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[redacted]

[redacted]

Re: Opiod Fetal Toxicity Summary

Dear Dr[redacted] ,

Please find attached the summary for evidence and potential pharmacological mechanisms underlying development of opiod fetal toxicity. Please add this documentation to your expert witness testimonial. The time spent on this write-up totals ten hours as requested.

Brief Summary:

An abundance of literature suggests that opioid exposure in utero may have acute and long-lasting impact on infant and child development. There is no question that maternal ingestion of opioids are transferred to the fetus with direct actions detected in utero. Perinatal opioid exposure delays physical growth and interferes with normal behavioral outcomes, likely due to augmented development of the nervous system. The majority of reports show behavioral and motor complications: hyperresponsiveness, impulsivity, reduced self-control, poor motor coordination and poor attentional focus. While the underlying mechanisms are unclear, preclinical evidence supports reductions in neural development which produces generalized deficits in synaptogenesis and synaptic function and the involvement of multiple transmitter systems. These neural effects could play a causal role in the behavioral deficits observed in opioid fetal toxicity.

Thank you,

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OPIOID FETAL TOXICITY SUMMARY

Opioids (and opiates) are substances derived from the opium poppy plant which bind to receptors in the brain and induce a variety of effects, most notably being pain relief. The differing designations refer to naturally occurring alkaloids derived from the poppy (i.e., opiates such as morphine and codeine) and semisynthetic derivatives of opiates or synthetic compounds that bind to the body's opioid receptors, causing similar clinical effects (i.e., opioids such as heroin and oxycontin). The term "opioids" is generally used to describe all substances that act at opioid receptors. Opioids may vary in structure and their effects on the body, but in general exhibit similar properties with depressant effects on the central nervous system[i].

Opioids include a variety of prescription pills and injectables such as morphine, fentanyl, hydrocodone, oxycontin and codeine. Most commonly, opioids are used medicinally to alleviate severe and chronic pain associated with ongoing illness or due to an injury. All opioids are controlled substances ranking from Schedule I through Schedule V depending on their prescribed medical indication, risk for abuse, and risk for development of physical dependence. Opioids also include heroin, which is an illegal substance used for its euphoric effects.

While used most for the analgesic properties, opioids also activate reward neurocircuitry in the brain to produce a hedonic ('rewarding') effect that underlies the misuse and abuse of these drugs. Opioids are the most widely abused substances in America today. When abused, opioids cause dependence, addiction, overdose and even death[ii].

Opioid Mechanism of Action

Opioids bind to multiple receptors in the CNS including the Mu, Kappa and Delta receptors [iii]. Subtypes demonstrate varying effects but in general, all receptors induce analgesia. The Mu and Kappa receptors are responsible for euphoric and psychomimetic effects, respiratory depression and physical dependence. The analgesic effects are propagated through activation of opioid receptors located on nociceptive C and A delta fibers which indirectly inhibit calcium channels, decreasing cAMP levels and block the release of neurotransmitters that relay pain signals, such as glutamate, substance P, and calcitonin gene-related peptide[iv]. The hedonic effects of opioids relates to activation of opioid receptors expressed in limbic structures of the brain such as the nucleus accumbens, ventral tegmental area and the ventral pallidum[v]. Activation of mu and possibly delta opioid receptors located within the mesolimbic dopamine system is considered a key mechanism underlying the abuse liability of these drugs[v]. Indirect increase of dopamine in these critical reward structures in the brain are responsible for the rewarding properties of these drugs.

Opioid Toxicity

In general, opioid toxicity presents as decreased responsiveness, hypopnea, slowed speech, and constricted pupils. The most toxic effect is the opioid action on respiration. Opioids decrease respiratory rate and depth, which can progress to apnea. Other complications (e.g., pulmonary edema) and death result primarily from hypoxia. Delirium, hypotension, bradycardia, decreased body temperature, and urinary retention are also common toxicities[vi]. The toxic effects of opioids can lead to long-term damage and significant impact on the brain and other organ systems. Through a variety of mechanisms, opioids cause multi-organ system adverse effects including gastrointestinal, respiratory, cardiovascular, central nervous system, musculoskeletal, endocrine and immune system damage. Adverse events related to opioid use can cause significant declines in health-related outcomes[vii].

