Opioids affect the fetal brain: reframing the detoxification debate

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Medication-assisted treatment is recommended for individuals with an opioid use disorder, including pregnant women. Medication-assisted treatment during pregnancy provides benefits to the mother and fetus, including better pregnancy outcomes, reduced illicit drug use, and improved prenatal care. An alternative approach, medically supervised withdrawal (detoxification), has, in recent reports, demonstrated a low risk of fetal death and low rates of relapse and neonatal abstinence syndrome. The rates of relapse and neonatal abstinence syndrome are questioned by many who view medically supervised withdrawal as unacceptable based on the concern for the potential adverse consequences of relapse to mother and baby. The impact of opioids on the fetal brain have not been integrated into this debate. Studies in animals and human brain tissues demonstrate opioid receptors in neurons, astroglia, and oligodendrocytes. Age-specific normative data from infants, children, and adults have facilitated investigation of the impact of opioids on the human brain in vivo. Collectively, these studies in animals, human neural tissue, adult brains, and the brains of children and newborns demonstrate that opioids adversely affect the human brain, primarily the developing oligodendrocyte and the processes of myelinization (white matter microstructure), connectivity between parts of the brain, and the size of multiple brain regions, including the basal ganglia, thalamus, and cerebellar white matter. These in vivo studies across the human lifespan suggest vulnerability of specific fronto—temporal—limbic and frontal—subcortical (basal ganglia and cerebellum) pathways that are also likely vulnerable in the human fetal brain. The long-term impact of these reproducible changes in the fetal brain in vivo is unclear, but the possibility of lasting injury has been suggested. In light of the recent data on medically supervised withdrawal and the emerging evidence suggesting adverse effects of opioids on the developing fetal brain, a new paradigm of care is needed that includes the preferred option of medication-assisted treatment but also the option of medically supervised opioid withdrawal for a select group of women. Both these treatment options should offer mental health and social services support throughout pregnancy. More research on both opioid exposure on the developing human brain and the impact of medically supervised withdrawal is required to identify appropriate candidates, optimal dose reduction regimens, and gestational age timing for initiating medically supervised withdrawal.

Key words: accumbens area, amygdala, astroglia, brainstem, buprenorphine, detoxification, cerebellum, cerebral cortex, fetal neurobiology, medically supervised opioid withdrawal, medication-assisted treatment, magnetic resonance imaging, methadone, MRI, neural pathways, oligodendrocytes, opioids, opioid dose reduction or elimination, opioids, putamen, pallidum, superior and inferior longitudinal fasciculus and white matter

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Current Perspectives: Medication-Assisted Treatment (MAT)

MAT is currently the recommended approach for individuals with an opioid use disorder.[1-4] This approach uses medications, most commonly methadone and buprenorphine, to minimize or eliminate opioid withdrawal symptoms and minimize cravings. These medications are combined with counseling and behavioral therapies to optimize treatment outcomes. MAT is endorsed by the Substance Abuse and Mental Health Services Administration, the American Society of Addiction Medicine, the World Health Organization, and the American College of Obstetricians and Gynecologists.

One of the foundational pillars of the MAT approach for pregnant women with an opioid use disorder is the well-documented benefits to the mother and fetus, including better pregnancy outcomes, a consequence of improved prenatal care, and a reduced or eliminated exposure to illicit drugs and their potential concomitants, such as prostitution, exposure to sexually transmitted disease, complications from intravenous drug use, death, and incarceration.[1–4] Opioid use disorder is recognized as a chronic condition that requires continuing care rather than episodic acute-care treatment. Pregnant women with an opioid use disorder commonly suffer from medical comorbidities and polysubstance abuse. Unfortunately, limited resources are generally available to address this issue in a comprehensive fashion.

