced by a translational, multidisciplinary understanding. Therefore, in this minireview, we summarize evidence defining the

physiological, cellular, and molecular actions of opioids during key periods of brain development, describe the effects of fetal opioid use on neurobehavioral development, and recommend specific medical, behavioral, and legislative actions to ameliorate the impact of this crisis.

Neurodevelopmental expression patterns and function of opioid-related drug targets

Opioid receptors are G protein-coupled receptors and are classified into three classes: mu, kappa, and delta. Studies have demonstrated expression of all three receptors within the central nervous system (CNS) during critical phases of brain development.[7–9] Pharmacological activation of these receptors during prenatal development alters a number of important markers of neuronal differentiation and synaptogenesis.[10–12] Although beyond the scope of the current review, it is also worth mentioning that maternal cannabis exposure alters the expression and function of endogenous opioid receptor systems,[13–15] suggesting that increased recreational marijuana use may produce related effects.

For example, in the developing striatum, the mu opioid receptor appears early during mid-gestational development and is expressed in a patch-like distribution throughout postnatal development and into adulthood. The spatiotemporal expression pattern of the mu opioid receptor appears to match the functional maturation of corticostriatal glutamate transmission.[16] Corticostriatal projections, in turn, are essential components of forebrain circuits and subserve motivated behaviors. Abnormalities within this circuit are implicated in the pathophysiology of several neurodevelopmental, neuropsychiatric, and neurological disorders, including autism, obsessive-compulsive disorder, psychosis, movement disorders, drug addiction, and major depressive disorder. Moreover, mu opioid receptor activation modulates the proliferation of neural progenitor cells, particularly in the dorsal telencephalon (for review, see Kibaly *et al*.[17]). Of note, these effects are developmental stage- and cell type-specific; given the precise regional and temporal gradients of neural progenitors in the developing brain, these data suggest that prenatal opioid exposure will have complex and highly individualized impacts on the developing fetus based on the exact timing of exposure in a pregnant woman.

Developmental exposure to opioid drugs and accompanying mechanisms

Opioid drugs can alter the developing fetus directly or indirectly via multiple maternal mechanisms (for review, see Ross *et al*.[18]). Opioids are capable of crossing the placenta[19–21] and subsequently act directly on endogenous opioid receptors in the fetal brain. Opioids can also enhance maternal secretion of cortisol and subsequently augment the secretion of stress hormones in the embryo; this produces long-term effects because the hypothalamic–pituitary adrenal axis has important roles on neural and behavioral development.[22] Postnatally, opioids alter lactation and maternal behaviors, resulting in additional processes through which neuronal maturation and behavioral resilience may be affected.[23] Additionally, although not yet directly studied, it is quite likely that maternal opioid exposure and/or addiction alters the vaginal microbiome and therefore the pioneering maternal microbiota that colonizes the offspring gastrointestinal tract; this has recently been described as a mechanism contributing to the effects of prenatal stress.[24]

A full analysis of the literature on developmental effects of opioids is beyond the scope of this minireview, but we will describe a few particularly salient studies. Animal model studies have demonstrated altered birth weights and growth patterns as well as increases in congenital malformations and stillbirths.[25,26] Even in the absence of teratological outcomes, exposed offspring exhibit long-lasting deficits in cognitive function including learning and memory,[27–30] motor hyperactivity,[31] and enhanced vulnerability to future drug use.[32,33]

