Developmental Consequences of Fetal Exposure to Drugs: What We Know and What We Still Must Learn

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Most drugs of abuse easily cross the placenta and can affect fetal brain development. *In utero* exposures to drugs thus can have long-lasting implications for brain structure and function. These effects on the developing nervous system, before homeostatic regulatory mechanisms are properly calibrated, often differ from their effects on mature systems. In this review, we describe current knowledge on how alcohol, nicotine, cocaine, amphetamine, Ecstasy, and opiates (among other drugs) produce alterations in neurodevelopmental trajectory. We focus both on animal models and available clinical and imaging data from cross-sectional and longitudinal human studies. Early studies of fetal exposures focused on classic teratological methods that are insufficient for revealing more subtle effects that are nevertheless very behaviorally relevant. Modern mechanistic approaches have informed us greatly as to how to potentially ameliorate the induced deficits in brain formation and function, but conclude that better delineation of sensitive periods, dose–response relationships, and long-term longitudinal studies assessing future risk of offspring to exhibit learning disabilities, mental health disorders, and limited neural adaptations are crucial to limit the societal impact of these exposures.

INTRODUCTION

Substance use disorders among pregnant women continues to be a major public health concern, posing risk to the child's development, and imposing socioeconomic burdens on society by increasing needs for medical and social services. Given the crucial roles for the major protein targets of drugs of abuse in shaping brain development (Bhide, 2009; Bonnin and Levitt, 2011; Frederick and Stanwood, 2009; Hohmann, 2003; Kater and Lipton, 1995; Lauder, 1993; Money and Stanwood, 2013; Stanwood and Levitt, 2004), it should not be surprising that fetal drug exposures have been linked to a wide variety of brain deficits. In this review, we will focus on: (1) what is currently known about the likely pattern of substance use among pregnant or women of childbearing age; (2) the cellular and molecular pathways by which prenatal drug exposure may influence structural and functional brain development; (3) current studies on outcomes of exposed individuals across various areas of functioning (neurobiol-

ogy, physical growth, intelligence, executive functioning, behavior, and psychopathology); (4) reviews of current experimental animal models, and (5) current limitations in understanding and potential avenues for future research. While beyond the scope of the current review, untreated drug abuse/addiction also typically coincides with poor nutrition and prenatal care, which increases the risk of obstetric complications and disrupted developmental processes in the fetus. Thus, beyond the specific developmental biology of individual drugs, there are additional common factors that can produce deficits in neurodevelopmental trajectories.

Recent data suggest that nearly 25 million Americans aged 12 or older are current illicit drug users; this estimate represents 9.2 percent of the population. Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used non-medically (Substance Abuse and Mental Health Services Administration, 2013). Current illicit drug use among pregnant women aged 15–44, has remained constant at 5.9% despite efforts of prevention and education programs (Substance Abuse and Mental Health Services Administration, 2013). In fact, the pattern of rates of current illicit drug use among young adolescent females has grown to where they are now more likely than males in their age group to be current non-medical users of psychoactive drugs.

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Legal drugs such as alcohol and nicotine also represent a significant hurdle regarding unintended effects on the fetus. The 2012 NSDUH also found that among pregnant women aged 15–44, the prevalence of reported current alcohol and cigarette usage rates has not changed substantially in the past decade. Although the US population as a whole is smoking less, the past month cigarette use among pregnant women aged 15–44 has held at ~16–17% over the past 2 years (as compared with 18% in 2002–2003). An annual average of ~8.5% also reports current alcohol use during pregnancy. As described below, legality of a drug does not necessarily correlate with its safety profile, and as researchers and clinicians, we need better therapies and educational strategies for pregnant and/or breastfeeding women.

Different drugs and biological processes are often modeled in different animal species, each with its own unique developmental timeline (Figure 1) and advantages/disadvantages. This greatly complicates translatability to humans. Rodents (mice, rats) and lagomorphs (rabbits) are born relatively early, as compared with humans, and thus those offspring must be treated with drugs postnatally if the aim is to model third trimester human exposure (Figure 1). However, this omits the transplacental transfer that is inherent in human fetal drug exposure. Issues of accurate dose levels, route of administration, and pharmacokinetics/bioavailability are also often underappreciated in animal models.

Moreover, drugs can alter fetal development through a wide variety of mechanisms (Figure 2). For example, if the drug crosses the placenta (and the vast majority of drugs of abuse do cross), then it can directly act on its molecular target in the fetus. Drugs can also act directly on the uterus and/or placenta. These effects would include altering placental secretory activity or uteroplacental blood flow, for example. Finally, the drug can produce effects on the mother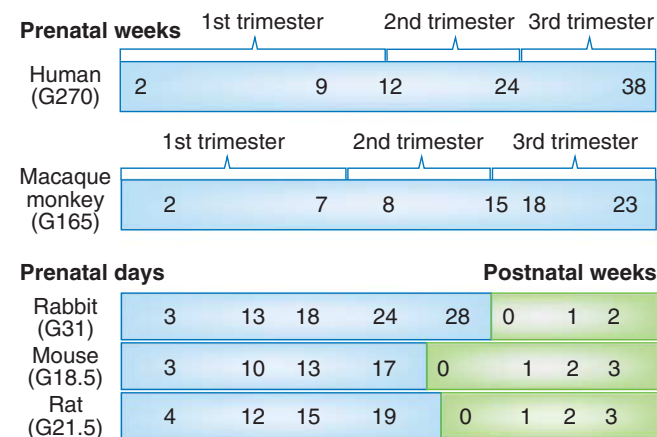's physiology that may secondarily influence the fetus, such as increased secretion of stress hormones or altered maternal health behaviors attributable to the mother's addiction. And although it is beyond our scope to review it here, it has recently become clear that paternal exposures, to drugs such as cocaine, during spermatogenesis, can also influence offspring brain development and neurobehavioral development through epigenetic mechanisms, at least in animal models (Killinger et al, 2012; Rodgers et al, 2013; Vassoler et al, 2013). This topic is thus extremely complicated; nevertheless, we will do our best to review both animal models and clinical and imaging data from longitudinal human cohorts following fetal exposure to specific drugs of abuse.

PSYCHOSTIMULANTS

Methamphetamine

Methamphetamine (METH) is metabolized in rat and human livers to the main metabolites, amphetamine, and 4-hydroxymethamphetamine (Caldwell et al, 1972) (prenatal amphetamine exposure discussed below). Due to the addition of a methyl group, METH has a higher lipophilicity than amphetamine, allowing more rapid transport of the drug across the blood–brain barrier (Barr et al, 2006). METH has a high potential for abuse and
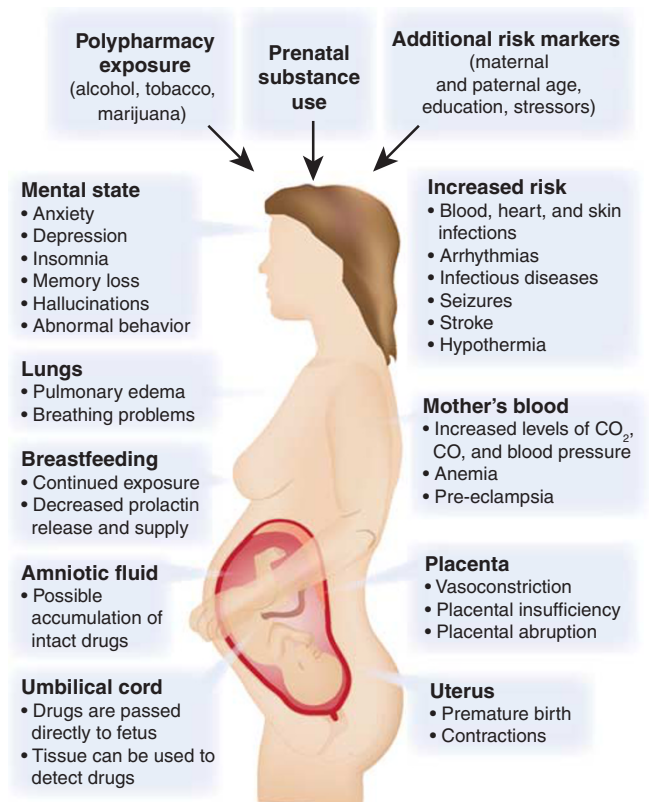

Figure 1. Major neurodevelopmental events across species. Schematic diagram that aligns human brain development with several animal models (monkey, rabbit, rat, and mouse) often used in studies of fetal drug exposure. Note in particular that the rodent equivalent of third trimester fetal development occurs postnatally.

Figure 2. Biological targets of fetal drug exposures. Drugs of abuse not only target the developing fetal brain directly, but can exert effects through a variety of organs with the mother, including the uterus, placenta, heart, lungs, and brain.

addiction compared with other amphetamine-type stimulants, affecting the serotonin (5-HT) plasma membrane transporter (SERT) and activating the psychological reward system by triggering a cascade of the massive release of dopamine (DA) in the brain. This release of DA occurs by multiple mechanisms including: binding to reuptake transporter (DAT), the displacement of vesicles and inhibition of monoamine oxidase, and enhancing DAT-mediated reverse transport of DA transport across the plasma membrane (Scott et al, 2007). These targets of METH appear by mid-gestation in the fetal brain (Bhide, 2009; Frederick and Stanwood, 2009; Malanga and Kosofsky, 1999; Money and Stanwood, 2013).

The use of METH in the United States and in other parts of the world still remains a serious public health concern. According to the United Nations, 1.3% of the general population in Central and North America use amphetamine-type stimulants (UNODC, 2013). There are few studies that have surveyed the prevalence of METH use among pregnant women. The only large-scale investigation to report METH prevalence for pregnant women has been the Infant Development, Environment, and Lifestyle (IDEAL) study. They found that ~5% of women self-reported METH use during their pregnancy (Arria et al, 2006) in areas of the United States where METH use was of high concern. Furthermore, over 40% of the women enrolled in the IDEAL study continued using the drug during their third trimester, and approximately half did not significantly change their personal use during the course of the pregnancy (Della Grotta et al, 2010).

Despite the fact that METH has been utilized by pregnant women for many years, relatively little is known about the effects of METH during early infancy and even less is known about the long-term effects. The most common effects noted in newborns indicate that METH use is associated with growth restriction, decreased weight, length, and head circumference (Little et al, 1988; Nguyen et al, 2010; Smith et al, 2003; Smith et al, 2006b). Echoencephalography has revealed congenital anomalies in exposed neonates include cardiac anomalies, cranial abnormalities, and abnormal brain development closely resembling those in ill, asphyxiated infants (Dixon and Bejar, 1989). Mild withdrawal symptoms have also been noted in newborns (Oro and Dixon, 1987; Smith et al, 2003), although these symptoms are not as common. In animal models, increased DNA oxidation and postnatal functional deficits in motor coordination were documented in neonatal METH-exposed mice (Jeng et al, 2005).