The use of opioids in pregnancy is not contraindicated however use during pregnancy can have serious consequences for mother and infant. Current opioid guidelines with respect to pregnancy are based on limited evidence. Pregnant patients who use opioids represent a distinct group: it is important to differentiate between opioid use as it relates to medical care, opioid abuse, and untreated opioid use disorder (OUD). Methadone (and to a lesser extent, buprenorphine) has been referred to as the 'gold standard' for opioid treatment in pregnant women who have a history of OUD. Neither methadone nor buprenorphine have been approved by the FDA for use in pregnant women. The FDA classifies both drugs as Teratogenic-Pregnancy Category C, which indicates that studies in animal reproduction have revealed an adverse effect on the fetus and that there are no well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite the potential risk[viii].
The product insert for methadone states "Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." [viii]

Elucidating the direct interaction between fetal toxicity and opioid exposure is complicated by confounding factors, logistics and methodology caveats. Most compelling would be direct evidence from controlled clinical studies, however research with patients who are currently engaging or have a history of drug abuse presents many uncontrolled factors that need to be considered. These factors include the pharmacological purity of substances ingested, dosing, other drug intake and the accuracy of reporting from the patient on their patterns of drug use. In addition, data collected postnatally may be impacted by other factors such as maternal and infant malnutrition, health care accessibility, infant exposure to toxins, exposure of infants to drugs postnatally and suboptimal child-rearing environments in families with drug abuse. Despite these caveats, clinical data is essential to evaluate the impact of fetal opioid exposure.

Maternal Transfer of Opioids to Fetus

Opioid drugs pass from the mother to the fetus in utero with varying pharmacokinetic properties. Following infusion of methadone, peak transfer and concentration is observed in the umbilical vein within two minutes. An umbilical venous-arterial gradient is present for 10-15 minutes indicating transfer and uptake of methadone to the fetal tissue. The transfer of opioids from mother to fetus shows approximately 2-5 times lower concentrations in the fetus[ix]. Methadone is rapidly distributed to the fetus from the mother, but concentrations remain lower than maternal concentrations. In comparison to morphine, methadone is cleared from the mother to fetus about 15 times faster and the fetal nonplacental clearance of methadone is also higher than that of morphine [x].

In Utero Effect of Opioid Exposure on the Fetus

Several studies demonstrate that in utero exposure of opioids has physiological effects on the fetus. Fetal monitoring conducted at various time points during gestation demonstrates that buprenorphine-exposed fetuses have higher levels of fetal heart rate variability, more accelerations in fetal heart rate and greater coupling between fetal heart rate and fetal movement[xi]. Group differences were found for the number of fetal heart rate accelerations, non-reactive nonstress test (NST) and biophysical profile scores for methadone and buprenorphine-exposed fetuses. Significant decreases occur following methadone and buprenorphine for mean fetal heart rate, fetal heart rate accelerations, reactive NST and fetal movement. Reductions in accelerations and reactive NST were significant only in methadone-exposed fetuses, and this resulted in a lower likelihood of a reactive NST. When comparing buprenorphine to methadone, less suppression of mean fetal heart rate, fetal heart rate reactivity and the biophysical profile score after drug delivery is observed[xii]. Methadone-maintained pregnancies are significantly associated with a higher incidence of nonreactive nonstress tests (NST), longer intervals to achieve reactive NSTs and lower NST scores compared to controls. This may reflect methadone-induced changes in the fetal central nervous system neurotransmitters and fetal behavior[xiii,xiv]. Overall, these studies demonstrate that in utero, the delivery of opioids exert direct effects on the fetus which can be detected using fetal monitoring.