Preclinical models are ideally suited to study the underlying cellular and molecular mechanisms that arise from developmental opioid exposures. Studies have described several structural and functional circuitry alterations that contribute to fetal opioid-induced effects on brain structure and function, including alterations in neuronal proliferation, synaptic structure and plasticity, and neurochemical functions (for review, see Ross *et al*.[18]). A classic study demonstrated decreased dendritic length and branches in the perinatal rodent cerebral cortex following morphine exposure, importantly showing receptor specificity in that coadministration of the antagonist naltrexone blocked the effect.[34] Synaptic plasticity and proteins associated with synaptic transmission are reduced by developmental opioid exposure,[35–37] suggesting likely reductions in neural adaptability and modulation. Of note, most studies to date have focused on a single opioid drug, exposure period, and/or limited analyses of a few endpoints. Systematic investigations using "modern" opioids, proper interspecies scaling methods, litter-based designs, and diverse structural and functional neural endpoints are sorely needed. For example, there are multiple studies examining morphine and heroin, but very few addressing the neurodevelopmental effects of prescription painkillers or synthetic opioids such as fentanyl. Animal model studies often rely on intraperitoneal or subcutaneous injections when oral or intravenous administration would be more translatable to humans. Brain development across different model organisms proceeds at different rates than humans, and dose calculations need to account for allocentric scaling and extrapolation of inter-species doses. Shared genetic and maternal environment (intra-litter likeness) are sometimes not appropriately analyzed. In addition, sex differences in neuro(mal)adaptations and potential epigenetic transmission of paternal opioid history (for review, see Goldberg and Gould[38]) are also up-and-coming areas of study that require additional examination.

Neurobehavioral effects of developmental opioid exposures—Human studies

There is a greater likelihood of a number of dangerous birth complications associated with opioid use during

pregnancy including preeclampsia, placental insufficiency, placental abruption, prenatal growth retardation, preterm labor, and even fetal death.[39–41] Even when labor and delivery is fairly uneventful, newborns often have low birth weight and smaller head circumference, and sometimes experience symptoms of opioid withdrawal (see below).[42–45] Studies have also suggested increased prevalence of structural heart defects,[46] autonomic dysregulation,[47] and oculomotor dysfunctions[48,49] in children exposed prenatally to opioids. Regarding long-term outcomes, some studies have reported that at preschool and elementary school stages, these children demonstrate impairments in motor control and cognition,[44,45,50,51] inattention,[52,53] hyperactivity,[52] and an increase in attention-deficit/hyperactivity disorder when exposed prenatally to heroin.[54] Taken together, studies to date demonstrate highly variable consequences, which suggests complex underlying mechanisms—likely influenced by the dose, type and length of drug use, timing with respect to neurodevelopmental processes, and underlying behavioral and genetic risk factors. Related to these complexities, a recent study isolated extracellular vesicles and synaptosomes from fetal neural samples in humans and observed complex changes in endogenous opioid and endocannabinoid receptor levels.[55,56] The study identified distinct effects between the two membrane preparations that were analyzed, and between the two opioids that participants in this study were using—buprenorphine and methadone. Moreover, microRNA sequencing revealed sex-dependent effects on expression pattern.

Within this context of potentially deleterious effects from pre- and perinatal exposure to opioids, the rise in prescription opioid use is alarming. From 1992 to 2012, reports of prescription opioid abuse among pregnant women increased 14-fold, from 2% to 28%.[57] Demographic characteristics of opioid admissions amongst pregnant women also changed between 1992 and 2012 in that rates increased significantly for younger women, along with criminal justice system involvement, and comorbid mental health condition diagnoses. Unfortunately, only about one-third of women using opioids during pregnancy actually received medication-assisted therapy (MAT)—despite MAT representing the standard of care. This increasing incidence of opioid use during pregnancy has produced an escalation in adverse neonatal outcomes including NAS/NOWS. NAS/NOWS is a collection of withdrawal syndrome, whereby opioid-exposed infants experience a rebound in excitability within the CNS shortly after birth. From 2004 to 2014, the number of infants diagnosed with the syndrome grew five-fold (and in some states 10-fold).[58,59] In 2014 alone, over 32,000 babies were diagnosed with NAS/NOWS, equaling a baby born with NAS/NOWS every 15 min nationwide.[4,60] Hospital costs associated with NAS/NOWS totaled $532 million in 2014, with $462 million being Medicaid-financed births.[4,61] Between 2004 until 2012, neonatal intensive care unit hospital days for NAS/NOWS infants increased by six to seven times during this time.[62] While alarming, these numbers do not capture the true gravity of opioid use in pregnancy because it does not include babies experiencing other complications from usage (e.g. placental abruption) or concurrent use of other substances in pregnancy. Even when adverse neurobehavioral effects may not be apparent in neonates and infancy, they may become more salient as children develop and reach preschool and school age.[63]