The second foundational pillar of MAT is the concern for relapse seen with most opioid-withdrawal strategies and the potential harms to the fetus and mother from opioid withdrawal. Rates of relapse during medically supervised withdrawal vary widely, ranging from 0% to 100%,[5] but in large (>30 cases), well-documented series of medically supervised withdrawal with mental health and social support services, relapse rates ranged from 23% to 53% and averaged 35% (157/446).[6–9] These rates are viewed as unacceptable because of concern regarding the loss of the aforementioned benefits of MAT.[10–12]

The concern for direct fetal harms, mostly fetal death, from opioid-withdrawal strategies is based in part on earlier work that demonstrated elevated levels of epinephrine and norepinephrine in the amniotic fluid from women undergoing medically supervised withdrawal.[13,14] Additional fetal concerns have been expressed over medically supervised withdrawal, including the unknown effect of withdrawal stress on the developing brain.[12]

Current Perspective: Medically Supervised Withdrawal (Detoxification)

Methadone was approved by the Food and Drug Administration for treatment of opioid use disorders in 1972. Before that time, medically supervised withdrawal of pregnant women with an opioid use disorder was the standard of care in most obstetrical facilities. Recidivism rates were very high. The option of medically supervised withdrawal became less appealing after the report from Zuspan et al in 1975 demonstrating elevated amniotic fluid catecholamines with withdrawal.[13] Recently, however, Bell et al[8] reported no fetal deaths in 300 women undergoing medically supervised withdrawal, challenging one of the fundamental pillars of those advocating MAT. Similar findings suggesting a low rate of fetal death during medically supervised withdrawal have been reported by others.[6,7,15,16] Whether medically supervised withdrawal is associated with nonlethal fetal harms has not been fully explored, but pregnancy outcomes in these series do not demonstrate maternal or fetal harms; however, the number of women studied is small, and uncommon adverse outcomes may surface with wider adoption of this approach.

Advocates of medically supervised withdrawal suggest that rates of neonatal abstinence syndrome are lower than rates reported with MAT.[7,8,15,16] A recent systematic review[5] and a meta-analysis,[17] however, have challenged this assertion. Rates of 0% to 100% of neonatal abstinence syndrome in infants of mothers undergoing medically supervised withdrawal were reported in the systematic review, but the authors reported that the published data were of poor quality.[5]

A possible explanation for the wide range of neonatal abstinence syndrome occurrence may relate to the years under study, the criteria for defining neonatal abstinence syndrome, how those who did not complete medically supervised withdrawal were counted. and differences in the support mechanisms in place for the woman undergoing medically supervised withdrawal. In the largest studies of medically supervised withdrawal with documented mental health and psychosocial support throughout pregnancy, the rates of neonatal abstinence syndrome ranged from 0% to 26%.[6,7,15,16,18] In the largest recent published studies of MAT, the rates of neonatal abstinence syndrome are greater, ranging from 26% to 68%, with the majority being closer to the 58%.[19–23] At our institution, neonatal abstinence syndrome was reported in 58% of 716 infants cared for between 2013 and 2015[24]; this rate is similar to the one reported in the Mother study.[23]

The relapse rate among those undergoing medically supervised withdrawal with mental health and social services support (23%-53%, average 35%)[6–9] is another major concern of those advocating MAT; yet, in the Mother study, a highly cited and well-designed and implemented study involving 175 women enrolled in an MAT program, 24% of mothers discontinued clinical care. Among those retained in the study, 34% did not complete the study and 12% had a positive drug screen other than the prescribed medication at delivery. Another recent study found similar results with 23% of women in a MAT program discontinuing clinical care and opioid usage was 45% despite MAT.[25] Thus, the rate of relapse in women undergoing medically supervised withdrawal must be judged by the rate of relapse in those undergoing MAT. Unfortunately, reported data on relapse rates do not provide the granularity needed to objectively ascertain the risk; factors such as the rapidity of withdrawal, support mechanisms in place, and whether the withdrawal was mandated or selected by the patient may affect the rate of relapse and possible fetal effects. Whether the relapse rate among those undergoing medical supervised withdrawal is 35% or 60%, those women completing a medically supervised withdrawal program could be opioid free during a part of their pregnancy. For those who cannot complete opioid withdrawal, the option to return to their previous dose could minimize the possibility of disengagement from clinical care, particularly if social service and mental health support are continued throughout the pregnancy.