Several recent studies have examined the effects of METH exposure on childhood growth patterns and behavior after birth. Focusing on physical growth patterns, Zabaneh et al (2012) found children exposed prenatally to METH have a modest decrease in height during the first 3 years of life with no observed difference in weight, head circumference, or weight-for-length trajectories. Prenatal METH exposure also is associated with significantly reduced caudate nucleus volume and cortical thickness increases in perisylvian and orbital–frontal cortices (Derauf et al, 2012; Zabaneh et al, 2012). Diffusion tensor imaging (DTI) suggests lower diffusion and higher fractional anisotropy in METH-exposed children at 3–4 years of age, indicating that fetal METH may alter white matter tracts (Cloak et al, 2009). In a magnetic resonance spectroscopy (MRS) study, METH-exposed 3–4 year-old children exhibited higher total creatine, N-acetyl compounds, and glutamate + glutamine concentrations in the frontal white matter, but lower myoinositol and myoinositol/creatine in the thalamus (Chang et al, 2009). The higher metabolite concentrations of N-acetyl compounds, total creatine, and glutamate + glutamine suggest a higher neuronal density or cellular compactness in the white matter, whereas lower myoinositol suggests lower glial content in the thalamus. Furthermore, the METH-exposed children performed significantly worse on a visual motor integration task, which correlated with lower myoinositol in the thalamus (Chang et al, 2009). In another magnetic resonance imaging (MRI) study on children ranging from 3 to 16 years of age, exposed children scored lower on measures of visual motor integration, attention, verbal memory, and long-term spatial memory. There were no differences among the groups in motor skills, short delay spatial memory, or measures of nonverbal intelligence. Despite comparable whole brain volumes in each group, the METH-exposed children appeared to have subtle but significant decreases in size or volume in certain brain regions, including the putamen, globus pallidus, and hippocampus. These reductions correlated with poorer sustained attention and delayed verbal memory (Chang et al, 2004). It is important to note that although the study had an impressive age range, sample sizes were limited.

Concentrating on long-term motor skills after birth, Smith et al (2011) observed a subtle METH exposure effect on fine motor performance at 1 year, with the poorest performance observed in the most heavily exposed children. However, by 3 years of age, no differences in fine motor performance were observed. These findings suggest METH exposure has modest motor effects in the first year of life, but that this may be mostly resolved by 3 years of age. The IDEAL study found that prenatal METH exposure was associated with child externalizing behavioral problems at 5 years and parenting stress and psychological symptoms experienced by primary caregivers were associated with increased child behavioral problems; indicating these effected children may have more difficulties negotiating the increasing complex academic and social demands of school-age children (LaGasse et al, 2012; Twomey et al, 2013).

Animal models may give us insight and provide correlation to these studies examining the effects of prenatal METH exposure and if these effects will remain into adulthood. Results from mouse exposure to METH during a time period equivalent to the third trimester of human fetal gestation (see Figure 1) impaired weight gain, reduced novel location recognition, and impaired novel object

recognition in both male and female mice during adolescence. In rats, neonatal exposure to METH produces deficits in latency and memory in a Morris water maze (Vorhees et al, 2000). Both prenatal and neonatal exposure also caused impaired spatial learning (Slamberova et al, 2005; Williams et al, 2003b; Williams et al, 2003d; Williams et al, 2002) and neonatal exposure altered the adrenal response to a forced swim stressor, suggesting that the adrenal output during learning may contribute to the spatial learning deficits (Williams et al, 2003a). Rats exposed to METH in utero showed changes in the mesolimbic dopaminergic system and were more sensitive to the administration of the acute dose of METH in adulthood (Bubenikova-Valesova et al, 2009). This indicates that offspring exposed to METH in utero could be more sensitive to METH and potentially to other psychostimulants (Bubenikova-Valesova et al, 2009).

Although relatively little is known about the effects of METH during early infancy or the following long-term effects, recently there have been studies attempting to examine children exposed to METH in utero. Further studies are important to aid in prevention programs and treatment for these individuals. Comparing the effects of prenatal METH exposure on infant and childhood growth between the United States and New Zealand demonstrated that the effects of prenatal METH differed across countries (Abar et al, 2013). In the study, the prenatal METH-exposed children in New Zealand fared better than exposed children in the United States. In addition, according to the United Nations, 1.3% of the general population in Central and North America use amphetamine-type stimulants (UNODC, 2013). This reported use is at higher levels than the global average of 0.7% of the general population (UNODC, 2013). These studies suggest that the United States needs improved prevention programs, better pre- and postnatal treatments, and caregiver support for this exposed population.

Amphetamine

Amphetamines (alpha-methyl-phenethylamine) (AMPH), commonly known as 'Speed', continue to be widely used by women of childbearing age. The users are either legally prescribed AMPHs for medical reasons or are nonmedical users. For example, attention deficit hyperactivity disorder (ADHD) affects $\sim 5\%$ of adults (Fayyad et al, 2007) in the United States. Although ADHD is less common in females than males, a significant percentage of women of childbearing age are thus likely prescribed AMPH or other stimulants as a treatment for ADHD. The prevalence of women of childbearing age using non-medical AMPH is currently unknown, and even less is known about the frequency of use during pregnancy. Further studies are required to determine the true frequency of illegal AMPH-exposed pregnant and lactating women, so that appropriate care can be provided for mother and her family.

After prenatal exposure, AMPH has been detected in human umbilical cord (Jones et al, 2009), plasma (Dearlove

and Betteridge, 1992), and placenta as early as the first trimester (Joya et al, 2010). The cellular actions of AMPH are nearly identical to METH (see section above), including increasing the levels of norepinephrine (NE), DA, and 5-HT in the synaptic cleft via transporter reuptake inhibition. This increased availability allows the monoamines to act upon post-synaptic receptors. The use of AMPHs during pregnancy increases the risk of adverse effects on the outcome of pregnancy, such as placental hemorrhage (Figure 2). This is mediated, at least in part, by stimulation of contractions in the uterus and by targeting NET and SERT in the human placenta (Cordeaux et al, 2008; Ramamoorthy et al, 1995). These actions have been hypothesized to contribute to preterm labor associated with AMPH exposure (Cordeaux et al, 2008). To date, fetal AMPH exposure has not been proven to be directly teratogenic; however, in primary human cell cultures, AMPH reduced folic acid uptake and this could potentially lead to placental and/or fetal toxicity (Keating et al, 2009). Animal studies revealed at a prepubertal age, an enhancement of D1 receptors in the dorsal striatum and nucleus accumbens (NAc) and a decrement of the D3 receptors in NAc, olfactory tubercle, and the islands of Calleja. In contrast, at a postpubertal age, the authors instead measured an increase in the levels of DAT in the NAc and striatum, and a decrease in D2 receptor expression in the NAc shell. In addition, acute AMPH induces a marked decrease in locomotor activity in rats following prenatal AMPH exposure (Flores et al, 2011). These developmental and behavioral changes in animal models associated with in utero AMPH exposure provide insights to the mechanisms causing changes in affective, behavioral, and cognitive outcomes in exposed children.

A meta-analysis of 10 studies of low-to-moderate risk of bias submits that AMPH exposure in pregnancy is associated with higher odds of preterm birth, low birth weight, and small size for gestational age (Ladhani et al, 2011). Birth weight as a continuous variable was also found to be significantly lower among exposed women. Gestational age, however, was not found to be significantly different (Ladhani et al, 2011). The most extensive follow-up data on affective, behavioral, and cognitive outcomes following prenatal AMPHs are provided by Swedish researchers who tracked a cohort of 65 AMPH-exposed children from birth to age 14. They reported in children with continuous AMPH exposure throughout gestation, a variety of adverse physical, cognitive, emotional, and social effects, including increased prevalence of ADHD, aggression, and learning difficulties attributed to deficits in attention, memory, and motivation (Eriksson et al, 1994; Eriksson et al, 2000). Furthermore, a relationship between head circumference at birth and at 1 year of age predicted language and mathematics proficiency at 14 years of age (Eriksson et al, 2000). As with its parent drug METH, further studies on prenatal AMPH exposure is needed to better understand effects from prescribed AMPHs or non-medical users (Oei et al, 2012).

3,4-Methylenedioxymethamphetamine

3,4-Methylenedioxymethamphetamine (MDMA), commonly known as Ecstasy, is a derivative of AMPH that has both stimulant and hallucinogenic properties. It acts as a powerful releasing agent of 5-HT, NE, and DA and also acts as a reuptake inhibitor of their high-affinity transporters (de la Torre et al, 2004; Rudnick and Wall, 1992). MDMA is actively transported through the plasma membrane and can then inhibit the vesicular monoamine transporter, resulting in increased concentrations of 5-HT, NE, and DA in the cytoplasm. MDMA can also directly bind a number of receptors with moderate affinity, including α2-adrenergic (adrenaline) and 5-HT2A receptors (de la Torre et al, 2004). A single MDMA injection to pregnant rat dams results in MDMA transfer into the fetal compartment (Campbell et al, 2006). However, emerging data also suggests key roles for maternal and placental 5-HT in regulating brain development (Bonnin et al, 2011; Bonnin and Levitt, 2011) (Figure 2).

In the United States, data from the 2012 National Survey on Drug Use and Health estimate that about 6.2 percent of individuals aged 12 or older had used Ecstasy at least once in their lifetime. In addition, ∼900 000 individuals tried Ecstasy for the first time in 2012. Although data from pregnant women was not presented, the prevalence of at least once in lifetime Ecstasy use in 2012 saw a significant increase from past-year use, and past-year use for eighth through twelfth graders remained stable (UNODC, 2013).

To date, there are only a few studies examining prenatal exposure to MDMA in humans, despite concerns about its potential harmful effects to the fetus (Ho et al, 2001; McElhatton et al, 1999; Singer et al, 2012; van Tonningen-van Driel et al, 1999). Very little is known about the characteristics of pregnant women who use Ecstasy. Using data collected regarding women contacting the Motherrisk Helpline in Toronto (Ho et al, 2001), MDMA users tended to be younger, single, Caucasian, binge drinkers, and had a higher prevalence of psychiatric symptoms. Most of these users discontinued MDMA once pregnancy was known, but because the recruitment was based on contact initiated by the mothers, the sample likely overrepresented more 'motivated' women. The few available studies demonstrate that pregnant MDMA users exhibit a clustering of reproductive risk factors that contribute to neurobehavioral and teratological outcomes. A retrospective report of 136 babies exposed to Ecstasy in utero noted premature births, a significantly increased risk of congenital defects, cardiovascular anomalies, and musculoskeletal anomalies (McElhatton et al, 1999). Another study in the Netherlands reported congenital cardiac malformation and spontaneous abortions (van Tonningen-van Driel et al, 1999). A recent neurobehavioral outcome study suggests that prenatal MDMA exposure predicts poorer infant mental and motor development at 4 and 12 months of age in a dose-dependent manner (Singer et al, 2012).

Only a handful of animal models of pre- and perinatal MDMA exposure have been developed as well. A rat study of prenatal MDMA exposure (E14–E20) described increases in dopaminergic fibers in the prefrontal cortex, striatum, and NAc—areas critical in novelty responses, reward, attention, and motor behavior (Thompson et al, 2009b). It also appears to increase NE fiber density in the prelimbic region of the prefrontal cortex and in the hippocampus (Thompson et al, 2012).

Further studies suggest that developmental MDMA, particularly during a time analogous to the early third trimester, can produce persistent reductions in DA and 5-HT metabolites (Koprich et al, 2003a; Koprich et al, 2003b). Meyer et al (2004) determined that MDMA exposure from P1 to P4 can decrease 5-HT levels in the hippocampus on P25 and P60, and suggested that MDMA treatment stimulates apoptotic cell death during early postnatal development. Significant reductions in 5-HT fiber density were observed in the cerebral cortex with a hyperinnervation in the caudate–putamen and NAc in 9–month-old animals, demonstrating enduring effects (Meyer et al, 2004). The early hippocampal changes were not observed in adulthood, suggesting a recovery of damaged serotonergic fibers following neonatal exposure. The Meyer lab further demonstrated that developmental MDMA administration can lead to long-lasting functional abnormalities including enhanced sensitivity to the drug later in life (Piper et al, 2009; Piper and Meyer, 2006).