Clinical Evidence for Opioid Fetal Toxicity

Ideally, complete abstinence from opioids during pregnancy is the safest for both mother and fetus, however withdrawal during pregnancy is not recommended. Repeated cycles of opioid use and withdrawal are associated with fetal distress that can cause placental insufficiency and subsequent pregnancy loss, intrauterine growth restriction, preterm labor and premature birth [xv,xvi,xvii]. Pregnant mothers with OUDs are commonly placed on long-acting opioid agonist medication-assisted treatment (i.e., methadone or buprenorphine) to prevent potential relapse and overdose. Treatment with methadone and buprenorphine maintains opioid blood levels that reduce maternal drug craving and thus improves pregnancy outcomes in the context of untreated opioid use or opioid withdrawal. Investigations into the relationship between exposure to opioids in utero, including methadone and buprenorphine, are ongoing [xviii].

A systemic and meta-analysis review of in utero effects of buprenorphine and methadone on the fetus and child show potential for spontaneous fetal death, fetal/congenital anomalies, reduced growth outcomes, increased risk of preterm birth, lower birth weight, abnormalities in neurodevelopment and lower head circumference. Several studies evaluated malformations or other defects at birth or pregnancy loss and identified chromosomal defects and cardiovascular, central nervous system, craniofacial and musculoskeletal malformations[xviii].

Physical development

Numerous studies report reductions in various parameters of growth and physical development. Low birth weight and head circumference are observed following in utero exposure to opioids. The proportion of infants with low birth weights (i.e., <2500 grams at birth) averages to 45% for heroin-exposed infants, 25% for methadone-exposed infants and 15% for unexposed infants[xix]. Lowered birth weights of methadone-exposed infants were not related to pre-term birth and appear to be related to fetal growth retardation. Lower birth weights are noted in heroin-exposed infants versus methadone. This is likely due to better prenatal care and medical oversight for mothers enrolled in methadone programs. Other parameters of fetal growth include head circumference size and height. Multiple reports demonstrate a reduction of 0.5 to 2.0 cm in opioid-exposed neonates[xx,xxi,xxii,xxiii]. It is suggested that low birth weight and reduced head circumference are related to symmetric growth retardation as a result of an insult during pregnancy. Indeed, Naeye et al. report low birth weight and brain weight related to a reduced cell number in heroin-exposed fetuses evaluated at a mean gestational age of 30 weeks[xxiv]. Higher proportions of methadone-exposed children are below targeted percentiles for height[xxv]. Overall, evidence suggests that opioid exposure is at least one contributor to reduced growth in exposed children. Reduced birth weight and head circumference are attributed to intrauterine growth retardation and potential deficits in growth hormone release or reduced uterine/placental blood flow.

Behavioral development

Behavioral deficits are noted in both infants and children following opioid exposure. Clinical and laboratory findings support abnormal neonatal behaviors following in utero exposure to opioid drugs[xix]. Infants are hyperresponsive and easily aroused. This pattern may be related to withdrawal, however neurobehavioral development after the neonatal period also shows abnormal patterns. Rosen et al., showed greater incidence of neurological abnormalities in methadone-exposed children. These included nystagmus, strabismus, tone and coordination[xxvi]. One study showed behavioral disturbances (hyperactivity, brief attention span, temper outburst) identified in 50% of infants observed 1 year or longer with 14% also showing neurological abnormalities [xxvii].

Children born to methadone-maintained mothers have higher predictors of developmental difficulties including delayed motor development, greater vulnerability of males to adverse environmental conditions and behavioral abnormalities [xxviii]. Infants exposed to opioids in utero generally have poor motor coordination, display hyperactivity

and poor attention spans[xix]. Abnormal attentional functioning tends to appear later on (>1 year) and may be an indicator of a permanent neurobehavioral syndrome and related to ADHD.

Studies which have followed opioid-exposed children into early childhood show reduced function in auditory memory and perceptual performance. Johnson et al report a higher incidence of abnormal neurological findings in methadone-exposed infants. They report 45% of methadone-exposed children showed deficits in tone, gross and fine motor coordination, balance and hyperactivity compared to only 20% of unexposed children. Subjective ratings from parents describe opioid-exposed children (ages 3-6 years) as having greater challenges with areas of self-adjustment, social adjustment, and physical adjustment. Children were also scored with higher impulsiveness, uncontrolled tempers, poor self-confidence, aggressiveness, and difficulty with socializing[xxvi].