Intervention models for prenatal and childhood exposure to substance use and other neurodevelopmental risk

Even within the framework of a medical model of addiction, pregnant women often face discrimination and criminalization as a result of their addiction and drug use. This context contributes to under-treatment of these women and their children and is reminiscent of societal responses to the crack cocaine epidemic of the 1980s. Implicit and explicit discouragement of intervention through stigmatization and criminalization is ineffective and costly to the individuals, families, and society.[64] In fact, the American College of Obstetricians and Gynecologists have called for universal screening for substance abuse. It is recommended that such screening be included in standard obstetrical care. Ideally, this would occur at the first prenatal visit in partnership with the patient.[65]

Studies of developmental disabilities consistently point to early intervention as a crucial component to normalizing neurodevelopmental trajectory, regardless of the molecular or cellular origin of the disease. The ability of positive family, educational, and biological environments to ameliorate the effects of developmental perturbations has been demonstrated for children with neurodevelopmental risk.[66] As described by the Center on the Developing Child at Harvard,[67] key core principles of such interventions include (1) support responsive relationships for the child, (2) strengthen fundamental life skills, and (3) diminish sources of stress in the everyday experiences of children and their families. At the simplest level, the earlier an intervention can be effectively deployed, the greater its long-term impact and cost-effectiveness.[68] For example, early deployment of intensive multidisciplinary behavioral, cognitive, motor, and educational therapies have been shown to be successful in treating children with autism spectrum disorder,[69] premature birth,[70] and following *in utero* exposure to cocaine.[71]

Family-centered treatment strategies have been suggested as optimal for women with substance use disorders. The Substance Abuse and Mental Health Services Administration presented a five-level continuum of family-based services for this population,[72] including: (1) services for women with substance use disorders, (2) women's treatment while accompanied by children, (3) women and children's social services, (4) family services, and (5) family-centered treatment. Overall, the strategy is to ensure the provision of appropriate treatment plans which respond to the mother's (and any other affected family member's) need for substance use and/or mental health disorder treatment. This may range from providing direct care to the infant experiencing neurodevelopmental, physical, or withdrawal symptoms from exposure to the substance in utero, to clinical and community services that

improve the caregivers' ability to care for the child and promote resiliency. More research is needed to assess the optimal intervention strategies. For example, in a comparison of characteristics of pregnant women on methadone-maintenance versus a comparison group, it was noted that almost 50% of the women utilizing this MAT method met criteria for clinical diagnosis of major depressive disorder as compared to 8% of controls.[73] It needs to be determined whether augmenting or sequencing other interventions with MAT, including therapies directed to comorbid mental health conditions, will improve long-term treatment outcomes for women and their families.

Public policy: Approaches and implications

The American College of Obstetricians and Gynecologists has issued recommendations on opioid use during gestation. A proposed best practice is universal screening with standardized and valid tools as early in pregnancy as possible, but this is not occurring nationwide or through a treatment-focused lens.[65] Screening based on only subset features, such as poor adherence to antenatal care or previous adverse pregnancy outcome, leads to under-identification of women at risk and contributes to stigmatization. For patients of child-bearing age experiencing chronic pain, strategies should include minimizing the use of opioids for pain management, and conversely emphasizing non-pharmacologic pain therapies including exercise, physical rehabilitation, and cognitive-behavioral approaches) and non-opioid pharmacotherapies. Healthcare providers must do everything they can to be certain that opioids are necessary before prescribing them. This includes a discussion of the risks and benefits of opioid medications and a thorough review of treatment goals with patients within the context of their individual history of substance use. These providers need to consistently review the Prescription Drug Monitoring Program to ascertain whether previous opioid prescriptions have been provided. Nursing should be encouraged when mothers are not using illicit drugs and are stable on MAT, but mothers should also be counseled about suspending breastfeeding in the event of a relapse. Access to appropriate postpartum services should be made available, including medical care, psychosocial support, and treatment for relapse. Lastly, access to contraception and counseling should be a standard component of treatment of women of child-bearing ages.