Other studies have shown few effects of MDMA exposure in developing animal models. This could possibly be because of time period of treatment—embryonic versus postnatal—or doses (once again, please see Figure 1 for a description of human and animal development timelines). For example, when rats were exposed to MDMA twice a day from E12 to E15, no differences were seen in hippocampal levels of 5-HT, DA, NE, or metabolites when assayed on P21 (Winslow and Insel, 1990). In addition, no changes in 5-HT or DA levels in various brain regions were observed in rat offspring whose mothers were exposed to 20 mg/kg MDMA once per day every other day beginning at E6 until birth (Aguirre et al, 1998).

As adults, prenatal MDMA-exposed rats exhibit increased activity, risk-taking behavior, and altered spatial learning; however, it did not affect their feeding or food reward, or alter cocaine self-administration behaviors or locomotor responses (Thompson et al, 2009b). Neonatal administration of MDMA also produces impaired path integration learning (Broening et al, 2001; Vorhees et al, 2004; Williams et al, 2003c). Neonatal MDMA exposure alters the release of DA and 5-HT at P70 in the striatum and hippocampus, and reduces sucrose preference (an index of reward systems) at P70 (Galineau et al, 2005).

The detailed mechanisms through which prenatal/perinatal MDMA exposure produces alterations in neurodevelopmental trajectory are thus not fully understood. Heavier use has been associated with impaired motor and intellectual development in infants, but whether there are long-lasting changes in neurobehavioral outcomes is not yet known. A major concern is possible serotonergic

dysfunction produced by repeated and/or high doses of the drug. A recent animal report suggests that that the simultaneous abuse of alcohol and Ecstasy during pregnancy, even for short periods of time, may cause much more significant abnormalities in neurocognitive development than either drug alone (Canales and Ferrer-Donato, 2014). Given the widespread recreational use of MDMA (Ecstasy), pregnant women should be cautioned about possible developmental effects in offspring. Animal models need to be designed to include relevant doses and human developmental periods to best ascertain the developmental effects of MDMA (for an excellent review, see Skelton et al (2008)).

Cocaine

Currently the percentage of women of childbearing age consuming cocaine is unknown and less information is known about the current frequency of use during pregnancy. According to the latest figures from (UNODC, 2013), cocaine was the third largest abused illicit drug (Substance Abuse and Mental Health Services Administration, 2013) within the past year. Among women ages 12 and older, including women of childbearing age, 0.3% were current users of cocaine (Substance Abuse and Mental Health Services Administration, 2013). Thus, cocaine use in women continues to be a major public health concern. It has been noted that prenatal cocaine exposure alone accounts for over 26 million dollars per year in special education services in the United States (Levine et al, 2008).

Studies of cocaine in animal models, using a variety of species, have demonstrated cocaine easily crosses both the placenta and blood–brain barrier and can have teratogenic effects on the developing fetus (Mayes, 1994). The negative outcomes and effects from neonatal exposure to cocaine can result from the pathophysiology originating from three possible pathways; first, cocaine directly inhibits the reuptake of multiple monoamines at the presynaptic junction, leading to increased concentrations of DA, 5-HT, and NE within the synaptic cleft. Also, neonatal cocaine exposure has been attributed to indirect vasoconstrictive effects and higher levels of activation in the catecholaminergic system (Nassogne et al, 1998). In addition to the neurochemical and vascoconstrictive effects of cocaine on fetal development, cocaine may also act by altering genetic programming (Lester and Padbury, 2009).

Clinical reports of the impact of prenatal cocaine have been varied; some suggest global and severe physical malformations, others document specific deficits in physical, cognitive, and emotional development, and yet other studies indicate no effects. It is important to note that the magnitude of these effects depend upon the dosage, gestational timing, duration of exposure, and/or postnatal care. Some of the disparities in the human literature arose from the problem that many of the early studies were poorly controlled and produced media hysteria around so-called 'crack babies'. Nevertheless, well-controlled studies have demonstrated that prenatal cocaine exposure does in fact affect fetal physical growth, and results in an increase of premature birth, and generalized growth retardation—including decreased birth weight, shorter body length, and smaller head circumference (Bigsby et al, 2011; Covington et al, 2002; Gouin et al, 2011; Mayes et al, 2003). Abnormal infant behavioral outcomes have also been documented; these outcomes include abnormalities related to lower arousal, poorer quality of movement and self-regulation, higher excitability, jitteriness, and more non-optimal reflexes (Lester et al, 2002; Richardson et al, 2008; Singer et al, 2000; Tronick et al, 2005). Studies have revealed that the behavioral outcomes observed at birth continue and sometimes worsen after 12 months of age (Bigsby et al, 2011; Chiriboga et al, 2007; Mayes et al, 2003; Richardson et al, 2008).

Growth restriction among prenatal cocaine exposure children has been documented to continue well past infancy (Minnes et al, 2006) and may persist in children as old as 10 years of age (Covington et al, 2002; Richardson et al, 2013). While consistency exists in the reports of reduced fetal growth and development, some follow-up studies at later ages have suggested catch-up growth. Shankaran et al (2011) found that children exposed to prenatal cocaine were similar in weight to non-exposed children at 6 years of age. Interestingly, children who had been exposed to high levels of prenatal cocaine, and were born full-term, were reported to have a higher body mass index and blood pressure changes. These variable outcomes of prenatal cocaine exposure on physical growth and development are in part the result of important covariates such as amount of drug use and timing throughout pregnancy. Other possible variables are disturbances in physiological regulation, such as the respiratory sinus arrhythmia and cardiac development (Finger et al, 2014). Studies in animal models also provide evidence for a programming effect resulting in detrimental long-term changes to the heart induced by fetal cocaine exposure (Meyer and Zhang, 2009). Overall, additional long-term follow-up studies of children with neonatal cocaine exposure and its effects on health outcomes are needed to help identify mechanisms that result in abnormal growth and development.

Although prenatal cocaine exposure alone does not appear to lower global intelligence, there is consistent evidence of poor cognitive performance in language skills, behavior, and executive functioning. Longitudinal studies have reported that prenatal cocaine is associated with impaired language development through early adolescence (Bandstra et al, 2011; Lewis et al, 2007; Lewis et al, 2011). However, some studies suggest a general improvement in receptive language starting in adolescence through age 17 (Betancourt et al, 2011). Furthermore, adoption or foster care appears to enrich the children's linguistic environment and helps to protect children against some language delays (Lewis et al, 2011).

Long-term studies have described varying effects on executive function in exposed children. Executive function is a set of mental processes for the management of cognitive

operations that include attention, behavior, cognition, working memory, and information/problem solving. Richardson et al (2013) found that first trimester cocaine exposure has been associated with less sociability, more withdrawn behavioral problems, more anxious/depressed behaviors and symptoms in the children. These behaviors may be precursors of later psychiatric problems. By caregiver reports, higher cocaine use was associated with disruptive behaviors including aggression and delinquent behavior at 9 years of age (McLaughlin et al, 2011). Moreover, caregiver reports indicate overall issues of executive function in 12 year-old children with higher amounts of prenatal exposure; in particular, females had greater problems with initiation activities, working memory, and organization (Minnes et al, 2014). Carmody et al (2011) further documented cocaine exposure affected the attention and inhibitory control performance of males, but not females, in children at ages 6, 9, and 11. The neurobiological mechanisms leading to gender-dependent differences in disrupted executive function following prenatal cocaine are not currently understood; however, this is an important consideration for future investigation.

These longitudinal studies have described varying effects on executive function in exposed children; however, it is also important to know the structure, function, and pharmacology of the brain that is possibly being altered by the drug exposure. Neuroimaging—for example, structural MRI, functional magnetic resonance imaging (fMRI) and DTI—is valuable in examining the underlying neural circuitry and connectivity. Recent reports describe long-term structural alterations in brain regions such as cortical and limbic regions (Rando et al, 2013). Lower fractional anisotropy in the right arcuate axons and higher mean diffusivity in the splenium of the corpus callosum has also been observed (Lebel et al, 2013). Cortical thickness of the right dorsolateral prefrontal cortex appears to be thinner in adolescents following prenatal cocaine (Liu et al, 2013), and cocaine-exposed adolescents have reduced ventral prefrontal cortex activation in response to increased memory load. Reduced structural connectivity between the ventral prefrontal cortex and the amygdala was also observed through DTI measurements (Li et al, 2013).

Overall, fetal cocaine exposure can affect fetal and long-term growth patterns, as well as cause language deficits, behavior defects, and executive functioning abnormalities. Animal models, across multiple species, give us further insight on the pathophysiological mechanisms that are possibly occurring during the developmental changes and are not accessible to study in vivo. Animal models confirm that prenatal cocaine exposure results in specific and long-lasting behavioral, cellular, and molecular changes (Bhide, 2009; Dow-Edwards, 2011; Harvey, 2004; Lidow et al, 2003; Mactutus et al, 1994; Malanga and Kosofsky, 1999; Mayes, 2002; Stanwood and Levitt, 2004). Moreover, animal models of prenatal exposure have disrupted cortical neurogenesis and migration during and after birth, reduction of neuronal numbers and density in the cortex, and differences in

dopaminergic function (Crandall et al, 2004; Hamilton et al, 2010; McCarthy and Bhide, 2012; McCarthy et al, 2012; Ren et al, 2004). Specific anatomical defects include aberrant growth of dendrites of cortical projection and interneurons, suggesting disruption of local circuitry, and behavioral abnormalities that involve learning and stereotypic motor behavior (Mayes, 2002; Stanwood et al, 2001b; Thompson et al, 2005). Data suggest that the equivalent of the second trimester may be the most 'sensitive period' for the actions of fetal cocaine (Stanwood et al, 2001a). Alterations in the fetal development of the monoaminergic system can affect short- and long-term attention and cognitive development. Perhaps a point of origin for the disturbances from the effects of cocaine is the reduction of the coupling of the D1 receptor to its G protein-coupled receptor (Jones et al, 2000; Stanwood et al, 2005; Zhen et al, 2001). This uncoupling is sustained into adulthood and is specific for D1 receptors. Behavioral changes in response to cocaine exposure have also been reported in multiple animal models, including deficits in attention and emotional reactivity (Gabriel et al, 2003; Garavan et al, 2000; Harvey et al, 2001; Morrow et al, 2002a, b; Stanwood and Levitt, 2003; Thompson et al, 2005; 2009a). These findings correspond with the human clinical literature, which reports disturbances in both attention and emotion regulation in children exposed prenatally to cocaine. Gestational cocaine also increases the sensitivity to the conditioned rewarding effects of cocaine in male rats and modestly affected females (Dow-Edwards et al, 2014), indicating alterations in the development of reward circuits.

This brief discussion of prenatal exposure to cocaine clearly emphasizes the complexity of determining the pathophysiological mechanisms and associated risk factors. Given the consistently large number of affected individuals, there is a constant need for furthering research and medical, mental health, and educational services for this impacted population.

