Assessment and Treatment of Prenatally Exposed Infants and Children

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Case 1: Opioids

Benjamin is a 3-year-old male with a history of prenatal exposure to opioids. He appears to demonstrate delays in both verbal and motor domains and has been followed by the newborn follow-up clinic associated with the hospital where he was born. His face is also slightly dysmorphic, with wide-set exotropic eyes. There were concerns about whether Benjamin's exposure to opioids in utero might have affected his brain development and subsequent developmental difficulties.

In cases of prenatal substance exposure, it is ideal for a multidisciplinary team to provide assessments of developmental functioning at regular intervals throughout early childhood. As part of this process, it is of paramount importance to obtain a thorough prenatal, postnatal, and developmental history given that the timing and type of substance(s) to which the fetus was exposed may impact development. Understanding that substance use is often associated with profound family and parental stress, it is also important to obtain a detailed family and social history.

According to Benjamin's mother, she had used methamphetamine throughout her 20s before initiating opioid use in her 30s. Like many individuals who become opioid-dependent, Benjamin's mother initially gained access to opioid prescription painkillers after a medical procedure. At age 31, she was in a minor car accident requiring a subsequent hand surgery, at which time she was treated with oxycodone. She reported that these pain pills helped with her physical pain as well as the emotional pain she was experiencing secondary to her stressful circumstances at the

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time and her history of childhood adversity. Specifically, Benjamin's mother had witnessed domestic violence and experienced physical and emotional abuse throughout her childhood. Given the relief she found through opioid use, she continued to endorse physical pain to various doctors in order to obtain oxycodone prescriptions. She transitioned to using heroin almost exclusively about 1 year later at age 32, citing that it was cheaper and easier to access than prescription pain pills. She met her current partner, Benjamin's father, through a group of individuals who were buying, using, and selling opioids in the local community. His history was positive for witnessing domestic violence, as well as parental substance use, and emotional neglect. Benjamin's parents began dating about 3 months after meeting, and Benjamin's mother became pregnant at age 33.

Upon learning of her pregnancy, Benjamin's mother was using only opioids. At the beginning of her second trimester of pregnancy (around 14 weeks' gestation), she entered residential substance use treatment at a facility for pregnant and parenting women. There, she received individual and group substance use counseling, began taking methadone, and stopped using heroin and prescription pain pills. Throughout her pregnancy, Benjamin's mother did well in treatment, did not relapse into illicit drug use, and did not drink alcohol; however, she continued to use tobacco. She remained in a relationship with Benjamin's father, who entered outpatient substance use treatment. Benjamin's father moved in with his parents who had a history of substance use, though they were not actively using at this time.

Benjamin was born prematurely at 36 weeks, as is the case with up to 30% of opioid-exposed infants [1]. However, given that Benjamin's mother (like many methadone-maintained mothers) experienced high levels of stress during pregnancy, it is likely that Benjamin's early birth may have been caused in part by stress during pregnancy. Given that opioids including methadone and buprenorphine cross the placental barrier and enter the fetus' bloodstream [2], Benjamin also tested positive for opioids in his system at birth as confirmed by urine and meconium analysis [3]. He experienced some perinatal health complications associated with neonatal abstinence syndrome (NAS) including low birth weight, loose stools, poor feeding, vomiting, nasal stuffiness, and moderate tremors.

Multipronged non-pharmacological intervention is now considered the standard of care for all prenatally exposed infants. Non-pharmacological intervention was initiated for Benjamin and his mother in the nursery in order to address the effects of NAS via the promotion of maternal responsiveness and nurturance, dyadic bonding, and infant self-regulation and self-organization [4]. Interventions for dyads like Benjamin and his mother should be individualized based on the infant's neurobehavioral profile as well as the mother's strengths and weaknesses.