Of importance, the Child Abuse Prevention and Treatment Act (CAPTA) was most recently modified by Section 501 of the Comprehensive Addiction and Recovery Act of 2016 (CARA). CARA made several updates to CAPTA, including: (1) eliminating the term "illegal" as it relates to drug use; (2) requiring that a plan of safe care addresses the needs of both the child *and* the affected family/caregiver (rather than just the infant); (3) requiring that states develop and implement systems to monitor the implementation of such plans; and (4) specifying data variable reporting by states. The intent, at least in part, is to determine whether and how local entities are providing referrals to and delivery of appropriate services for the infant and their caregivers. This includes reporting as much as possible on affected infants in the plans of safe care. In addition, multiple components to data monitoring should be addressed including identifying the incidence of children affected by maternal use and associated NAS/NOWS symptoms, identifying the number of affected neonates/infants for whom a plan of safe care was developed, and identifying the number of affected neonates/infants for whom referrals for services were generated. CARA also amended a funded residential treatment program for women during pregnancy and immediately post-partum, and created a new pilot program that will award competitive grants to state agencies in order to detect disparities in service deployments and hopefully develop new methods to provide high-quality services supported by evidence of success.

Even beyond any specific issue of opioid exposures during pregnancy, we note that the rate of maternal death in the US is higher than that of most other high-income countries. The rate has risen over the last 20 years, and significant racial, ethnic, and socioeconomic disparities have been described.[74] Responsible opioid prescribing practices are essential, as are expanding the availability of MAT and standardizing care of infants at risk of NAS/NOWS.[63,75,76] Efforts to criminally penalize pregnant women and the presence of any damaging consequences for disclosing substance use to medical practitioners are damaging and counter-productive; these deter women from seeking prenatal care, counseling, social support, and other healthcare services while pregnant.[77–79] Providers need to advocate for health policies informed by evidence-based medicine and practices. This will serve to increase resiliency in both the individual and societal levels and should optimize outcomes for mothers and their infants.

Summary and next steps

The devastating impact of opioid abuse and dependence on the individual, family, and society are well known but extremely difficult to combat. Pregnancy and postpartum periods represent critical windows for which willingness to engage in treatment and its impact on maternal and perinatal health may be at its height. Endogenous opioids contribute to the formation and function of the developing nervous system; thus, it is not surprising that exogenous opioid drug use alters brain and behavioral development. Somewhat surprising, however, is the relative lack of well-designed and powered research studies examining the affected neurological and neurobehavioral systems after fetal opioid exposure. Data to date suggest highly variable consequences, which imply complex underlying mechanisms. It is vitally important to bridge the gap between what biomedical and social science informs us about the neurodevelopmental impact of fetal drug exposure and how we use this science to inform clinical treatment and

public policy. Many current policy initiatives produce unintended harm on both mothers and their children and exacerbate the public health problem. Scientists and clinicians must reframe this issue, productively engage policymakers and the public, and address this pressing challenge.

Authors' contributions: All authors participated in the writing and review of the article.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

We thank the Florida State University College of Medicine for funding our time to write this manuscript. Other funding includes R21-MH116429 (GDS), R03-MH110749 (DLG), and Sage Therapeutics (HAF).