OPIOIDS

Opiate receptors are G protein-coupled receptors and fall into three groups: mu, delta, and kappa. In situ hybridization of the adult rat brain identified mRNA for all three receptors throughout the central nervous system as well as numerous peripheral tissues (Wittert et al, 1996). Opioid receptor expression (Barg and Simantov, 1989; Lenoir et al, 1984) and endogenous opioid concentrations in the fetus and neonate differ from that in adults (Barg and Simantov, 1989). Thus, administration of opiates in utero may have more distinctive effects compared with adult exposure (Pertschuk et al, 1977).

Illicit opiate use has been steadily increasing in the past decade and a large part of this increase is in the 18–25 age bracket, which includes women of reproductive age (Substance Abuse and Mental Health Services Administration, 2013). The probability of preeclampsia, premature labor and rupture of membranes, placental insufficiency,

abruptio placentae, intrauterine growth retardation, and intrauterine death increases greatly with illicit opiate use during pregnancy (Bashore et al, 1981; Hulse et al, 1998; Kaltenbach et al, 1998). Even with a successful labor and delivery, neonates often have low birthweight and smaller head circumference as well as experience symptoms of opiate withdrawal (Binder and Vavrinkova, 2008; Hunt et al, 2008; Kandall et al, 1976). Some clinical studies have also suggested an increased prevalence of heart defects, autonomic dysregulation (Paul et al, 2014), nystagmus (Gupta et al, 2012), and strabismus (Gill et al, 2003) in children exposed prenatally to opiates. At the pre- and elementary school ages, these children show motor and cognitive impairments (Bunikowski et al, 1998; Guo et al, 1994; Hunt et al, 2008), inattention (Hickey et al, 1995; Ornoy et al, 1996), hyperactivity (Ornoy et al, 1996), and an increase in ADHD when exposed prenatally to heroin (Ornoy et al, 2001). The damage of prenatal opiate exposure is debilitating and long lasting, and physicians must continue to track cohorts of exposed children to further understand the impact into adulthood.

Similar to human clinical studies, rodents exposed to heroin or morphine have a lower birthweight (Eriksson and Ronnback, 1989; Lu et al, 2012; Zagon and McLaughlin, 1977b, c) and impaired learning and memory (Steingart et al, 2000a; Wang and Han, 2009). Numerous structural and functional alterations have been found that could underlie the effects of prenatal opiates on cognition, including perturbations in dendritic length, synaptic plasticity, neuronal proliferation, and cholinergic function. Prenatal heroin or morphine exposure decreases dendritic branch length in layer II/III pyramidal neurons in somatosensory cortex, which is thought to be specific to opiate receptor activation, as it can be blocked by co-administration of an opiate receptor antagonist (Lu et al, 2012; Ricalde and Hammer, 1990). Long-term potentiation, long-term depression, and proteins associated with synaptic transmission are all attenuated with perinatal morphine exposure (Villarreal et al, 2008; Yang et al, 2006). Decreased proliferation in the developing striatum (Harlan and Song, 1994) and increased apoptosis in dopaminergic cell cultures and the hippocampus have been observed with perinatal heroin or morphine exposure (Oliveira et al, 2003; Oliveira et al, 2002; Svensson et al, 2008; Wang and Han, 2009).

The Yanai lab has provided substantial evidence to suggest that the deficits in spatial learning and memory may be tied to hippocampal cholinergic alterations. They found increased hippocampal levels of a cholinergic receptor (muscarinic M1 receptor) and the choline transporter with perinatal heroin (Steingart et al, 2000a; Steingart et al, 2000b). In addition, they observed altered levels and activity of protein kinase C—a signaling protein downstream of the M1 receptor- and enhanced inositol phosphate induction by cholinergic agonists (Steingart et al, 2000a; Steingart et al, 2000b; Yaniv et al, 2004). Whether a cholinergic deficit is found in cohorts of opiate-exposed children is unknown.

Perinatal heroin and morphine exposure also disrupt maturation of the opiate receptor system. Postnatal morphine exposure decreases mu opioid receptor binding in the striatum, NAc, amygdala, hypothalamus, and spinal cord (Hammer et al, 1991; Kirby, 1983; Tempel, 1991). Perinatal morphine exposure also induces morphine tolerance (Chiang et al, 2010; Eriksson and Ronnback, 1989; Hovious and Peters, 1984), although an increased sensitivity to morphine analgesia has been reported in female offspring (Arjune and Bodnar, 1989). Aroyewun and Barr (1982) proposed that postnatal morphine also accelerates the maturation of some aspects of opiate-dependent behaviors, such as opiate antagonist-induced anorexia, that normally only occurs after P14. Postnatal morphine exposure accelerated the appearance of this behavior to P10 and 12 (Aroyewun and Barr, 1983), but the observed hypophagia could also have been induced by the precipitation of opiate withdrawal. In addition, perinatal morphine or heroin has also been shown to alter sexual behavior (Vathy and Katay, 1992), NE turnover and release (De Vries et al, 1991), neuroendocrine function (Litto et al, 1983), and several other important structures and processes that this review cannot cover (for a comprehensive review of the developmental effects of illicit opiates see Slamberova (2012)).

Opiate Maintenance Therapies

The American Academy of Pediatrics and American College of Obstetricians and Gynecologists recommend opioid maintenance therapy as the first line of treatment for opioid dependence during pregnancy (ACOG Committee, 2012). Untreated illicit opiate use is associated with poor prenatal care, nutrition, and fetal health, which is improved with opioid maintenance therapy (Binder and Vavrinkova, 2008; Kandall et al, 1976; Maas et al, 1990). Initiation of an effective opioid maintenance therapy facilitates better prenatal care, decreased illicit use of opiates and other drugs, and a continuous dosing regimen that prevents maternal/fetal withdrawal. Opiate withdrawal is not recommended during pregnancy unless the mother refuses opiate maintenance therapy due to increased likelihood of relapse (ACOG Committee, 2012). Animal studies have demonstrated in utero withdrawal to increase fetal activity and perinatal mortality (Kirby and Holtzmann, 1982; Kuwahara and Sparber, 1981; Lichtblau and Sparber, 1981).

Opioid maintenance therapies are not without substantial risk, as they can cross the placenta and alter development. Withdrawal from illicit or prescribed opiates incites Neonatal Abstinence Syndrome in neonates, which often requires treatment with morphine, diluted tincture of opium, or methadone with or without diazepam (Finnegan et al, 1975; Jansson et al, 2009). However, incidence, peak severity score, duration, and length of required hospital stay due to Neonatal Abstinence Syndrome symptoms are less severe in neonates born to women following medically controlled maintenance therapies compared near-term mothers still

using illicitly (Binder and Vavrinkova, 2008; Kandall *et al*, 1976; Maas *et al*, 1990).

Methadone

Methadone is considered the current gold standard opioid maintenance therapy for pregnant women. It is a long-acting full mu opioid receptor agonist that is distributed as a daily dose only at licensed methadone clinics; allowing a tightly regulated, appropriately titered dosing regimen, and decreased abuse. Even though methadone reduces symptoms compared with illicit opiate use, clinical cohorts have demonstrated that prenatal methadone exposure can lead to increased premature birth (Cleary *et al*, 2012; Fajemirokun-Odudeyi *et al*, 2006; Lejeune *et al*, 2006), decreased birthweight (Cleary *et al*, 2012; Hulse *et al*, 1997; Kandall *et al*, 1976; Sarfi *et al*, 2009; van Baar *et al*, 1994), and smaller head circumference (Brown *et al*, 1998; Hans, 1989; Rosen and Johnson, 1985; van Baar *et al*, 1994; Welle-Strand *et al*, 2013; Wilson *et al*, 1981). Additional reports indicate an increased incidence of respiratory insufficiency at birth (Maas *et al*, 1990), altered corrected QT interval on electrocardiogram during the first postnatal week (Parikh *et al*, 2011), postnatal hyperphagia (Martinez *et al*, 1999), disrupted auditory event related potentials (Paul *et al*, 2014), and myelination deficits (Walhovd *et al*, 2012). However, the prevalence of cognitive impairments produced by prenatal methadone has been questioned because some studies have not observed differences in cognitive development (de Cubas and Field, 1993; Hans, 1989; Rosen and Johnson, 1985) or performance (Bauman and Levine, 1986; Soepatmi, 1994; van Baar, 1990; van Baar and de Graaff, 1994; van Baar *et al*, 1994). These variations may be in part due to socioeconomic status and other variables (Hans, 1989).

In clinical studies of opiate maintenance therapies, we are aware of the prenatal opiate exposure dose, which allows researchers to mimic physiologically relevant plasma concentrations of the drug. Most animal studies do not measure plasma concentrations, but variations in dose and method of delivery are common issues in prenatal exposure studies. Despite these differences, fairly consistent alterations have been seen with prenatal methadone exposure in animals. Similar to models of perinatal heroin and morphine exposure, perinatal methadone exposure leads to decreased birthweight (Enters *et al*, 1991; Ford and Rhines, 1979; McLaughlin *et al*, 1978; Zagon and McLaughlin, 1977a; 1983), mu opioid receptor binding (Hou *et al*, 2004), hyperactivity (Hutchings *et al*, 1992) and reduced performance on learning and memory tasks (Vargas *et al*, 1975; Zagon and McLaughlin, 1979; Zagon *et al*, 1979). Decreased brain and cerebellar weight and brain DNA content (Ford and Rhines, 1979; McLaughlin *et al*, 1978; Zagon and McLaughlin, 1977a; 1983) as well as cortical thickness (Ford and Rhines, 1979) have also been seen. Zagon and McLaughlin (1982) found reduced cerebellar area and decreased number and density of internal granular neurons

in the cerebellum with perinatal methadone exposure. A delay of developmentally timed behaviors was reported by the same group (Zagon and McLaughlin, 1978). Consistent with the cardiac abnormalities in neonates by Parikh and colleagues, rodent perinatal methadone exposure delays cellular development of the heart evident by altered levels of polyamines (Slotkin *et al*, 1982).

Alterations in the levels and/or activity of multiple neurotransmitter systems occur with perinatal methadone exposure. Studies have shown decreased hippocampal NE (Robinson *et al*, 1997), and disrupted striatal cholinergic activity compared with controls (Guo *et al*, 1990; Robinson, 2002; Robinson *et al*, 1996; Robinson and Wallace, 2001). McGinty and Ford found decreased DA in the forebrain at P1 and P20 in methadone-exposed rodents (McGinty and Ford, 1980). Prenatal only methadone exposure may decrease striatal DA turnover whereas combined pre- and postnatal exposure appears to increase it (Robinson *et al*, 1996). However, postnatal methadone exposure was required to decrease DA turnover in the frontal cortex (Robinson *et al*, 1997), which paints a complex picture of altered DA neurotransmission in perinatal methadone exposure. The 5-HT system shows irregularities in the transport system in the cortex and hippocampus (De Montis *et al*, 1983) and increased basal levels in the parietal cortex with perinatal methadone (Robinson *et al*, 1997). Additional disruptions in monoamine oxidase B levels (Tsang *et al*, 1986), METH sensitization (Wong *et al*, 2014), and startle response (Hutchings *et al*, 1993; Zmitrovich *et al*, 1994) also have implications for cognition and addiction vulnerability.