Although the standard of care for prenatally exposed infants has shifted from pharmacological treatment to non-pharmacological care, evidence-based evaluation and pharmacologic management is still used with some infants [5]. The Finnegan

Neonatal Abstinence Scoring System [6] initially placed Benjamin in Category IV of NAS severity and he was placed in the NICU for stabilization. After stabilization, he was treated in the nursery and his symptoms were monitored every 4 h using the Finnegan system. He was treated pharmacologically with an alcohol-free oral morphine sulfate preparation (0.4 mg/mL) and was fully weaned from an initial dose of 0.16 mg over the course of 3 weeks in the hospital.

Benjamin's sensory reactivity, behavioral states and state regulation, motor and tone control, and autonomic signs of stress (e.g., tachypnea, yawning, sighing, sweating, sneezing, hiccups, gagging, spitting up, frequent bowel movements, color changes, mottling) were used to guide his individualized non-pharmacological treatment [4]. In terms of sensory processing, Benjamin became easily overwhelmed by sound and touch as evidenced by becoming visibly agitated. Benjamin's apparent overresponsiveness was characterized by crying, vocalizing, closing his eyes, having erratic limb movements, spitting up, hiccupping, and even having bowel movements. As a result, care was taken to ensure a quiet, dimly lit environment in the nursery. This also helped address Benjamin's dysregulated sleep-wake states. Benjamin's impaired motor control was evident in tremors, problematic feeding, and inability to latch to breast or bottle. These issues were addressed with the use of swaddling, light tactile pressure, a pacifier, and small frequent high-calorie meals.

Additionally, treatment for NAS requires educational and psychological intervention aimed at improving the mother's responsiveness to the infant's needs [4]. A key feature of this approach centers around building the mother's confidence and ensuring that she does not misinterpret or internalize the infant's dysregulated behaviors. Nurses taught Benjamin's mother about the importance of providing a calm, non-overwhelming environment for him due to his sensory sensitivities. They also showed her specific holding and swaddling techniques that worked well for Benjamin in the nursery and allowed her to practice and master these before discharge. She was encouraged to continue participation in the group parenting intervention program, *Circle of Security (CoS)*, that she was already enrolled in at the residential substance use treatment facility [7]. She was also referred to individual parenting intervention, *Mothering from the Inside Out (MIO)*, targeting the neural stress and reward circuitry of mothers in substance use recovery [8]. Given that high emotional arousal triggers craving responses in addicted individuals, MIO aims to reduce emotional arousal in the caregiver through a process called *mentalization* (i.e., understanding behavior by examining one's own and others' underlying thoughts and feelings). MIO thus helped Benjamin's mother to understand her own emotional states and become regulated, thus expanding her ability to mentalize for her son and allowing her to experience the reward of parenting him [8]. The intervention team also worked with Benjamin's mother around her expectations for her parenting role and her worries about the impact of her drug use on her son.

Research Pearl #1: Maternal Responsiveness as an Important Consideration for Prenatally Exposed Infants

In addition to the physiological effects of prenatal substance exposure, child development is also shaped by maternal/adult responsiveness, which can be hampered by substance use as well. First, substance use alters the *stress and reward systems* in the brain. When infants cry, for example, these cues are experienced as more stressful to mothers with substance use disorders compared to mothers who do not use substances. For nonaddicted mothers, an infant cry triggers a caregiving response, and the process of soothing the infant is experienced as rewarding. In contrast, for mothers with substance use disorders, infant cries trigger a craving response, and the use of substances to regulate in the face of stress is experienced as rewarding [9].

Second, mothers' *internal working models* (i.e., mental representations) of their infants begin to take shape during pregnancy [10] and have a strong influence on mother-child attachment. Risk factors such as substance use can affect the formation of these internal working models [11], which can also disrupt maternal responsiveness, negatively impact bonding between mother and child, and increase the risk of insecure attachment relationships. As we know from decades of attachment research, insecure relationships formed very early in life often have long-lasting consequences including dissociation, anxiety, conduct problems, and substance use [12]. As a result, maternal responsiveness is a key point of intervention for this population and can be addressed via treatments that target internal representations of infants and/or neural stress and reward circuitry. One such empirically supported treatment that specifically targets mothers in recovery from substance use problems is *Mothering from the Inside Out* [8]. This treatment works to enhance mothers' own stress-regulatory capacities via mentalization, with the goal of helping mothers achieve more balanced mental representations of their children, thereby improving their responsiveness, the reward they experience from parenting their children, and the overall quality of the parent-child relationship.