Current Perspective: Neonatal Abstinence Syndrome

Neonatal abstinence syndrome reflects opioid withdrawal and involves irritability of the central and autonomic nervous systems and the gastrointestinal tract. Severe neonatal abstinence syndrome can result in extreme distress that may progress to seizures.[26,27] Neonatal abstinence syndrome is defined most often by various scoring systems, with those proposed by Finnegan et al and Lipsitz and Blatman being the most commonly used.[28,29] The identification of neonatal abstinence syndrome is critical to enable the infant to be treated with medications that are slowly tapered to minimize withdrawal effects and to assure that the infant is not discharged before symptoms appear, which would prevent critically important care to the infant and training for the mother. Neonatal abstinence syndrome increases newborn hospital stays and increases the financial burden to the healthcare system.[26,27] The long-term impact of neonatal abstinence syndrome has not been well explored. Neonatal abstinence syndrome is an outcome that draws considerable attention, yet that condition is likely a surrogate for opioid occupancy in the infant's brain opioid receptors. Although there is considerable debate, when objective measures of exposure such as meconium or umbilical cord tissue are used, it appears that the individual newborn's risk of neonatal abstinence syndrome reflects its exposure in utero to opioids.[30,31] Those infants without neonatal abstinence syndrome likely have had a lower exposure to or were protected from the effect of opioids either by placental factors (efflux transporters), the mother's or fetus's metabolic machinery (polymorphisms of the phase 1 or 2 enzymes), or some other genetic mechanism (opioid receptor polymorphisms).[32] How the diagnosis of neonatal abstinence syndrome relates to changes in the baby's brain development has not been thoroughly explored.

Current Perspective: Opioids and Neurobiology

Developmental Neurobiology

The changes in the fetal brain during pregnancy are dramatic and highly orchestrated, resulting from interactions between genetic, epigenetic, and environmental factors. Studies in animals, human tissues, and in human infants using functional magnetic resonance imaging (MRI) have served to define the ontogeny of brain development as well as those factors that affect the developing brain.[33–35] Neuronal proliferation and migration occur to a large degree in the first half of pregnancy.[33,34] The second half of pregnancy is marked by glial proliferation and apoptosis. Axon and dendrite sprouting and synapse formation are dynamic processes abundant in the second half of pregnancy. Connections between various brain regions within functional networks and the myelination of these connections begin in the third trimester and progress into the first year of life.[33–36] Neurotransmitters (acetylcholinergic, catecholinergic, and glutamate) are seen as early as the first trimester.[33,36,37]

These neurotransmitters can affect neuronal migration and differentiation. Opioid receptors are demonstrable in neurons, astroglia, and oligodendrocytes. Stimulation of these receptors can affect rates of proliferation and growth and in preoligodendrocytes affect myelination.[37] The role of myelin is now appreciated to be more than an axon sheath that enhances signal transmission and protects the axon. Myelin regulates axonal extension and radial growth. Myelin-forming oligodendrocytes are involved in electrical coupling to astrocytes and bidirectional glial–neuronal communication and are critical to neuronal survival and axonal function and integrity.[38,39]

Opioid Effects on Brain: Preclinical Studies

The effects of opioid exposure on the brain have been evaluated in studies of animals, human neural tissues, adult humans, children, and newborns. In animals, opioids such as buprenorphine and methadone appear to have many adverse effects, but specific change in oligodendrocyte maturation and myelinization are consistent themes with alterations in axon size and myelin thickness, the generation of cholinergic neurons, and reduced expression of nerve growth factor in the striatum.[40–42] In addition, morphine exposure in utero reduces Purkinje cell number and size in the cerebellum of infant mice exposed to the drug in utero.[43] Pups of pregnant mice exposed to heroin demonstrate altered expression of apoptosis proteins in the hippocampus, which plays a key role in learning and memory.[44] Morphine also increases apoptosis in human fetal microglial and neuronal cells.[45]

Opioid Effects on Brain: Clinical Studies—Imaging

Using multimodal MRI techniques, one can see that the specific brain changes induced by opioids in animals also are seen in humans (Figure 1). Studies of the human brain with advanced MRI techniques are able to delineate connectivity between the various brain regions, quantify size of various brain areas, and assess white matter microstructure that can be correlated with axonal and other elements of myelin integrity.[46–48] These techniques have been used to develop age-specific normative data for infants and children as well as adults and allow investigation of the impact of opioids on human brain in vivo (Table 1).[49–56]