Buprenorphine

Buprenorphine is a partial mu opioid receptor agonist and a kappa opioid receptor antagonist that is given as an outpatient opioid maintenance therapy. Buprenorphine is not currently the recommended prenatal opioid maintenance therapy in the United States, although it is widely used elsewhere. A recent review of double-blind randomized control trials found insufficient evidence to recommend buprenorphine over methadone during pregnancy (Minozzi *et al*, 2013). This recommendation was largely based on a slightly superior retention of pregnant women in maintenance therapy with methadone, although buprenorphine may produce less severe neonatal abstinence syndrome (Minozzi *et al*, 2013). The American College of Obstetricians and Gynecologists has urged that buprenorphine be considered first-line treatment, but methadone is likely still the gold standard due to slightly higher adherence, more tightly controlled dosing, and insufficient evidence that buprenorphine is superior than methadone treatment (ACOG Committee, 2012). Observation of clinical cohorts has suggested that prenatal buprenorphine may produce fewer neurobehavioral problems (Coyle *et al*, 2012), higher birthweight, and larger head circumference compared with methadone (Welle-Strand *et al*, 2013).

Several studies have found no difference in growth patterns between buprenorphine-exposed and non-exposed neonates (Bakstad et al, 2009; Fischer et al, 2000; Schindler et al, 2003; Sundelin Wahlsten and Sarman, 2013). Yet, hyperactivity, visual/motor impairment, and memory problems (Sundelin Wahlsten and Sarman, 2013) as well as an increase in premature birth compared with non-exposed neonates have been observed. Therefore, although there are still developmental perturbations observed with prenatal buprenorphine, the risk to the fetus may be less than with prenatal methadone, and we encourage physicians to consider buprenorphine as a first-line maintenance therapy with pregnant patients.

Fewer animal studies have been published for perinatal buprenorphine than methadone and heroin/morphine, but perinatal buprenorphine appears to produce alterations common to opiate exposure. Like other opiates, perinatal buprenorphine produces morphine tolerance (Chiang et al, 2010; Robinson and Wallace, 2001), delayed acquisition of developmentally timed behaviors (Robinson and Wallace, 2001), and increased sensitization to METH (Chiang et al, 2013). Chiang et al (2013) also found decreased D1 receptor mRNA, basal cyclic AMP, and D1 receptor induced adenylyl cyclase activity in the NAc of buprenorphine-exposed offspring, suggesting disrupted signal transduction may underlie the increased METH sensitization. Although mu opioid receptor binding is decreased at birth, it corrects by postnatal day 7 (Belcheva et al, 1998; Belcheva et al, 1994; Hou et al, 2004). Perinatal buprenorphine does not appear to cause hyperactivity in animal models to date, although this has been reported in some clinical studies (Hutchings et al, 1996; Sundelin Wahlsten and Sarman, 2013). Effects on striatal acetylcholine levels are dose dependent with high doses causing a decrease at P4 and 21 but low doses producing an increase at P21 (Guo et al, 1990; Robinson, 2002). Altered myelination, which has been observed in clinical studies of opiate-exposed neonates (Walhovd et al, 2012), also occurs, producing increased myelinated axon caliber with disproportionately thin myelin sheaths potentially due to changes in myelin basic proteins and myelin-associated glycosylation (Sanchez et al, 2008). Additional observations in animal models of perinatal buprenorphine exposure have been reviewed comprehensively by others (Farid et al, 2008).

Naltrexone

Naltrexone is a long-acting, nonselective opioid receptor antagonist used more commonly outside of the United States to prevent relapse in opiate addicts due to its ability to block the euphoric effects of opioid agonists, low tolerance and abuse potential, and modest adverse effects (Jones et al, 2013). Newly developed depot formulations allow for dosing every 4–6 weeks, improving patient adherence and making this an increasingly preferred treatment option. Inadvertent exposure due to conception after naltrexone depot implant placement in Australia, Portugal,

and the United Kingdom has been cited, showing unremarkable neonatal and obstetric features compared with national averages as well as improved outcomes relative to methadone maintenance during pregnancy (Hulse and O'Neil, 2002; Hulse et al, 2003; Hulse et al, 2004; Hulse et al, 2001). However, these studies did not address the complications of pain management during labor and delivery or effects on postnatal development.

Animal studies suggest that caution should be taken with naltrexone exposure during pregnancy. Endogenous opioid growth factor and the zeta receptor (this was subsequently renamed the 'opioid growth factor receptor') are found in both rodents and humans developmentally and decrease cell proliferation (Zagon et al, 1992; Zagon et al, 1999). At supratherapeutic dosing, animal models show increased birth weight and brain and cerebellar weight likely through attenuation of endogenous opioid growth inhibition with no remarkable effects on gestation (McLaughlin et al, 1997a, b; Zagon and McLaughlin, 1984; Zagon et al, 1998). Zagon et al (1998) supported this hypothesis by showing decreased cerebellar proliferation with perinatal naltrexone (Zagon and McLaughlin, 1987). Perinatal naltrexone also alters opioid receptor expression and function (Bardo et al, 1982; 1983; Medina Jimenez et al, 1997). High perinatal doses (50 mg/kg) also increase dendritic arbor and spine growth in the cerebellum and hippocampus (Hauser et al, 1987; 1989). In contrast, low doses of perinatal naltrexone appear to produce decreases in dendritic length, proliferation, and overall growth (Farid et al, 2012; Hauser et al, 1989; Zagon and McLaughlin, 1984, 1987). Although these data advocate that naltrexone exposure during pregnancy may not be harmless, dosing discrepancies with human studies confound interpretations. Postnatal human studies with accurate measurements of dose and timing of exposures along with neurobehavioral endpoints are needed.

Prenatal exposure to opiates thus causes long-lasting alterations in growth, cognition, and motor and visual abilities. Although evidence suggests that any treatment for opiate addiction improves maternal and fetal outcomes, each form of medical treatment brings their own risks. The gold standard, methadone, has good patient retention but causes a more pronounced neonatal abstinence syndrome whereas buprenorphine has higher abuse potential but causes a shorter, less severe neonatal abstinence syndrome. Both of these mu opioid receptor agonists may alter developmental trajectory and negatively impact cognition. The increasing use of opioid antagonist (naltrexone) depot formulations to treat opioid addiction will bring more cases of fetal exposure to naltrexone and an increased risk of opioid overdose and relapse during pregnancy.

CANNABIS/delta-9-tetrahydrocannabinol

Cannabis, also known as marijuana or, in its more concentrated form, hashish, is an illicit drug derived from the Cannabis sativa plant and is commonly smoked or, less

frequently, ingested orally. For the purposes of this review, we will focus on the more commonly used form, marijuana, in its most popular route of administration, smoking. Marijuana is the most commonly abused form of illicit drug in the US, with over 42% of the population aged 12 years and over trying the drug within their lifetime. Over 38% of US females aged 12 and over will try the drug at some point in their lives, with 5% of females using the drug within the past month (Substance Abuse and Mental Health Services Administration, 2013). These statistics include women of childbearing age, and nearly 5% of pregnant women report smoking marijuana within the first trimester of pregnancy, although these numbers decrease in the second (2.9%) and third trimesters (1.4%) (Substance Abuse and Mental Health Services Administration, 2009). Given that cannabis has been recently legalized in Washington and Colorado and decriminalized in other states, with many others likely to follow suit, prenatal exposure to it is of growing concern.

Marijuana elicits a sedative-like effect, primarily due to its active ingredient, delta-9-tetrahydrocannabinol (THC). THC binds to the cannabinoid-1 (CB-1) receptor to induce this effect (for review, see Trezza et al (2008b)). Transcript for the CB-1 receptor is present in the second embryonic week in rodents (Buckley et al, 1998) and in the second trimester in humans (Wang et al, 2003), indicating that exposure to marijuana in the womb might have developmental consequences. Furthermore, THC can cross the placenta with reasonable efficiency (Hutchings et al, 1989), although unlike many other drugs of abuse, the placenta appears to limit fetal exposure to marijuana, as fetal THC concentrations have been documented to be lower than maternal concentrations in studies of various animal species (Behnke and Smith, 2013). Endogenous cannabinoids (endocannabinoids) are crucial for proper development in utero, and exogenous cannabinoids such as marijuana alter fetal growth trajectories (El Marroun et al, 2009), an effect that can have long-term consequences (for review, see Keimpema et al (2011)). Marijuana users can become dependent on the drug. Moreover, the THC content of marijuana has greatly increased over the years (Mehmedic et al, 2010), causing additional concern for fetal exposure.

Despite the overwhelming use among pregnant women, there are relatively few clinical studies looking at the effects of marijuana on the offspring. Studies have shown that fetuses exposed to marijuana during gestation exhibited stunted growth outcomes, as assessed by fetal weight and foot length (Hurd et al, 2005). Shorter gestation lengths, decreased birth weights, and deficits in other growth measures have been reported (Cornelius et al, 1995; Fergusson et al, 2002; Fried et al, 1999; Fried et al, 1984; Linn et al, 1983), although others have shown little to no effect on birth outcomes (Day et al, 1991; Witter and Niebyl, 1990). While the gestational and newborn growth outcomes remain equivocal, postnatal neurobehavioral outcomes are only slightly less so. Our understanding of the role of prenatal marijuana exposure derives primarily from two

long-term longitudinal studies: the Ottawa Prenatal Prospective Study (OPPS) and the Maternal Health Practices and Child Development Study (MHPCD). The OPPS study, initiated in 1978, consists of primarily 'low-risk' middle class subjects, while the MHPCD, begun in 1982 in Pittsburgh, focuses on 'higher risk' subjects of lower socioeconomic status. As outlined below, evidence from these studies and others suggests that prenatal marijuana exposure has deleterious effects on exposed children in particular domains, although these results are not definitive (for review, see Fried and Smith (2001) and (Campolongo et al (2009)).

Newborns exposed to marijuana exhibit sleep disturbances (Scher et al, 1988), a problem that persists through age 3 (Dahl et al, 1995), as well as a shorter, high-pitched cry (Lester and Dreher, 1989). Altered responses to visual stimuli and increased startles and tremors were noted in newborns exposed to marijuana (Fried, 1982; Fried and Makin, 1987; Fried et al, 1987), with some such symptoms lasting for at least 30 days after birth (Fried et al, 1987), although others, also using the Brazelton Neonatal Behavioral Assessment Scale, have shown no significant differences on these outcomes (Tennes et al, 1985). Differential results were also seen in the MHPCD and OPPS cohorts using the Bayley Scales of Infant Development. Decreased mental scores in marijuana-exposed children at 9 months of age were found in the Pittsburgh group, an effect attributed to exposure during the third trimester, although at 19 months, no significant differences were seen relative to controls (Richardson et al, 1995). Meanwhile, others have shown no significant cognitive deficits in children ages 1–3 years that were prenatally exposed to marijuana (Astley and Little, 1990; Fried and Watkinson, 1988; 1990). However, exposed children at 3 years of age from the higher risk MHPCD study demonstrated attenuated cognitive development, including decreased short-term memory, verbal, and visual skills (Day et al, 1994). These effects correlated with exposure during the first and second trimester yet that can in some populations be ameliorated by environmental enrichment (Day et al, 1994).