ORCID iD

Gregg D Stanwood https://orcid.org/0000-0001-6005-1203

REFERENCES

1. Volkow ND, Koroshetz WJ. The role of neurologists in tackling the opioid epidemic. *Nat Rev Neurol* 2019;**15**:301–5
2. Leen JLS, Juurlink DN. Carfentanil: a narrative review of its pharmacology and public health concerns. *Can J Anesth/J Can Anesth* 2019;**66**:414–21
3. Quality CfBHSa. *2013 National Survey on Drug Use and Health*. Rockville, MD: Services SAaMH, Administration, 2014
4. Honein MA, Boyle C, Redfield RR. Public health surveillance of prenatal opioid exposure in mothers and infants. *Pediatrics* 2019;**143**: e20183801
5. Holbrook A, Kaltenbach K. Co-occurring psychiatric symptoms in opioid-dependent women: the prevalence of antenatal and postnatal depression. *Am J Drug Alcohol Abuse* 2012;**38**:575–9
6. Jones HE, Heil SH, O'Grady KE, Martin PR, Kaltenbach K, Coyle MG, Stine SM, Selby P, Arria AM, Fischer G. Smoking in pregnant women screened for an opioid agonist medication study compared to related pregnant and non-pregnant patient samples. *Am J Drug Alcohol Abuse* 2009;**35**:375–80
7. Tong Y, Chabot JG, Shen SH, O'Dowd BF, George SR, Quirion R. Ontogenic profile of the expression of the mu opioid receptor gene in the rat telencephalon and diencephalon: an in situ hybridization study. *J Chem Neuroanatomy* 2000;**18**:209–22
8. Barg J, Levy R, Simantov R. Expression of the three opioid receptor subtypes mu, Delta and kappa in guinea pig and rat brain cell cultures and in vivo. *Int J Dev Neurosci* 1989;**7**:173–9
9. Rius RA, Barg J, Bem WT, Coscia CJ, Loh YP. The prenatal development profile of expression of opioid peptides and receptors in the mouse brain. *Brain Res Dev Brain Res* 1991;**58**:237–41
10. Matus-Leibovitch N, Ezra-Macabee V, Saya D, Attali B, Avidor-Reiss T, Barg J, Vogel Z. Increased expression of synapsin I mRNA in defined areas of the rat Central nervous system following chronic morphine treatment. *Brain Res Mol Brain Res* 1995;**34**:221–30
11. Steingart RA, Barg J, Maslaton J, Nesher M, Yanai J. Pre- and postsynaptic alterations in the septohippocampal cholinergic innervations after prenatal exposure to drugs. *Brain Res Bull* 1998;**46**:203–9
12. Vatury O, Barg J, Slotkin TA, Yanai J. Altered localization of choline transporter sites in the mouse hippocampus after prenatal heroin exposure. *Brain Res Bull* 2004;**63**:25–32
13. DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P, Dow-Edwards D, Hurd YL. Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. *Biol Psychiatry* 2011;**70**:763–9
14. Spano MS, Ellgren M, Wang X, Hurd YL. Prenatal cannabis exposure increases heroin seeking with allostatic changes in limbic enkephalin systems in adulthood. *Biol Psychiatry* 2007;**61**:554–63
15. Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. Discrete opioid gene expression impairment in the human fetal brain associated with maternal marijuana use. *Pharmacogenomics J* 2006;**6**:255–64
16. Wang H, Cuzon VC, Pickel VM. Postnatal development of mu-opioid receptors in the rat caudate-putamen nucleus parallels asymmetric synapse formation. *Neuroscience* 2003;**118**:695–708