Benjamin's mother visited him daily in the nursery. With pharmacological [5] and non-pharmacological intervention [4], Benjamin's central and autonomic nervous systems became more regulated. His feeding and elimination improved, weight increased, vomiting and tremors stopped, and overall irritability dissipated.

Upon discharge Benjamin came to live with his mother at the women's residential substance use treatment facility. They remained at this facility for the first 8 months of Benjamin's life, where they were provided with a safe, substance-free, low stress environment in which they were able to form a healthy bond. This

approach reflects optimal care, which is unfortunately quite rare for most opioid-exposed mother-child dyads. Afterward, Benjamin and his mother moved into the paternal grandparents' home. Benjamin and both biological parents moved to the local homeless shelter when Benjamin was approximately 2 years old due to the paternal grandparents' financial hardships (i.e., foreclosure) and his parents' difficulty finding employment. They continue to reside at the homeless shelter presently.

Benjamin's mother reported that he was a happy and social baby throughout infancy. After overcoming NAS fully, he was easy to soothe, cried infrequently, and was relatively quiet. He continues to be very friendly and smiles often at others despite little familiarity with them. He demonstrates appropriate eye contact, though this is impacted somewhat by exotropia (i.e., divergent strabismus), a condition that is ten times more likely to occur in prenatally exposed children than in the general population [13, 14]. He tends to withdraw and close his eyes when faced with loud noises or bright lights. Despite his interest in others, his verbal communication is still limited to only a few short phrases at 3 years of age. He communicates mostly in two-word utterances. His language delay is likely multi-determined, caused in part by the direct effects of prenatal exposure on brain development, as well as other factors often associated with prenatal exposure (e.g., poverty, living in a high stress environment at the homeless shelter, low levels of parental education and literacy, and his parents' continued methadone maintenance treatment which could have dampened their responsiveness and engagement with him) all of which are known factors in language acquisition [15, 16].

With regard to motor delays, Benjamin's gross and fine motor skills have been slow to develop. At birth, he had difficulty latching which affected his feeding. As an infant, he did not show much interest in physically exploring his environment and was content to remain seated. Unlike many infants with NAS, Benjamin did not exhibit hypertonia. Rather, his lack of motor control was apparent as he did not frequently reach for objects, and when others attempted to hand him items, he often did not grab or hold them successfully. He took his first steps around 15 months of age and began walking independently at 16 months. His gait continues to be clumsy at present, and he often is transported by his mother in a stroller. He does not fuss or protest when placed in his stroller and he easily tolerates being strapped in. In fact, he becomes calm when he experiences the tactile sensory input and light pressure across his chest provided by the straps of his stroller.

Given his history of NAS and related stay in the NICU, Benjamin has been continuously followed by a multidisciplinary medical and developmental follow-up program associated with the hospital. Benjamin was assessed at 6, 9, 12, 18, 24, and 36 months of age. This is yet another example of the optimal care that was provided to Benjamin and that not every prenatally exposed infant is fortunate enough to receive. The Bayley Scales of Infant Development-Third Edition (Bayley-III; [17]) have been used to assess Benjamin's development in the domains of cognitive, language, and motor skills.