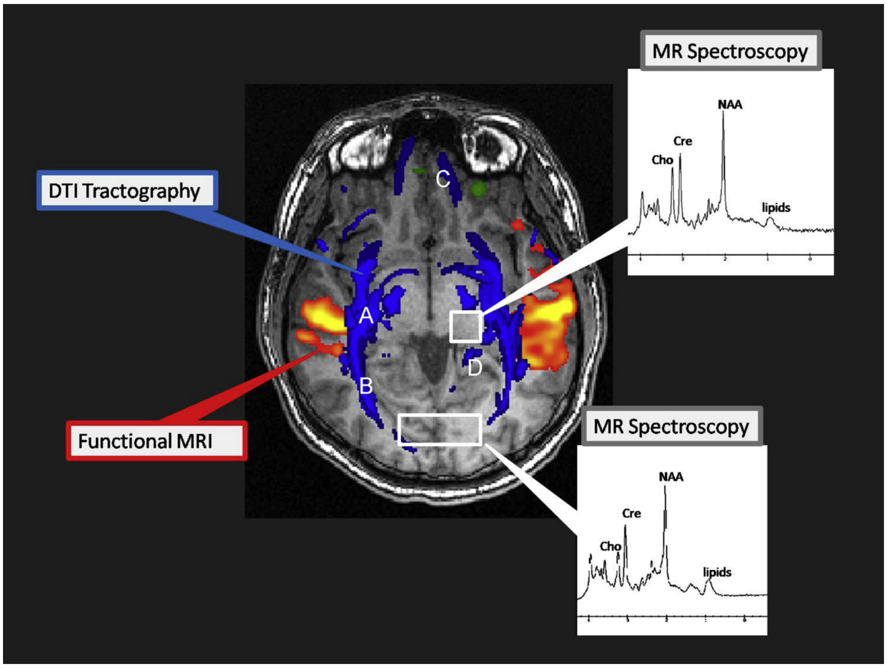
Opioid Effects on Brain: Clinical Studies—Adults

Adults who chronically use opioids demonstrate dysfunctional connectivity patterns in multiple brain regions, such as the prefrontal cortex, ventral striatum, insula, amygdala, and hippocampus.[57] These brain regions are associated with affect, impulse control, reward, and motivation functions. Lin et al[58] randomized adults with back pain to placebo or morphine for 1 month; those treated with morphine demonstrated decreased gray matter volume in the amygdala and cortex and other demonstrable changes in other regions of the brain. Bora et al[53] compared brain images in subjects with chronic opioid use and those not exposed to opioids and demonstrated myelinization pathology in the corpus callosum, thalamic radiation, and inferior longitudinal fasciculus (Figure 1, Table 1). Prescription opioid–dependent subjects likewise demonstrate regional volumetric loss in the amygdala, microstructural white matter alterations, and functional dysconnectivity when compared with subjects not using opioids.[52] A recent neuroimaging meta-analysis of opioid-dependent subjects reported gray matter deficits in several parts of the brain but primarily in the frontotemporal and cerebellar regions.[49] These regions provide neural substrate for impulsivity, compulsive behaviors, and affective disturbances. These studies in adults provide evidence that opioids can affect specific pre-frontal and paralimbic–limbic neural circuitry in the mature brain.

Opioid Effects on Brain: Clinical Studies—Children

Studies that evaluate the brain of in utero opioid–exposed children with these advanced neuroimaging techniques are limited (Table 1). Walhovd et al[50] used diffusion tensor imaging to evaluate white matter microstructure in 16 children aged 9–14 years who were exposed to opioids in utero. Compared with