17. Kibaly C, Xu C, Cahill CM, Evans CJ, Law PY. Non-nociceptive roles of opioids in the CNS: opioids' effects on neurogenesis, learning, memory and affect. *Nat Rev Neurosci* 2019;**20**:5–18
18. Ross EJ, Graham DL, Money KM, Stanwood GD. Developmental consequences of fetal exposure to drugs: what we know and what we still must learn. *Neuropsychopharmacology* 2015;**40**:61–87
19. Fokina VM, Patrikeeva SL, Zharikova OL, Nanovskaya TN, Hankins GV, Ahmed MS. Transplacental transfer and metabolism of buprenorphine in preterm human placenta. *Am J Perinatol* 2011;**28**:25–32
20. Gerdin E, Rane A, Lindberg B. Transplacental transfer of morphine in man. *J Perinatal Med* 1990;**18**:305–12
21. Nanovskaya TN, Nekhayeva IA, Hankins GD, Ahmed MS. Transfer of methadone across the dually perfused preterm human placental lobule. *Am J Obstet Gynecol* 2008;**198**:126.e1–4
22. Matthews S, McGowan P. Developmental programming of the HPA axis and related behaviours: epigenetic mechanisms. *J Endocrinol* 2019;**242**:T69–T79
23. Brunton PJ. Endogenous opioid signalling in the brain during pregnancy and lactation. *Cell Tissue Res* 2019;**375**:69–83
24. Jasarevic E, Howard CD, Morrison K, Misic A, Weinkopff T, Scott P, Hunter C, Beiting D, Bale TL. The maternal vaginal microbiome partially mediates the effects of prenatal stress on offspring gut and hypothalamus. *Nat Neurosci* 2018;**21**:1061–71
25. McLaughlin PJ, Tobias SW, Lang CM, Zagon IS. Opioid receptor blockade during prenatal life modifies postnatal behavioral development. *Pharmacol Biochem Behav* 1997;**58**:1075–82
26. McLaughlin PJ, Wylie JD, Bloom G, Griffith JW, Zagon IS. Chronic exposure to the opioid growth factor, [Met5]-enkephalin, during pregnancy: maternal and preweaning effects. *Pharmacol Biochem Behav* 2002;**71**:171–81
27. Davis CP, Franklin LM, Johnson GS, Schrott LM. Prenatal oxycodone exposure impairs spatial learning and/or memory in rats. *Behav Brain Res* 2010;**212**:27–34
28. Lu R, Liu X, Long H, Ma L. Effects of prenatal cocaine and heroin exposure on neuronal dendrite morphogenesis and spatial recognition memory in mice. *Neurosci Lett* 2012;**522**:128–33
29. Schrott LM, Franklin L, Serrano PA. Prenatal opiate exposure impairs radial arm maze performance and reduces levels of BDNF precursor following training. *Brain Res* 2008;**1198**:132–40
30. Wang Y, Han TZ. Prenatal exposure to heroin in mice elicits memory deficits that can be attributed to neuronal apoptosis. *Neuroscience* 2009;**160**:330–8
31. Sithisarn T, Legan SJ, Westgate PM, Wilson M, Wellmann K, Bada HS, Barron S. The effects of perinatal oxycodone exposure on behavioral outcome in a rodent model. *Front Pediatr* 2017;**5**:180
32. Chiang YC, Hung TW, Ho IK. Development of sensitization to methamphetamine in offspring prenatally exposed to morphine, methadone and buprenorphine. *Addict Biol* 2014;**19**:676–86
33. Ramsey NF, Niesink RJ, Van Ree JM. Prenatal exposure to morphine enhances cocaine and heroin self-administration in drug-naive rats. *Drug Alcohol Depend* 1993;**33**:41–51

