Topic DAT18-09: Effects of Opioids and their Antagonists on Fetal and Neonatal Brain Development (R01, R21, R03)

Purpose

To encourage research on the effects of maternal opioid (agonist or antagonist) exposure on embryonic, fetal, and post-natal brain and behavioral development, and other health outcomes, and the mechanisms underlying these effects.

Background

The National Survey on Drug Use and Health from SAMSHA indicates that in 2016, among pregnant women, 6.3% used any illicit drug while 1.2% used an opioid. Parallel to this epidemic, available date between 2004 and 2014 indicates that the number of infants born with neonatal opioid withdrawal syndrome (NOWS; also known as neonatal abstinence syndrome, or NAS) increased 433% from 1.5 to 8.0 per 1000 hospital births which translates into one neonate born with NOWS every 15 minutes. Fetal exposure to opioids may occur as a result of maternal use of either prescription or illicit opioids. As part of the standard of care, opioid dependent pregnant women are treated with the opioid agonist methadone, the partial agonist buprenorphine, or in rare cases, the antagonist naltrexone, resulting in additional opioid or opioid antagonist exposure to the developing fetus.

NOWS is just one of the sequela of *in utero* opioid exposure. Infants born to mothers with opioid use disorders (or treated with opioids or opioid antagonists) can be born preterm, and exhibit low birth weight. They often have thinner cortices, reduced cognitive ability, and display physical and behavioral deficits. In addition, studies have identified long term social, psychological and behavioral abnormalities and deficits among children who had embryonic or fetal opioid exposure, including lower IQ scores, poor social skills, and disruptive behaviors. The mechanisms underlying these deficits are not well understood. Factors such as genetics, polydrug exposure, environmental toxins, stress, and maternal care are likely to influence developmental outcomes in opioid-exposed embryos and fetuses.

Research Objectives

Areas of programmatic interest to NIDA include, but are not limited to:

- Effects of different medication-assisted therapies (e.g., methadone, buprenorphine, naltrexone) on NOWS.
- Effects of severity of NOWS on brain, cognition, and behavior in neonates, adolescents, and adults.
- Impact of maternal opioid exposure on children's stress responses.
- Effects of social attachment as treatment of NOWS, as well as how social attachment in neonates is affected by the exposure to opioids.
- Effects of maternal opioid exposure on child motor and cognitive development.
- Effects of neonatal exposure to opioids on social/emotional development, e.g., play, cooperation, empathy, conflict, hostility, violence and aggression.
- Role of sex/gender in outcome measures regarding severity of NOWS and impact on brain and behavioral development.
- Genomic and genetic factors, including gene regulation and gene expression, associated with the incidence and severity of NOWS.
- Impact of opioid agonists and antagonists, such as buprenorphine and naltrexone, on the developing brain at embryonic, fetal and early childhood stages, including brain morphology, anatomy, and functional connectivity.
- Cellular and molecular mechanistic studies of the effects of maternal opioid agonist and antagonist exposure on neuronal and glial differentiation, neuronal migration, pathfinding, neural and glial interactions, synaptogenesis and synaptic pruning, and neural circuit activities.

Instructions for submitting applications:

- Insert "**DAT**-" (four characters) in the beginning of the Project Title of the application. [Note: NIH limits the Project Title to 200 characters (including spaces and punctuation)].
- Insert the DAT Code (e.g., DAT18-01) before the first sentence of the abstract. (This is for internal NIDA tracking purposes only).

Relevant Funding Opportunities

Parent funding opportunities that can be used to pursue these and other research activities include, but are not limited to:

PA-18-484, NIH Research Project Grant (Parent R01, Clinical Trial Not Allowed)
PA-18-345, NIH Research Project Grant (Parent R01, Clinical Trial Required)
PA-18-489, NIH Exploratory/Developmental Research Grant Program (Parent R21, Clinical Trial Not Allowed)
PA-18-344, NIH Exploratory/Developmental Research Grant Program (Parent R21, Clinical Trial Required)
PA-18-488, NIH Small Research Grant Program (Parent R03, Clinical Trial Not Allowed)
PA-18-591, Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp Clinical Trial Optional)

Scientific/Research (Program Contacts)

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AREAS OF EXPERTISE

- Pharmaceutical treatments of Substance Use Disorders
- Pregnant (and neonatal) participants
- Clinical trial safety

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AREAS OF EXPERTISE

- Developmental neuroscience
- Preventative interventions
- Prenatal exposure to substances of abuse
- Normative child development

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AREAS OF EXPERTISE

- Genetics and genomics in brain development
- Brain structure and imaging
- Animal modeling of substance use disorders
- Stem cells, induced pluripotent stem cells, tissue chip and organoid studies
- Cellular and molecular neuroscience

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