As children approach school age, additional detrimental effects of prenatal marijuana exposure become apparent. These deficits are not generalized to overall cognition but are specific to higher order function, specifically, executive function. Impairments in verbal and memory tasks become apparent in children at age 4, despite exhibiting no such alterations when tested at younger ages (Fried and Watkinson, 1990). At 5–6 years of age, exposed children showed no overall deficits in cognition or language skills (Fried et al, 1992a), but 6–year-olds showed attention deficits, elevated impulsivity, and hyperactivity (Fried et al, 1992b; Leech et al, 1999). Deficits in short-term memory and verbal reasoning were apparent at this age as well (Goldschmidt et al, 2008). Over time, attention deficits remain and can escalate to increased delinquency and externalizing behaviors (Goldschmidt et al, 2000). Interestingly, a study on marijuana-exposed fetuses found elevated

levels of D2 receptor transcript in the amygdala of males (Wang et al, 2004), suggesting potential for altered emotional regulation. Alterations in visuospatial memory are also noted in early adolescence (Fried and Smith, 2001). Deficits in these more complex domains were seen at ages 9–12 (Fried and Watkinson, 2000; Fried et al, 1998), although other data indicate that deficits in visual and abstract reasoning can be detected as early as 3 years of age (Griffith et al, 1994). Perhaps most striking is that even in their early 20 s, exposed individuals still have deficits in visuospatial working memory and impulsivity (Smith et al, 2004, 2006a). Adolescents performed more poorly in some areas of academic testing (Fried and Smith, 2001; Fried et al, 2003; Goldschmidt et al, 2012). These data indicate that prenatal marijuana exposure has significant effects on multiple neurobehavioral outcomes—deficits that are enduring, particularly at the level of executive function.

Exposed children also exhibit signs of neuropsychiatric disorders and may be more susceptible to substance abuse (for review, see Jutras-Aswad et al (2009)). For example, children from the MHPCD cohort presented with signs of depression as early as 10 years of age (Gray et al, 2005). Moreover, decreased levels of D2 receptor transcript were found in the NAc of exposed fetuses, potentially linking susceptibility to drug use to prenatal marijuana exposure (DiNieri et al, 2011). Prenatally exposed children were also more likely to experiment with marijuana at an earlier age as well as smoke the drug more frequently (Day et al, 2006; Goldschmidt et al, 2012). Given that drug use and psychiatric disorders are burdens not only to the individual but also to society as a whole, in total these results indicate the prenatal marijuana exposure has persistent deleterious effects that can have considerable consequences.

Animal models of prenatal marijuana exposure support these findings. Exposed offspring showed reduced body weight at birth (Abel et al, 1981; Abel et al, 1980). As with humans, young rats exposed to THC throughout pre- and postnatal development had increased ultrasonic vocalizations (cries) when isolated, indicative of increased anxiety and potentially analogous to increased irritability in human infants (Trezza et al, 2008a). In this same study, rats showed deficits in social behaviors during adolescence and elevated anxiety in adulthood. Increased locomotor activity has been demonstrated as well (Borgen et al, 1971; Mereu et al, 2003; Rubio et al, 1995), although others have shown either no changes in locomotion or significant hypoactivity (for review, see Navarro et al (1995); Schneider (2009)).

As previously mentioned, marijuana exposure during human prenatal development appears to affect 'higher order' facets of learning and memory. Similar results have been found in animal models as well. Using either the CB-1 receptor agonist WIN55,212-2 (Mereu et al, 2003) or THC (Campolongo et al, 2007), researchers found that developmental exposure resulted in impairments in passive avoidance, indicative of diminished memory retention. Furthermore, the THC-treated group also was unable to discriminate between a novel and a familiar rat in the social discrimination test. These effects are not limited to a particular phase of life, as in utero-exposed rats showed deficits in learning and memory tasks throughout the lifespan (Silva et al, 2012). These data and others (Campolongo et al, 2009; Schneider, 2009) indicate that marijuana exposure during pregnancy impacts learning and memory. Marijuana exposure during development may also result in increased likelihood of drug experimentation later in life. Exposed rats exhibited decreased levels of D2 receptor expression and binding in the NAc, a key reward center, and increased sensitivity to the rewarding properties of opiates (DiNieri et al, 2011). Others have shown that exposure to THC during a period equivalent to mid-gestation in humans resulted in increased heroin-seeking behavior in offspring (Spano et al, 2007). Following a similar exposure paradigm, rats administered AMPH in adulthood were less sensitive to its locomotor-stimulating effects (Silva et al, 2012), indicative of aberrant responsiveness to psychostimulants. While the preclinical data support the clinical findings, further research is needed to understand the mechanism and circuitry underlying these deficits.

TOBACCO/NICOTINE

According to the 2010 Pregnancy Risk Assessment Monitoring System data from the CDC, 12.3% of pregnant women in the US continue to smoke throughout pregnancy (Tong et al, 2013), and these numbers might be higher worldwide (Bloch et al, 2008). Over 7000 different chemicals are found in cigarette smoke, many of which are toxic and/or carcinogenic (U.S. Department of Health and Human Services, 2010). Nicotine, the primary psychoactive component of tobacco, and its metabolite, cotinine, readily pass through the placenta, and fetal concentrations of these compounds are significantly greater than those achieved by the mother (Lambers and Clark, 1996). Nicotine is an agonist of the nicotinic acetylcholine receptor (nAChR), which is expressed in the first trimester in humans and by the second gestational week in rodents (see review Dwyer et al (2008); Dwyer et al (2009)). Acting through this receptor, developmental exposure to nicotine disrupts the cholinergic system, a key modulator of brain development, and alters synaptogenesis, neuronal migration, neurotransmitter release, and a host of other molecular and functional endpoints (see review of Slotkin 2004). However, nicotine is only 1 of more than 4000 compounds to which the fetus is exposed through maternal smoking (Behnke and Smith, 2013).

Maternal smoking is not the only exposure to nicotine for the fetus. Maternal exposure to secondhand smoke (SHS) is also highly detrimental to proper fetal development and can cause long-term neurobehavioral alterations on its own (Chen et al, 2013). In addition, nicotine replacement therapies (ie, lozenges, patches, gum, etc.) are prescribed more and more to reduce fetal exposure to the additional

compounds found in cigarette smoke (Coleman, 2008). However, nicotine alone, based on animal studies, is highly toxic in and of itself, and these devices should not be considered 'safe' for pregnant women to use, although the risks are significantly less compared with cigarette smoking alone (for review, see Bruin et al (2010)). Along those same lines, electronic cigarettes (e-cigarettes) have become increasingly popular as they eliminate SHS by delivering nicotine as an inhalable vapor. These devices should be used with caution, as they expose not only the user, but also passerby to aerosolized nicotine (Czogala et al, 2013). Similarly, maternal use of smokeless (chewing) tobacco not only decreases birth weight (England et al, 2003), a risk factor for long-term neurobehavioral consequences (Rosenthal et al, 2011), but also results in higher Lipsitz scores, a neurobehavioral test used to measure drug withdrawal symptoms such as tremor, increased muscle tone and reflexes, and irritability in newborns (Hurt et al, 2005).

There is a wealth of data examining the effects of prenatal exposure to tobacco in both humans and animals, and a number of very detailed reviews exist on the consequences of prenatal tobacco exposure (Abbott and Winzer-Serhan, 2012; Bublitz and Stroud, 2012; Cornelius and Day, 2009; Pauly and Slotkin, 2008; Slotkin, 2008). For this review, we will provide an overview of some of the findings pertaining to neurobehavioral outcomes. At birth, exposed infants tend to be smaller in body weight, height, and head circumference, effects attributable to third and possibly second trimester exposure (Espy et al, 2011; Himes et al, 2013). There is also a greater likelihood of exposed infants to be admitted into the neonatal intensive care unit relative to unexposed controls (Adams et al, 2002). Newborns exposed in utero to nicotine are more irritable and have poorer attention than unexposed infants, and they exhibit hypertonicity, increased tremors and startle responses, and deficient speech processing as well (Espy et al, 2011; Fried et al, 1987; Key et al, 2007; Mansi et al, 2007; Reijneveld et al, 2002; Stroud et al, 2009a). Within the first month of life, exposed infants show signs of poorer self-regulation and require more handling by caregivers (Stroud et al, 2009b). Newborns also demonstrate an attenuated response to auditory stimuli, an effect that can contribute to language and learning impairments later in life (Kable et al, 2009; Mansi et al, 2007).

Following birth, the consequences of prenatal nicotine exposure are persistent, with some outcomes being consistently shown by multiple independent reports. Children age 6 and younger had decreased receptive language skills (Fried et al, 1992a; Fried and Watkinson, 1990; Lewis et al, 2007), which can contribute to language comprehension deficits. Exposed children also show poorer academic achievement or cognitive scores than peers (Agrawal et al, 2010; Fried et al, 1992a; Fried and Watkinson, 1990). These effects are not limited to young children. Older adolescents also exhibit cognitive deficits, as 16–18 year olds, exposed to tobacco in utero and were current smokers themselves, showed deficits in sensory

processing (ie, visuospatial memory) when abstinent from nicotine (Jacobsen et al, 2006). Interestingly, this effect was absent when subjects were allowed to smoke freely, indicating that the deficit was withdrawal-induced and that smoking was a means to compensate for this deficit. Furthermore, there was no difference between subjects exposed to tobacco throughout pregnancy or during only the first trimester, emphasizing the necessity of smoking cessation before pregnancy. In a test of working memory (N-back test) combined with fMRI, there was differential activation of various brain regions following correct responses in exposed versus unexposed adolescents, indicating abnormal function or circuitry following exposure (Bennett et al, 2013). Moreover, pallidum volume was smaller in adolescents following prenatal tobacco exposure, and increased impulsivity was correlated with thalamic volume following prenatal tobacco (Liu et al, 2013).

Attention is also a key area where a great number of deficits are seen following gestational tobacco exposure. Studies have shown that children as young as 6 years old show attention deficits, including diagnosis with ADHD, an effect seen well into the late teens (Bennett et al, 2009; Cornelius et al, 2011; Cornelius et al, 2007; Jacobsen et al, 2007; Kotimaa et al, 2003; Langley et al, 2007; Lindblad and Hjern, 2010). Both second (Cornelius et al, 2007) and third (Cornelius et al, 2011) trimester exposures have been correlated to attention problems. Interestingly, individuals with self-reported ADHD or attention problems were more likely to smoke than their peers (Kollins et al, 2005), further corroborating a link between attention disorders and nicotine use. While gestational exposure to nicotine appears to be a primary indicator for attention deficits, confounding factors such as maternal diagnosis of ADHD, environmental factors, socioeconomic status, and exposure to other drugs are often not accounted for in these studies (Agrawal et al, 2010; Ball et al, 2010; Langley et al, 2012). Thus, more thorough research to eliminate these factors as confounding variables is necessary.

Conduct and behavioral disorders are other domains frequently associated with prenatal tobacco exposure. Children as young as 18–24 months show increases in externalizing behaviors (Stene-Larsen et al, 2009; Wakschlag et al, 2006a) as well as internalizing and total problem scores following prenatal tobacco exposure (Carter et al, 2008). A study of 3-year-olds exposed gestationally to tobacco determined that increases in oppositional behavior were correlated to third trimester exposure (Day et al, 2000). Similar behavioral issues, including aggression, oppositional defiance, and delinquency, have been noted in older children (6–16 years old) (Bennett et al, 2009; Cornelius et al, 2011; Cornelius et al, 2007; Indredavik et al, 2007; Langley et al, 2007; Wakschlag et al, 2006b; Weitzman et al, 1992). It would appear that no level of tobacco exposure may be safe, as children aged 7–15 years, born of non-smoking mothers with SHS exposure during pregnancy, showed increased externalizing behavior (Gatzke-Kopp and Beauchaine, 2007). Moreover, children with only

prenatal exposure to tobacco were more likely to exhibit abnormal behaviors relative to children exposed only during the postnatal period (Ruckinger *et al*, 2010), thus emphasizing that gestation is a critical period in the development of behavioral disorders.