Clinical Pearl #1: NICU Follow-Up Clinics
In keeping with best practice guidelines, high-risk infants like Benjamin benefit from follow-up by multidisciplinary teams consisting of individuals in the fields of neonatology, neuropsychiatry, clinical psychology, developmental behavioral pediatrics, occupational therapy, nutrition, nursing, and social work. These professionals collaborate to generate a comprehensive conceptualization of the infant in order to inform recommendations that will increase the infant's chances of positive developmental outcomes. These teams also track the infant's development in many domains in addition to cognitive, language, and motor skills. These assessments aid in determining if interventions are needed or are working. They can also detect any regressions in development that may be signs of more serious problems. Although ideal, this model has unfortunately not yet been adopted as the current standard of care in all hospitals. Funding for this type of care is relatively limited, and when it is available, parents with substance use problems often face issues with accessing such care. For example, parents of prenatally exposed infants may be experiencing psychosocial stressors that make it difficult to attend appointments. They may also face issues with accessing care due to the stigma surrounding substance use during pregnancy or due to their fear of judgment from health professionals [18].

Benjamin's cognitive abilities have remained relatively stable over time and have rated within the average range at each of his follow-up assessment visits. Although research studies on the effects of prenatal opioid exposure on cognitive development have revealed inconsistent results [1], Benjamin's case supports findings suggesting minimal impact on intellectual functioning [19, 20].

In contrast, Benjamin's language skills placed within the low average range initially. Within this domain, however, there was significant variability. Upon further analysis, it was evident that his receptive communication abilities fell within the average range and were significantly stronger than his expressive communication abilities which fell within the extremely low range. Social work facilitated a referral to a local early intervention agency, and home-based speech-language services began when Benjamin was approximately 12 months of age. His expressive language skills have improved over time with intervention, though he still struggles somewhat in this area. His most recent assessment of language skills at 36 months revealed that his receptive communication continues to be in the average range and his expressive communication abilities are now within the high end of the borderline range.

Benjamin's motor skills also began in the borderline range initially, with his gross and fine motor abilities being similarly developed. When Benjamin began speech-language services, he also began home-based occupational therapy

through the same early intervention organization. These services targeted fine motor skills such as reaching, grasping, and feeding, as well as gross motor skills such as walking and standing up from a seated position. He has made progress in both areas, and his most recent assessment of motor skills at 36 months revealed that both his gross and fine motor skills now fall within the low average range.

Overall, the importance of early and continuous follow-up and intervention cannot be stressed enough in cases like Benjamin's. Although he still exhibits some delays in language and motor skills, his abilities in these domains have improved with the interventions that were made possible by the initial identification of his delays and by the multidisciplinary follow-up program. In addition, Benjamin's positive developmental trajectory was also impacted greatly by the pharmacological and non-pharmacological treatment of his NAS in the hospital nursery. As his medical team determined what worked best to address his symptoms, his mother observed and learned techniques to soothe and bond with him. Benjamin's mother's involvement in mentalization-based intervention geared specifically toward mothers in recovery from substance use disorders [8] also has proven to be integral for bolstering the parent-child relationship and buffering against the effects of his prenatal exposure. Her ability to respond to him successfully will likely continue to shape a positive path for Benjamin as he continues to develop. In this spirit, given Benjamin's family history of substance use and current stressors of poverty, homelessness, and trauma recovery, other supports will continue to be necessary to help his parents remain as stable caregivers for him. For example, participation in relapse prevention services, recovery support groups, and individual trauma-focused treatment will be integral in maintaining their own mental health. Further, supports such as case management, vocational training, and supportive housing would be beneficial to address their more concrete needs. Overall, the ultimate goal of each of these supports is to halt the intergenerational cycle of substance use and stress for Benjamin.

Finally, it is worth noting that Benjamin's needs may not be solely associated with prenatal opioid exposure, but rather a combination of early life stress and drug effects. As a result, as Benjamin matures, he will likely benefit from other services aimed at addressing his experience of early life stress such as frequent transitions and moves, homelessness, poverty, and his parents' continued need for methadone maintenance. For example, participation in *Child Parent Psychotherapy (CPP)* with his mother and/or father would serve to help the family process Benjamin's stressful experiences, understand and organize his emotions, develop regulatory capacities, and further strengthen their safe relationships with one another [21]. It will remain to be seen if Benjamin will need further services when he is older, though it is hoped that with each of the services the family has received thus far, his likelihood of a positive developmental trajectory has increased dramatically.