34. Ricalde AA, Hammer RP Jr. Perinatal opiate treatment delays growth of cortical dendrites. *Neurosci Lett* 1990;**115**:137–43
35. Villarreal DM, Derrick B, Vathy I. Prenatal morphine exposure attenuates the maintenance of late LTP in lateral perforant path projections to the dentate gyrus and the CA3 region in vivo. *J Neurophysiol* 2008;**99**:1235–42
36. Wu PL, Yang YN, Suen JL, Yang YSH, Yang CH, Yang SN. Long-Lasting alterations in gene expression of postsynaptic density 95 and inotropic glutamatergic receptor subunit in the mesocorticolimbic system of rat offspring born to Morphine-Addicted mothers. *Biomed Res Int* 2018;**2018**:5437092
37. Yang SN, Liu CA, Chung MY, Huang HC, Yeh GC, Wong CS, Lin WW, Yang CH, Tao PL. Alterations of postsynaptic density proteins in the hippocampus of rat offspring from the morphine-addicted mother: beneficial effect of dextromethorphan. *Hippocampus* 2006;**16**:521–30
38. Goldberg LR, Gould TJ. Multigenerational and transgenerational effects of paternal exposure to drugs of abuse on behavioral and neural function. *Eur J Neurosci* 2018;
39. Hulse GK, Milne E, English DR, Holman CD. The relationship between maternal use of heroin and methadone and infant birth weight. *Addiction (Abingdon, England)* 1997;**92**:1571–9
40. Bashore RA, Ketchum JS, Staisch KJ, Barrett CT, Zimmermann EG. Heroin addiction and pregnancy. *West J Med* 1981;**134**:506–14
41. Jones HE, Martin PR, Heil SH, Kaltenbach K, Selby P, Coyle MG, Stine SM, O'Grady KE, Arria AM, Fischer G. Treatment of opioid-dependent pregnant women: clinical and research issues. *J Substance Abuse Treat* 2008;**35**:245–59
42. Binder T, Vavrinkova B. Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. *Neuro Endocrinol Lett* 2008;**29**:80–6
43. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, Ely EW, Grijalva CG, Cooper WO. Prescription opioid epidemic and infant outcomes. *Pediatrics* 2015;**135**:842–50
44. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Human Dev* 2008;**84**:29–35
45. Rosen TS, Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age. *J Pediatr* 1982;**101**:192–6
46. Ostrea EM, Chavez CJ. Perinatal problems (excluding neonatal withdrawal) in maternal drug addiction: a study of 830 cases. *J Pediatr* 1979;**94**:292–5
47. Paul JA, Logan BA, Krishnan R, Heller NA, Morrison DG, Pritham UA, Tisher PW, Troese M, Brown MS, Hayes MJ. Development of auditory event-related potentials in infants prenatally exposed to methadone. *Dev Psychobiol* 2014;**56**:1119–28
48. Gupta M, Mulvihill AO, Lascaratos G, Fleck BW, George ND. Nystagmus and reduced visual acuity secondary to drug exposure in utero: long-term follow-up. *J Pediatr Ophthalmol Strabismus* 2012;**49**:58–63
49. Gill AC, Oei J, Lewis NL, Younan N, Kennedy I, Lui K. Strabismus in infants of opiate-dependent mothers. *Acta Paediatrica* 2003;**92**:379–85
50. Bunikowski R, Grimmer I, Heiser A, Metze B, Schafer A, Obladen M. Neurodevelopmental outcome after prenatal exposure to opiates. *Eur J Pediatr* 1998;**157**:724–30
51. Guo X, Spencer JW, Suess PE, Hickey JE, Better WE, Herning RI. Cognitive brain potential alterations in boys exposed to opiates: in utero and lifestyle comparisons. *Addict Behav* 1994;**19**:429–41
52. Ornoy A, Michailevskaya V, Lukashov I, Bar-Hamburger R, Harel S. The developmental outcome of children born to heroin-dependent mothers, raised at home or adopted. *Child Abuse Neglect* 1996;**20**:385–96
53. Hickey JE, Suess PE, Newlin DB, Spurgeon L, Porges SW. Vagal tone regulation during sustained attention in boys exposed to opiates in utero. *Addict Behav* 1995;**20**:43–59
54. Ornoy A, Segal J, Bar-Hamburger R, Greenbaum C. Developmental outcome of school-age children born to mothers with heroin dependency: importance of environmental factors. *Dev Med Child Neurol* 2001;**43**:668–75
55. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and Meta-analysis. *BMC Psychiatry* 2014;**14**:104
56. Goetzl L, Thompson-Felix T, Darbinian N, Merabova N, Merali S, Merali C, Sanserino K, Tatevosian T, Fant B, Wimmer ME. Novel biomarkers to assess in utero effects of maternal opioid use: first steps toward understanding short- and long-term neurodevelopmental sequelae. *Genes Brain Behav* 2019;**18**:e12583