In addition to the aforementioned deficits, prenatally exposed children are more likely to develop substance use disorders. Lotfipour *et al* (2009) found that exposed children were more likely to experiment with drugs, an effect correlated to thinning of the orbitofrontal cortex. This same group also demonstrated that prenatal tobacco exposure, in combination with a genetic polymorphism of the α6 subunit of the nAChR, resulted in increased likelihood of smoking and drug use (Lotfipour *et al*, 2010). The combined environmental and genetic conditions altered brain development as well, as affected children had larger striatal volumes. Others have shown that exposed children begin to smoke and become regular users earlier than unexposed peers (Agrawal *et al*, 2010).

While preclinical models allow for more specific and controlled studies, variables such as species differences, pharmacokinetics, routes of administration, and the timing of the developmental exposure make comparisons or conclusions difficult. These studies, however, are invaluable in defining critical periods and insight into the underlying molecular mechanisms and circuitry following developmental nicotine exposure. For instance, tobacco smoke exposure in non-human primates during gestation and lactation resulted in neuronal cell loss, increased glia, and decreases in cell size (Slotkin *et al*, 2006). Following nicotine exposure *in utero*, changes to spine density, dendritic length, and dendritic branching were observed in juvenile (Muhammad *et al*, 2012) and adult (Mychasiuk *et al*, 2013) rats. Such changes can alter the trajectory of development and contribute to the functional deficits seen later in life (Pauly and Slotkin, 2008).

Changes in body weight are also found in animal models of developmental nicotine exposure. When pregnant dams were exposed to cigarette smoke throughout gestation, fetuses were significantly smaller than controls (Bassi *et al*, 1984; Esposito *et al*, 2008). Differences in body weight following other routes of administration or only postnatal exposure (equivalent to third trimester human exposure, see Figure 1) have been documented as well, although results are variable (see (Abbott and Winzer-Serhan (2012)) for review). In line with the clinical data, deficits in learning and memory and sensory processing have also been detected. Rodents exposed *in utero* to nicotine performed poorly on tests of learning and memory, including the radial arm maze (Levin *et al*, 1993; Sorenson *et al*, 1991) and two-way active avoidance (Vaglenova *et al*, 2008). Similarly, mice exposed to nicotine via injection took longer to reach criterion on the radial arm maze and had increased latencies to reach the platform on the Morris water maze (Yanai *et al*, 1992). Exposed mice exhibited deficits in sensory processing, as evidenced by hypersensitive passive avoidance (Heath *et al*, 2010). These researchers determined

that postnatal exposure—the equivalent of the human third trimester—was the key critical period for this effect. A study using a mouse model of inhaled cigarette smoke throughout gestation through weaning (simulating exposure throughout human pregnancy) resulted in deficits in spatial and reference memory as assessed via Morris water maze but not in route-based (egocentric) learning in the Cincinnati water maze (Amos-Kroohs *et al*, 2013). These findings bolster the clinical evidence that prenatal nicotine exposure alters long-term learning and memory function.

Clinical data on developmental nicotine exposure frequently refers to hyperactivity and attention deficits, effects that are found in the preclinical literature as well. Schneider *et al* (2011) found that rats exposed to nicotine during gestation performed more poorly in the 5-choice serial reaction time task in measures of sustained attention and impulsivity (Schneider *et al*, 2011). These data correspond to the clinical literature, specifically as attention deficits have been correlated to second trimester exposure (Cornelius *et al*, 2007). A similar exposure regimen in mice found that males and females exposed to nicotine were significantly more hyperactive than controls, especially during the dark (awake) cycle (Zhu *et al*, 2012). Moreover, nicotine-exposed mice responded to methylphenidate (MPH), a pharmacological treatment for ADHD, with attenuated locomotor activity. This low oral dose of MPH had no effect on control mice, just as humans without ADHD do not respond to MPH. Perhaps even more amazingly, the authors then demonstrated that the prenatal nicotine-induced hyperactivity can propagate transgenerationally via the maternal line of descent (Zhu *et al*, 2014). These data suggest that *in utero* exposure to substances even in previous generations may have a role in the increased incidence of neurodevelopmental disorders in modern society.

Finally, while conduct disorders *per se* are difficult to measure in animal models, comorbid conditions, such as anxiety, can be modeled. In fact, evidence exists that prenatal nicotine increases anxiety in rodents (Huang *et al*, 2007; Santiago and Huffman, 2013; Vaglenova *et al*, 2008), although also see Amos-Kroohs *et al* (2013). Exposed animals are more likely to self-administer nicotine later in life (Chistyakov *et al*, 2010; Levin *et al*, 2006). Others have shown that exposed rodents are more sensitive to the rewarding (Harrod *et al*, 2012) and locomotor-stimulating (Amos-Kroohs *et al*, 2013) properties of METH. Based on these data, further research into the long-term alterations resulting from developmental nicotine exposure, specifically into aggression, abnormal social behavior, and substance use disorders, is needed.

ALCOHOL

Alcohol consumption during pregnancy can result in a long-recognized fetal alcohol syndrome (FAS), which includes morphogenic effects on limb and facial development, reduced brain and birth weight, and cognitive delays

and impairments (Behnke and Smith, 2013; Foltran *et al*, 2011; Jones, 1986). However, even moderate exposure can impact brain development and these effects persist at least into young adulthood. While FAS represents the most severe manifestation of heavy maternal alcohol consumption during pregnancy, the term 'fetal alcohol spectrum disorders' (FASDs) has been applied to characterize a broad range of deficits present in individuals with or without facial dysmorphology who were exposed to alcohol prenatally (Foltran *et al*, 2011; Hoyme *et al*, 2005; Nash *et al*, 2008; Riley and McGee, 2005). Thus, moderate alcohol exposure during fetal development produces significant neurobehavioral consequences (Behnke and Smith, 2013; Day and Richardson, 1991; 2004; Fried and Watkinson, 1988; Jacobson and Jacobson, 1999; Jacobson *et al*, 1993; Nash *et al*, 2013), and FASDs currently represent the leading cause of mental retardation in North America, ahead of Down syndrome and cerebral palsy (Nash *et al*, 2008). As described in a 1996 Institute of Medicine Report to Congress—'Of all the substances of abuse (including cocaine, heroin, and marijuana), alcohol produces by far the most serious neurobehavioral effects in the fetus.' (Institute of Medicine, 1996). It has been estimated that at least 1 per 100 (1% of live births) are affected by FAS or FASDs (Sampson *et al*, 1997). Twelve percent of pregnant women self-report alcohol use within the past month (Substance Abuse and Mental Health Services Administration, 2008). A recent Australian study found that women who binged only before pregnancy were more likely to continue (55%) rather than reduce drinking (29%) once pregnant (Anderson *et al*, 2014). In 2002, the estimated societal cost for each individual with FAS was $2.0 million ($1.6 million for medical treatment, special education, and residential care for persons with mental retardation, and $0.4 million for lost productivity) (Lupton *et al*, 2004). The cost of FASD in the United States was last estimated at $4–8 billion annually (Popova *et al*, 2011). For comparison, the annual budget of the entire National Institute on Alcohol Abuse and Alcoholism is substantially less than 500 million.

In addition to total quantity, patterns of alcohol drinking can also modulate the severity of resultant deficits—for example 'moderate' drinking has much more impact on child development when the mother consumes several drinks in a single day than when she drinks the same quantity in doses of one to two drinks per-day over several days (Jacobson and Jacobson, 1999). Imaging studies reveal gray matter volume in the left cingulate gyrus, bilateral middle frontal gyri, right middle temporal gyrus, and right caudate nucleus following low-to-moderate exposure (De Guio *et al*, 2014; Eckstrand *et al*, 2012; Treit *et al*, 2013). Fetal alcohol has also been associated with a host of cognitive and behavioral impairments, including deficits in attention, memory, verbal fluency, executive functioning, reaction time, and motor learning (Coles *et al*, 2002; Howell *et al*, 2006; Mattson *et al*, 1998; Richardson *et al*, 2002; Riley and McGee, 2005; Willford *et al*, 2004). Maternal and fetal alcohol dehydrogenase polymorphisms also modulate risk (Warren and Li, 2005).

Ethanol has diverse cellular targets, and produces wide-ranging effects depending on the dose, duration, and timing of exposure. Current evidence suggests that alcohol produces many of its damaging effects by exerting specific actions on molecules that regulate key developmental processes (eg, L1 cell adhesion molecule, alcohol dehydrogenase, catalase), interfering with trophic factors that regulate neurogenesis and cell survival, and/or inducing excessive cell death via oxidative stress or activation of caspase-3 proteases (Conti *et al*, 2009; Farber *et al*, 2010; Goodlett *et al*, 2005; Ungerer *et al*, 2013). Several studies have identified effects of low amounts of alcohol exposure on the development of serotonergic neurons (Sari and Zhou, 2004; Zhou *et al*, 2003; Zhou *et al*, 2005), and suggested that these types of defects in the ontogeny of a specific neurotransmitter system may underlie the more 'subtle' deficits observed in human children diagnose with Alcohol Related Neurodevelopmental Disorder, rather than full-blown FAS (Zhou *et al*, 2003). Ethanol exposure disrupts the proliferation of glia and neuronal precursors in the developing central nervous system (Luo and Miller, 1998; Miller, 2007; Miller and Hu, 2009; Powrozek and Miller, 2009) and can dramatically alter behavior (Hellemans *et al*, 2010; Valenzuela *et al*, 2012). Transcriptional analyses of gene products regulated by fetal ethanol exposure in both mouse and human cells also highlight genes related to neural development, such as cell proliferation, neuronal migration, and differentiation (Hashimoto-Torii *et al*, 2011; Hicks *et al*, 2010). Emerging data also implicate microRNAs and epigenetic mechanisms (Balaraman *et al*, 2013; Mantha *et al*, 2014; Pappalardo-Carter *et al*, 2013; Ungerer *et al*, 2013). For example, fetal alcohol results in alterations in DNA methylation and microRNA expression and function (Pappalardo-Carter *et al*, 2013). An intriguing hypothesis suggests that fetal alcohol may induce a dual state of central nervous system insulin resistance and oxidative stress and proposes that adverse effects may be prevented or treated by treatment with peroxisome-proliferated activated receptor agonists (de la Monte and Wands, 2010).

Alcohol exposure continues to have potent effect on brain development postnatally in rodents, demonstrated by studies showing dramatic effects on the number of layer 2/3 cortical pyramidal neurons, on the branching patterns of their basilar dendrites (Granato *et al*, 2003; Granato and Van Pelt, 2003), and on dendritic excitability (Granato *et al*, 2012). The same group has gone on to also implicate distinct alterations in cerebral cortical and striatal interneuron distribution and morphology (De Giorgio *et al*, 2012; Granato, 2006). Rodent postnatal alcohol exposure also leads to a persistent disruption in ocular dominance plasticity, which can be treated, at least in part, with overexpression of serum response factor or inhibition of a phosphodiesterase (Medina *et al*, 2006; Paul *et al*, 2010). Once again, these time periods are most similar to late prenatal development in humans (Figure 1).