FIGURE 1
Multimodal neuroimaging tools in pediatric healthy controls



DTI tractography (*blue*) shows probabilistic tractography of white matter pathways shown to be vulnerable in opiate-exposed patients including the (**A**) inferior longitudinal fasiculus; (**B**) fasiculus, overlapping with optic radiations; (**C**) inferior frontal occipital fasiculus; and (**D**) posterior thalamic radiations. Functional MRI (*orange*) study using an auditory stimulus activating primary auditory pathways; two square voxels using magnetic resonance spectroscopy in subcortical gray matter and gray matter structures showing metabolic changes in the brain, including Cho, Cre, NAA, and lipids.
Cho, choline; *Cre*, creatine; *DTI*, diffusion tensor imaging; *MRI*, magnetic resonance imaging; *NAA*, N-acetyl aspartate.
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matched controls, differences in white matter microstructure were seen in multiple longitudinal cortical association tracts, including the superior and inferior longitudinal fasciculus. These investigators (Walhovd et al[51]) also reported that children demonstrated reduced regional cerebral volumes, including the cerebral cortex, amygdala, accumbens area, putamen, pallidum, brainstem, and cerebellum. Sirnes et al[59] compared regional cerebral volumes in 16 opioid-exposed children ages 10−14 years and found smaller volumes of the basal ganglia, thalamus, and cerebellar white matter when compared with matched controls. The neuroanatomic findings described previously in older children may be influenced by multiple factors to which the child is exposed after delivery, including the environment in which the child is reared, parenting, and genetics, to name a few. Despite the likely possibility of such confounding and other potential biases, the regional neuroanatomic vulnerability is strikingly similar to data reported in animals and human adults with opioid exposure (Table 1). These concordant preclinical and clinical translational findings establish biological plausibility for opioids affecting the neonatal and fetal brain.

Opioid Effects on Brain: Clinical Studies—Newborns

Opioids and opioid metabolites freely cross the human placenta[30] and the blood−brain barrier, as evidenced by the high prevalence of neonatal abstinence syndrome.[24] Ideally, to establish causation, imaging of opioid-exposed compared with non-exposed fetuses and newborns rather than older children would help reduce such biases, but it would not eliminate them. It is difficult to precisely define pregnancy exposures, as pregnant women with an opioid use disorder may not be forthcoming with all their drug exposures. In addition, there is concern for poly-substance abuse, and the effects of smoking and other possible confounders cannot always be accounted for, since the overwhelming majority (97% in the Mother study) of women with an opioid use disorder also smoked.[23] Despite these limitations, demonstration of altered neural circuitry in opioid-exposed newborns and infants compared with matched controls would provide convincing evidence of the impact of opioids on the fetal brain.

To this end, a few studies of newborns have compared brain changes in opioid-exposed newborns and compared neuroimaging findings with a matched control group of newborns (Table 1). Monnelly et al[54] evaluated 20 methadone-exposed and 20 nonexposed newborns via diffusion tensor imaging and identified differences in white matter microstructure in the centrum ovale, inferior longitudinal fasciculi, and both internal and external capsules. Walhovd et al[55] studied 13 methadone-exposed and 7 unexposed infants at a mean of 22−23 days of age with diffusion tensor imaging. Differences in white matter microstructure were observed in the superior longitudinal fasciculus. which connects the frontal, occipital, temporal, and parietal lobes of the brain.[55] Yuan et al[56] used structural MRI to assess regional cerebral volumes in 16 newborns who were exposed to opioids during pregnancy. When compared with population norms, opioid-exposed neonates demonstrated smaller whole brain and basal ganglia volumes when compared with matched controls.[56] These neuroanatomic findings are consistent with clinical data from newborns suggesting that opioid exposure is associated with a reduced head circumference.[60−62]

The neuroanatomic effects reported in these studies of human neonates are

TABLE 1
Summary of human in vivo advanced multimodal neuroimaging studies in opiate-exposed patients across the lifespan