Olofsson et al., evaluated 89 opioid exposed children at follow ups ranging from 1-10 years and reports only 25% of children with normal physical, mental and behavioral growth. A total of 62% of the children were hyperactive and aggressive with lack of concentration and social inhibition[xxix]. Follow-up of children (aged 2 months to 2 years, 8 months) with drug-addicted mothers showed a small percentage (3/15) exhibiting delayed speech development [xxx]

Wilson et al., followed 40 heroin-exposed children through elementary grade levels. Children were between 1st and 5th grade at the time of assessment. Wilson reports that 65% of opioid-exposed children required special educational services or were withheld from progressing to next levels of education. Approximately 66% of the children displayed problem behaviors, 50% showed problems with inattention and poor self-discipline and 33% showed low self-confidence, poor peer relations and failure to participate. Behavioral issues in school-aged and adolescents exposed to opioid prenatally emerge strongly during this developmental timeframe[xix,xxxi].

Overall, there is ample evidence suggesting abnormalities in development of children exposed to opioids prenatally. Physical and behavioral deficits are most notable among the literature. The neurological underpinnings are assumed however no studies to date have shown evidence for specific neurological structures affected by opioid exposure in utero.

Pre-clinical Literature

While clinical data provides the most compelling evidence for opioid-induced fetal toxicity, preclinical studies also provide valuable insights and supporting information. Animal studies suggest that in utero delivery of opioids results in structural and functional changes in the brain and altered behavioral outputs. Methadone-treated offspring show delayed growth, reduced brain weight and length, cerebral width and cerebellar weight and width[xxxii]. Exposure to morphine in utero alters adult hypothalamic norepinephrine levels in male and female rats. Morphine-induced alterations in hypothalamic norepinephrine levels were sexually dimorphic. In the hypothalamus of male rats,

norepinephrine content was increased 95%, whereas in the hypothalamus of female rats it was decreased 57% relative to controls[xxxiii]. One study demonstrated reduced brain weight and slowing of synaptogenesis and biochemical development of the brain in methadone-exposed pups. Results indicated, in part, that general growth deficits seen in perinatally-addicted pups were related to maternal undernutrition, but that delays in central synaptogenesis or in the pattern of biochemical maturation of the brain are independent of nutritional deficit.[xxxiv] Furthermore, methadone-exposed pups display a delay in cellular maturation in the brain leading to generalized deficits in critical neural development such as synaptogenesis and synaptic function, involving multiple transmitter systems[xxxv]. Fetal and neonatal methadone exposure results in increased stillbirths among prenatal methadone litters. Long-lasting growth retardation and less emotionality and activity were noted in pups exposed pre- and postnatally to methadone[xxxvi]. Rats demonstrate hyper-responsiveness (i.e., more avoidances, escapes and intertrial shuttles) when tested in a massed-trial avoidance procedure following methadone exposure. Behavior was attributed to subtle but lasting changes in limbic dopamine functions as a consequence of fetal exposure to methadone[xxxvii].

Conclusions

An abundance of literature suggests that opioid exposure in utero may have acute and long-lasting impact on infant and child development. There is no question that maternal ingestion of opioids are transferred to the fetus with direct actions detected in utero. Perinatal opioid exposure delays physical growth and interferes with normal behavioral outcomes, likely due to augmented development of the nervous system. The majority of reports show behavioral and motor complications: hyperresponsiveness, impulsivity, reduced self-control, poor motor coordination and poor attentional focus. While the underlying mechanisms are unclear, preclinical evidence supports reductions in neural development which produces generalized deficits in synaptogenesis and synaptic function and the involvement of multiple transmitter systems. These neural effects could play a causal role in the behavioral deficits observed in opioid fetal toxicity.

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