57. Martin CE, Longinaker N, Terplan M. Recent trends in treatment admissions for prescription opioid abuse during pregnancy. *J Substance Abuse Treat* 2015;**48**:37–42
58. Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol* 2015;**35**:650–5
59. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA* 2012;**307**:1934–40
60. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization – United States, 1999–2014. *MMWR Morb Mortal Wkly Rep* 2018;**67**:845–9
61. Winkelman TNA, Villapiano N, Kozhimannil KB, Davis MM, Patrick SW. Incidence and costs of neonatal abstinence syndrome among infants with medicaid: 2004–2014. *Pediatrics* 2018;**141**:pii:e20173520
62. Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, Clark RH, Spitzer AR. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med* 2015;**372**:2118–26
63. Larson JJ, Graham DL, Singer LT, Beckwith AM, Terplan M, Davis JM, Martinez J, Bada HS. Cognitive and behavioral impact on children exposed to opioids during pregnancy. *Pediatrics* 2019;**144**:pii:e20190514
64. Thompson BL, Levitt P, Stanwood GD. Prenatal exposure to drugs: effects on brain development and implications for policy and education. *Nat Rev Neurosci* 2009;**10**:303–12
65. American College of Obstetricians and Gynecologists. Opioid use and opioid use disorder in pregnancy. 2017. p. Report 711
66. Shonkoff JP, Levitt P. Neuroscience and the future of early childhood policy: moving from why to what and how. *Neuron* 2010;**67**:689–91
67. Center on the Developing Child at Harvard, https://developingchild.harvard.edu/ (accessed 8 October 2019)
68. Veenstra-VanderWeele J, Warren Z. Intervention in the context of development: pathways toward new treatments. *Neuropsychopharmacology* 2015;**40**:225–37
69. Zwaigenbaum L, Bauman ML, Choueiri R, Kasari C, Carter A, Granpeesheh D, Mailloux Z, Smith Roley S, Wagner S, Fein D, Pierce K, Buie T, Davis PA, Newschaffer C, Robins D, Wetherby A, Stone WL, Yirmiya N, Estes A, Hansen RL, McPartland JC, Natowicz MR. Early intervention for children with autism spectrum disorder under 3 years of age: recommendations for practice and research. *Pediatrics* 2015;**136**:S60–81
70. Cioni G, Inguaggiato E, Sgandurra G. Early intervention in neurodevelopmental disorders: underlying neural mechanisms. *Dev Med Child Neurol* 2016;**58**: 61–6
71. Bada HS, Bann CM, Whitaker TM, Bauer CR, Shankaran S, Lagasse L, Lester BM, Hammond J, Higgins R. Protective factors can mitigate behavior problems after prenatal cocaine and other drug exposures. *Pediatrics* 2012;**130**:e1479–88
72. Substance Abuse and Mental Health Services Administration. Family-centered treatment for women with substance use disorders – history, key elements, and challenges 2007; https://www.samhsa.gov/sites/default/files/family_treatment_paper508v.pdf (accessed 11 October 2019)
73. Davie-Gray A, Moor S, Spencer C, Woodward LJ. Psychosocial characteristics and poly-drug use of pregnant women enrolled in methadone maintenance treatment. *Neurotoxicol Teratol* 2013;**38**:46–52
74. Molina RL, Pace LE. A renewed focus on maternal health in the United States. *N Engl J Med* 2017;**377**:1705–7

75. Krans EE, Patrick SW. Opioid use disorder in pregnancy: health policy and practice in the midst of an epidemic. *Obstet Gynecol* 2016;**128**:4–10
76. Ko JY, Wolicki S, Barfield WD, Patrick SW, Broussard CS, Yonkers KA, Naimon R, Iskander J. CDC grand rounds: public health strategies to prevent neonatal abstinence syndrome. *MMWR Morb Mortal Wkly Rep* 2017;**66**:242–5
77. Roberts SC, Pies C. Complex calculations: how drug use during pregnancy becomes a barrier to prenatal care. *Matern Child Health J* 2011;**15**:333–41
78. Terplan M, McNamara EJ, Chisolm MS. Pregnant and non-pregnant women with substance use disorders: the gap between treatment need and receipt. *J Addict Dis* 2012;**31**:342–9
79. Bishop D, Borkowski L, Couillard M, Allina A, Baruch S, Wood S. Bridging the divide white paper: pregnant women and substance use: overview of research & policy in the United States 2017; https://hsrc.himmelfarb.gwu.edu/sphhs_centers_jacobs/5/ (accessed 11 October 2019)