Case 2: Cocaine

Tasha is a 9-year-old female with a history of prenatal cocaine exposure. Her biological mother became pregnant unexpectedly with an individual with whom she was not in a relationship. She discovered she was pregnant at 6 weeks, and at that time she made efforts to eat healthier, discontinued alcohol use, and decreased her cocaine use to some extent; however, she continued using cocaine and smoking cigarettes throughout her entire pregnancy. After Tasha was born, she experienced postpartum depression and resumed heavy use of cocaine throughout Tasha's infancy and toddlerhood. As a result, Tasha's maternal aunt has been involved as a support since her birth. She assumed full guardianship when Tasha was 18 months of age given that Tasha's biological mother's addiction had worsened and she was unable to care for herself or Tasha. It is presumed that Tasha's first 18 months were characterized by emotional and physical neglect. Per the maternal aunt's report, Tasha's biological mother was frequently consumed with various romantic relationships with men who were violent and sold drugs. She also reportedly spent much of her time either high or engaging in efforts to obtain drugs, often dropping Tasha off with her aunt or other family members for days at a time without a diaper bag, extra clothing, or other supplies needed for her care.

Despite this early life stress and disruption in her placement, Tasha bonded well with her aunt, and each of her developmental milestones was met within normal limits. Similar to many children who were exposed prenatally to cocaine, Tasha presented with executive functioning deficits [22–24] such as inattention, impulsivity, and hyperactivity, as well as symptoms of anxiety [25] and dysregulated arousal [26, 27]. At home, her aunt reported that she does not pay attention when being spoken to, frequently daydreams, often acts before thinking, is constantly moving, and appears tense and worried much of the time. At school, she has difficulty remaining seated, following directions, and distracting her classmates. Her school performance is also notable for long-standing learning difficulties and poor grades in reading and writing.

Given her academic underperformance, Tasha participated in psychoeducational testing at her school in the first grade when she was 6 years of age. The Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV; [28]) revealed low average overall intellectual functioning. Specifically, Tasha exhibited average verbal comprehension, very low fluid reasoning, low average working memory, and low average processing speed. The Wechsler Individual Achievement Test-Third Edition (WIAT-III) revealed average oral language skills, very low early reading skills, low average written expression skills, and very low math skills. These results prompted accommodations including extended time and preferential seating. Tasha also began receiving special education intervention to improve her reading, writing, and mathematics performance. Despite intervention and her average cognitive skills in the verbal comprehension domain, Tasha's grades continued to suffer.

Research Pearl #2: Cognitive Development and Learning Following Prenatal Cocaine Exposure

Overall, research suggests that prenatal cocaine exposure is related to subtle but persistent differences in children's brains, effects on their cognitive functioning, and especially on their stress-regulatory capacities [29]. Tasha's cognitive profile is remarkably similar to findings suggesting that cocaine-exposed youth suffer from deficits in perceptual reasoning, fluid reasoning, and problem-solving skills but have relatively unaffected cognitive abilities in the domains of verbal comprehension and memory [30, 31]. Despite average verbal skills and memory, we might expect Tasha to exhibit academic underperformance due to the impact that altered stress reactivity has on learning and cognition [32]. In other words, when cognitive resources are more quickly allotted to stress regulation due to prenatal cocaine exposure, the brain is less able to use resources for learning or attending to material presented in school.