Finally, although we focus here on fetal exposures, of great additional interest is the suggestion that adolescents

respond differentially to the acute cognitive, sensorimotor, and behavioral effects of alcohol consumption than adults (Spear, 2014; Spear and Varlinskaya, 2005). For example, studies from Brunell and Spear (2006) indicate that adolescents exhibit bimodal behavioral responses to alcohol, with both hypo- and hyperresponsive systems (Doremus et al, 2003; Long et al, 1992; Varlinskaya and Spear, 2002). These findings have important implications for the risks associated with recreational drinking in adolescents and young adults.

Taken together, alcohol exposure during development induces behavioral, cognitive, and neural alterations that are specific, replicable, persistent and highly dependent on the timing of the exposure. Given the staggering socio-economic toll of prenatal alcohol exposures, new strategies to prevent exposures must be considered, and better mechanistic understandings are needed to facilitate poten-tial ameliorative therapies.

CAFFEINE

There have been few studies about the effects of the naturally occurring adenosine receptor antagonist caffeine, which is ubiquitously consumed in coffee, tea, and cocoa-containing foods. Caffeine is likely the psychostimulant substance most consumed worldwide. Although considered a fairly innocuous drug, a recent animal study has provided compelling mechanistic data suggesting that developmental caffeine exposure transiently antagonizes adenosine recep-tor signaling resulting in discrete but persistent alterations in hippocampal structure and function (Silva et al, 2013). An accompanying editorial expressed concern that 'We must now heed the wake-up call sounded by Silva et al (2013) that exposure to psychoactive substances, even a seemingly innocuous, socially well-integrated substance like caffeine, before or soon after birth can alter brain development' (Kabir et al, 2013). Another team has suggested that embryonic caffeine exposure produces an increase in body weight ($\sim$10%), alters cardiac function and morphology, and produces long-lasting alterations in DNA methylation (Buscariollo et al, 2014). A third group has focused on the neuroendocrine consequences and found that prenatal caffeine ingestion induces an increased susceptibility to metabolic syndrome with alterations of glucose and lipid metabolic phenotypes that then propagate transgenerationally (Katayama et al, 1987; Xu et al, 2012a; Xu et al, 2012b).

These recent studies join a larger body of work also suggestive of caffeine-induced changes in developmental trajectories (for review, see Porciuncula et al (2013)). Gressens et al (2001) have documented caffeine-induced acceleration of the evagination of neuroepithelium into telencephalic vesicles (Sahir et al, 2000) and upregulation of sonic hedgehog (Sahir et al, 2004). Gestational caffeine also downregulates central adenosine receptors (Leon et al, 2005; Lorenzo et al, 2010), reduces NMDA antagonist-induced

locomotor activity (da Silva et al, 2005), and affects respiratory control (Bodineau et al, 2003; Saadani-Makki et al, 2004). Cognitive and motor deficits have also been reported in adult rodents exposed in caffeine during gestation and/or early postnatal life (Bjorklund et al, 2008; Soellner et al, 2009), although some impairments may be paradigm specific (Soellner et al, 2009).

The metabolism of caffeine and other methylxanthines is impaired in pregnant women, fetuses and neonates, leading to reduced clearance and potentially higher circulating levels (Aden, 2011). Several clinical studies have focused on concerns regarding caffeine-induced fetal growth restriction and have led to suggestions that women should reduce caffeine intake before conception and throughout preg-nancy (Bracken et al, 2003; CARE Study Group, 2008). Other studies have failed to find an association (reviewed in Brent et al, 2011). Regarding more subtle changes in developmental trajectories, a recent study from the Netherlands did not find significant effects of prenatal caffeine on neurobehavioral functions at 5–6 years of age (Loomans et al, 2012), although data on caffeine intake was obtained only once during the $\sim$16th week of gestation. In contrast, a Norwegian prospective study has reported a small but significant association between maternal caffeine intake and inattention/overactivity based on the Child Behavior Check List (Bekkhus et al, 2010). Given the fairly dramatic range in caffeine metabolism rates among individual women (based on CYP1A expression and activity), it seems crucial that future studies employ pharmacogenomics strategies and caffeine metabolite measurements, rather than simple self-report of intake. And when combined with a still-evolving literature implicating adenosine A1 and A2A receptors in establishing neuronal homeostasis, tuning the ability of synapses to undergo plasticity, and in modulating neurotoxicity (Dias et al, 2013), these data suggest that expanded study of this topic is sorely needed.

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

In summary, fetal exposure to drugs of abuse often produces long-lasting changes in brain structure and function (see Figure 3). These (mal)adaptations are regardless of whether the drugs are legal or illicit; it is in fact arguable that alcohol and nicotine produce more dramatic deficits than 'harder' drugs like cocaine. Adolescence encompasses another sensitive period of development; given that this is when illicit drug use typically begins, detailed research on how drugs of abuse alter relatively late-developing processes in the brain is also essential. Importantly, the molecular targets of psychoactive drugs sometimes have quite different actions in early development, as compared with their adult roles as synaptic modulators. In some cases, transgenerational effects via epigenetic changes have been documented. In addition, studies have repeatedly pointed out the crucial
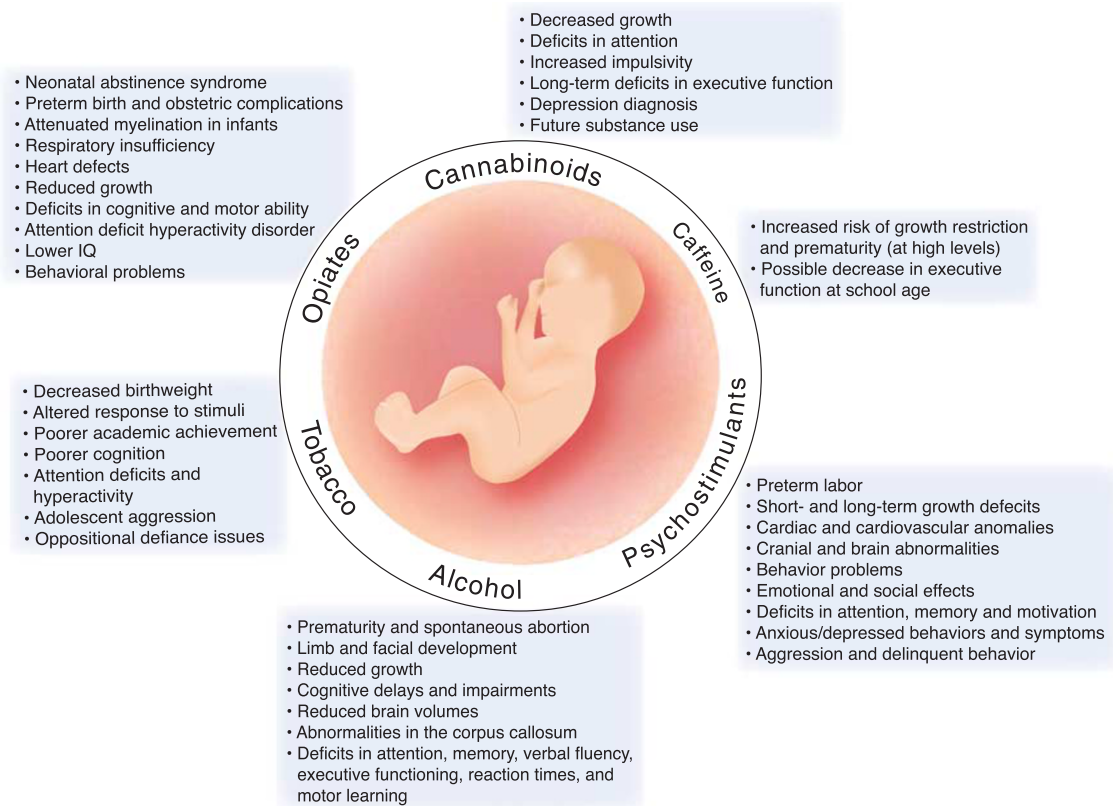
Figure 3. Schematic summary of effects of distinct drug classes on offspring development. A wide variety of significant structural and neurobehavioral deficits are induced by fetal exposures to abused substances. As described in the text, the drug class, timing, dose, and pattern of intake all substantially determine the long-term effects on the developing child.

covariates of postnatal environment and socioeconomic status. The developing brain is extremely plastic and adaptable; we continue to discover new and better strategies for intervention.

Surprisingly, research in this area is still in its formative stages, and more precise and mechanistic work will be necessary to characterize the extent of neurobehavioral alterations and how developmental timing, dosages, and genetics affect these processes. When costs for special education, long-term medical management, and lost productivity across the lifespan are considered, the socioeconomic impact is truly staggering. Moreover, societal responses continue to be misguided. For example, the state of Tennessee passed legislation in 2014 allowing women to be charged with assault if they have a pregnancy complication after using narcotics illegally. The desire to guard fetal health and outcomes is understandable; however, pregnant women who fear prosecution and the potential loss of their children will rarely seek essential prenatal and medical care. We already discovered the negative consequences of such practices during the peak of maternal cocaine exposures in South Carolina from 1989–1994, before their prosecution of these women was forced to cease (Annas, 2001; Budetti, 1993; Ferguson v. City of Charleston, 2001; McKnight v. State of South Carolina, 2008; Poland *et al*, 1993). Physicians

and scientists need to better engage and educate the public on these complex issues.

We do not claim to have all the answers, or even all of the questions. But as a field, we must do a better job of bridging the translational gap. Basic scientists must design their animal models with consideration to (a) whether the route of administration (to the dam or the pup) is the same as in human users, (b) whether pharmacokinetics and biotransformation of the drug differ between humans and the animal model, (c) whether the model encompasses the entirety of fetal development, and (d) how well the outcome measures being tested in the animals conform to relevant outcome measures in the clinical literature. Given that women rarely, if ever, begin using an abused drug during the third trimester of their pregnancy, postnatal-only administration in rodents will usually be inadequate (Figure 1). Given the great prevalence of polysubstance use in drug-abusing women (and men), more models of prenatal polydrug exposure seem warranted. Interactions between fetal drug exposure and other environmental variables, including toxicants and stressors, are also crucial (Graf *et al*, 2013). Clinicians must also make better use of the preclinical findings and predictions about the kinds of deficits to be expected in people who have been exposed to substances prenatally (Figure 3). Particular focus should be

paid when diverse types of models (species, dosing, timing, etc.) produce congruent effects on functional domains (even if the precise cellular mechanisms differ)—these are the maladaptations that will likely be most prevalent in the human population. The ability of animal data to potentially predict future health issues should also not be overlooked—for example, aging studies in animal models predict that prenatal exposure to cocaine or nicotine (Abreu-Villaca et al, 2004; Lawrence et al, 2008; Lloyd et al, 2006; Meyer et al, 2009) may produce higher risks or expression of cell death and/or neurodegenerative diseases later in life. While only time will tell, we will likely be facing additional societal and medical burdens as drug-exposed children continue to age—better animal models will allow us to predict and treat later-in-life disorders in these populations as they emerge.

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