Author	Age of patients	Type of neuroimaging	Neuroimaging abnormality	Neuroanatomic vulnerability
Wollman et al, 2017[49]	Children	Volumetric imaging	Reduced gray matter volume	Frontal—cerebellar Frontal—insular
Walhovd et al, 2010[50]	Children	Diffusion tensor imaging	Reduced fractional anisotropy (white matter integrity) (ILF) and (SLF)	Frontal—temporal Prefrontal
Walhovd et al, 2007[51]	Children	Volumetric imaging	Reduced gray matter volume—amygdala, basal ganglia, cerebellum, anterior cingulate, lateral orbital frontal	Frontal—cerebellar Frontal—insular
Upadhyay et al, 2010[52]	Adult	Structural imaging diffusion tensor imaging functional connectivity (BOLD)	Reduced volume of amygdala Decreased fractional anisotropy of the white matter tracts that project to the amygdala	Para-limbic and limbic
Bora et al, 2010[53]	Adults	Diffusion tensor imaging	Reduced fractional anisotropy (white matter integrity) in the ILF and corpus callosum and thalamic radiations	Frontal—temporal Prefrontal
Monnelly et al, 2017[54]	Neonates	Diffusion tensor imaging	Reduced fractional anisotropy (white matter integrity) in the ILF and internal and external capsules	Frontal—temporal Prefrontal
Walhovd et al, 2012[55]	Infants	Diffusion tensor imaging	Reduced fractional anisotropy (white matter integrity) in the ILF and SLF	Frontal—temporal Prefrontal
Yuan et al, 2014[56]	Infants	Volumetric imaging	Reduced gray matter volume	Basal ganglia

BOLD, blood oxygen—level dependent imaging; *ILF*, inferior longitudinal fasiculus; *SLF*, superior longitudinal fasiculus.

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potentially biased due to small samples size, limitations in adjusting for confounders, and specificity of the imaging findings[63]; however, the change described in these studies are concordant with the brain findings reported in preclinical and adult human studies following opioid exposure. The logical conclusion is that opioids can affect the fetal brain. However, large-scale studies are needed to examine the effect of opioids on the developing fetal and infant brain in relation to both multimodel neuroimaging biomarkers and behavior. The possibility that these neuroanatomic effects can be mitigated has been suggested by a report from Walhovd et al.[64] These investigators reported that the neuroanatomical and cognitive characteristics of children whose mothers with a polysubstance abuse disorder underwent medically supervised withdrawal during pregnancy were similar to a matched control group of nonexposed infants. However, visual acuity differences were seen in the 2 groups.

With the remarkable development of advanced fetal neuroimaging techniques,[51–57] it is likely that, in the near future, there will be more data on the impact of opioid exposure on the neural circuitry of the fetal brain. Nonetheless, the functional clinical impact and neurobehavioral outcome of the aforementioned neuroimaging findings associated with opioid use is, at this time, difficult to assess and is not addressed in this document, where the focus is on neuroanatomic findings. The newborn brain is characterized by plasticity and repair of injury or rewiring of dysfunctional areas is commonplace. The influence of environment, the caretaker, genetics, and brain plasticity as well as the sensitivity of the testing used clearly affect the assessment of a child's cognitive development and function. Unquestionably, this is an area in which more research is needed as the published literature is limited due to the possibility of bias.[63]

A New Paradigm

MAT is and should continue to be the approach recommended for all pregnant women who use opioids; however, the evidence that opioids may alter human fetal brain development is substantial, and this evidence should be integrated into strategies for caring for pregnant women with an opioid use disorder. Clearly, more research is needed to understand how the timing and duration of opioid exposure, the specific opioid used, and how maternal and fetal characteristics influence brain development and child health outcomes. In addition, knowledge of how these opioid-induced brain effects can be mitigated is key to developing an approach to clinical care. Ideally, any recommendation for medically assisted withdrawal should be based on completion of this research. However, because some women will refuse MAT or are only offered medically supervised withdrawal, medically assisted withdrawal will continue to be provided. The fetal neurobiological effects of opioids described in this Clinical Opinion and the recent reports of medically assisted withdrawal may lead to more women preferring medically assisted withdrawal. These women should be counseled about the risks reported for that approach, and they should receive behavioral and social services support. If the woman makes an informed decision to attempt medically supervised withdrawal, she should not be shamed, intimidated, or otherwise demeaned; she should receive full support by the care provider. Those women who cannot tolerate further dose reduction should be allowed to resume their previous maintenance dose without criticism. Such an approach will address the greatest concern of care providers of MAT, that the patient will relapse and remove herself from the all benefits of prenatal care and mental health and social services support. It has been 10 years since Walhovd et al[65] called for attention to data demonstrating that opioids adversely affect the fetal brain. This plea has not been heeded until recently.[66] This Clinical Opinion repeats that plea and encourages researchers and clinicians to consider the impact of opioids on fetal neurobiology when developing strategies for dealing with opioid use in pregnancy. ■

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