Because of continued scholastic difficulties as well as caregiver and teacher reports of symptoms of inattention, hyperactivity, and impulsivity, at age 7 Tasha was further evaluated using the Quotient ADHD System, a computerized objective test of inattention and motor movement. Tasha's performance provided evidence of significant inattention as well as hyperactivity and impulsivity. Tasha fell below the 16th percentile on most measures of inattention (e.g., accuracy, omission errors, variability, distractibility) and hyperactivity/impulsivity (e.g., head movements, head immobility duration, and area of movement). What providers failed to appreciate at the time, however, was Tasha's history of prenatal cocaine exposure. Consistent with literature suggesting elevated likelihood of ADHD diagnosis for children prenatally exposed to cocaine [33] and tobacco [34], she was diagnosed with ADHD.

Tasha was subsequently treated for ADHD with methylphenidate 18 mg extended release for approximately 6 months. Her executive dysfunction continued, as did her anxiety. Her aunt found it difficult to communicate her ongoing symptoms to doctors who simply encouraged her to engage in more consistent parent management and advocate for improved school programming.

At age 7.5, Tasha moved with her aunt to a different city in the same state. Her inattentive, hyperactive, and impulsive symptoms persisted. This prompted a referral by her new pediatrician for evaluation, management, and psychotherapy at an outpatient psychiatric clinic in their new city, where she continues to receive services presently. Tasha's new psychiatrist initially increased her dose of methylphenidate extended release to 36 mg to determine if her previous dose was simply insufficient. This was trialed for approximately 1 month with little benefit. In addition, her symptoms of anxiety increased.

In response, guanfacine 1 mg immediate release was added to her medication regimen in the evenings. The family was instructed to continue methylphenidate in the morning as well. Within a few days, Tasha exhibited fewer executive functioning difficulties; however, her anxiety and general emotional arousal persisted. Methylphenidate was removed 1 month later, and Tasha continued taking guanfacine 1 mg. With this adjustment, her executive functioning remained improved, with better ability to focus, follow directions, and inhibit impulses. Her anxiety, reactivity to stress, and emotional arousal also decreased when methylphenidate was removed.

Neuroscientific research [27] suggests that for all individuals, during calm times (i.e., at moderate levels of stimulation and arousal), alpha-2 systems are regulating prefrontal cortical activity with the functional result of optimal attention and executive control functioning. As arousal increases with stress or overstimulation, alpha-1 systems predominate with the resulting downregulation of prefrontal cortical systems and upregulation of more posterior cortical, automatic response systems. The threshold of stimulation at which an individual's alpha-1 systems take over is often referred to as the *neurochemical switch*, and this varies across individuals to a certain degree. It is hypothesized that prenatal cocaine exposure (and also excessive prenatal stress) can shift this neurochemical switch to activate alpha-1 systems too early, which is behaviorally displayed as impaired executive functioning, poor behavioral inhibition, difficulty with attentional shifting, and faster fight-or-flight response. Therefore, it is understandable that guanfacine, an alpha-2 adrenergic agonist, would help to regulate Tasha's arousal by reducing alpha-1 activation thus improving Tasha's symptoms of anxiety and her executive functioning. In addition, Tasha's positive response to guanfacine is noteworthy and corroborates findings that such medication improves executive functioning in cocaine-dependent women following stressful, anxiety-provoking stimuli [35].

Throughout this time, Tasha was engaged in outpatient clinical services that included executive functioning coaching. For example, Tasha learned techniques for self-monitoring her attention so she could begin to refocus upon noticing she had become off-task. Notably, executive functioning skills and strategies were taught separately from challenging academic material and before being applied to current coursework. Once Tasha learned these strategies, she was then taught when to apply them. She was provided with a visual "cheat sheet" listing these skills to remind herself of them until they became more automatic. In addition, Tasha was provided with a small electronic timer to remind her to engage in period self-monitoring of her on-/off-task behavior and attention at timed intervals (e.g., once every 15 min). Simply by tracking her performance/behavior, Tasha increased her awareness not only of the expectations but also of her ability to meet the expectations. Over time, tracking of behavior and increased self-monitoring abilities led to improvement in her performance.

Tasha's anxiety was targeted via cognitive behavioral therapy. This treatment included psychoeducation regarding the relationships between thoughts, emotions, and behaviors, as well as techniques regarding how to challenge negative automatic thoughts with evidence that supports more rational beliefs. Her overall level of

heightened arousal and reactivity to stressful stimuli was addressed through the training of relaxation strategies such as deep breathing, progressive muscle relaxation, and guided imagery.

Parent management intervention was also employed as part of Tasha's outpatient treatment. Her aunt was taught behavioral strategies to reward Tasha for on-task behavior, following directions, and inhibiting impulses. She also was taught Tasha's newly learned executive functioning strategies so she could help Tasha employ them at home during homework time, for example. Finally, the aunt learned the same relaxation techniques and CBT skills so she could help Tasha practice at home and encourage use of these strategies when needed during times of distress.

Overall, Tasha's grades improved with better executive functioning and lower levels of anxiety. She also had better relationships with her aunt and with her teachers, who no longer struggled to constantly redirect Tasha's attention and prompt her to follow directions. It was evident that when her providers appreciated the impact of her prenatal exposure to cocaine, the approach to treatment and the combination of pharmacological and non-pharmacological intervention benefited Tasha and her family greatly.

Lessons Learned About Neuropsychiatry

Although quite different, Benjamin's and Tasha's cases collectively have much to teach us about neuropsychiatry and the complex interaction of environmental stress and the biologic impact of exposure to psychotropic drugs in pregnancy. First and foremost, Benjamin and Tasha both demonstrate the fact that parental substance use and prenatal substance exposure do not occur in a vacuum. Rather these problems very often co-occur with other psychosocial stressors. In Benjamin's case, prenatal opioid exposure was one piece of a puzzle that also involved poverty, homelessness, many years of parental substance use, and parents who continued to need opioid maintenance therapy. In Tasha's case, prenatal cocaine exposure occurred in conjunction with tobacco and alcohol, exposure to violent relationships throughout infancy and toddlerhood, experience of early emotional and physical neglect, and her mother's continued substance use which led to their early separation and loss of contact.

Given that these risk factors so often co-occur, it can be difficult for the practitioner to tease apart the direct neurological effects of exposure from those caused by prematurity, low birth weight, continued parental substance use, chronic psychosocial stress, inconsistent caregiving, low socioeconomic status, trauma, and neglect [1, 36, 37]. Prenatal exposure also increases children's vulnerability to the effects of psychosocial stressors, leading to poorer outcomes than those of children who are prenatally exposed only or those with psychosocial stressors only [38]. Further, researchers have begun to demonstrate that there are likely epigenetic effects from the environmental stressors accompanying substance use and prenatal exposure that in turn may also impact children's development [39, 40].

Through these cases, we have also learned that different classes of substances affect the developing brain differently and lead to varying outcomes. Tasha's executive functioning deficits can be explained in part by corticolimbic changes in the prefrontal cortex due to prenatal exposure to cocaine. For example, research demonstrates reduced gray matter in the prefrontal and frontal brain regions in children with prenatal cocaine exposure [41]. In contrast, in utero opioid exposure impacts the fetus' developing brain diffusely, potentially impacting several brain regions and resulting in unpredictable neurobehavioral outcomes and various developmental deficits [42]. For example, research has shown that opioids interfere with the myelination process [43], which potentially played a role in Benjamin's language and motor delays [44].

Finally, the reality is that the majority of substance-exposed infants are polydrug-exposed and endure the aftereffects from in utero exposure to multiple potentially harmful agents [5]. Therefore, although studies have identified the specific effects of individual substances, the pediatric neuropsychiatrist should be prepared to encounter patients with a variety of symptom constellations following prenatal exposure. By understanding the neurobehavioral effects of the substance(s) to which a patient has been exposed, the practitioner will surely be better equipped to address his or her deficits successfully and with less guesswork. But above all, the practitioner is best served by understanding that prenatal exposure especially to illicit drugs involves complex interactions with environmental stress and disruption and thus, understanding and working with the family is a necessary part of treatment interventions.

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