NEONATAL WITHDRAWAL SYMPTOMS AND THE EFFECTS OF SUBSTANCE EXPOSURE

By

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Abstract

Neonatal Abstinence Syndrome is a commonly known form of neonatal withdrawal, which can affect infants prenatally exposed to opioids. Research has shown that prenatal substance exposure may induce withdrawal syndromes in infants prenatally exposed to other substances, as well. Thus, studies have investigated withdrawal-like symptoms in infants after various prenatal exposures. Neurobehavioral effects have been shown, though specific presentation may vary by substance, situation, and individual infant. Five categories of substances are described: opioids and opiates, SSRIs, nicotine, cocaine, and amphetamines and methamphetamines. For each category, known biological mechanisms in adults are described before presenting information from studies regarding neonatal withdrawal effects. After evaluating research related to neonatal withdrawal, a few commonalities emerged: (1) though infant withdrawal effects from nonopioid substances have been studied, different research reaches varying conclusions regarding the underlying mechanistic cause of symptoms, (2) researchers emphasize the need for additional symptom scoring systems, particularly to assess non-opioid exposures, and (3) publications encourage continued research in the field. In all cases, mothers and their newborns deserve care and consideration.

Introduction: The Opioid Epidemic and Neonatal Abstinence Syndrome

"Tomorrow I'm having my baby. She's going to be born addicted. Thankfully she's not going to remember. But to know that she's going to have to feel withdrawal because of my choices, knowing that she's going to feel pain because of my actions is horrible." - Jennifer Moshera mother of two from North Andover, Mass." (qtd. in Nachtwey)

The Opioid Epidemic reaches into every corner and chasm ("Our National Crisis". From magazine covers and exposing documentaries to academic discussions and medical literature, depictions of the Opioid Crisis have illuminated the significance of substance use in daily life ("Our National Crisis"; "Dr. Feelgood"; Wilkerson et al.). The Centers for Disease Control and Prevention estimates that opioid overdose claims about 900 lives every week, with an overall death toll of nearly 450,000 deaths between the years of 1999 and 2018 ("Understanding the Epidemic"). Opioids are not solely responsible for substance-related tragedy, however, as over 750,000 total deaths from overdose occurred within the same timeframe ("Data Overview"). Substance use disorders present a significant public health concern ("Substance Abuse"). Not only have overdose-related death rates in America increased significantly over the past decade, but the World Health Organization estimates nearly 31 million individuals worldwide to be affected by substance use disorders ("Overdose Death Rates"; "Management").

The seemingly omnipresent epidemic of substance abuse does not exclusively impact the users themselves ("Neonatal Abstinence Syndrome"). Friends, relatives, and others within the social circle of an individual suffering from a substance use disorder may adopt new roles and stressors ("Chapter 2 Impact"). Substance use during pregnancy presents a unique situation, as children exposed to drugs or medications in-utero may require additional medical consideration throughout development ("Substance Use in Women"). In particular, newborns may experience withdrawal symptoms after birth due to cessation of exposure to the maternally introduced substance ("Substance Use in Women"; Wexelblatt et al.). Withdrawal is defined by the World Health Organization as "symptoms of variable clustering and degree of severity which occur on cessation or reduction of use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period and/ or in high doses" ("Withdrawal State"). The recent surge in opioid use among pregnant women has revealed a concomitant increase in occurrence of Neonatal Abstinence Syndrome (NAS), the clinical term for infant withdrawal subsequent to maternal opioid use (Wexelblatt et al.). Though most medical literature details infant withdrawal from opioid exposure, other substances have been found to incite similar conditions ("Substance Use in Women"). Comprehensive neonatal patient care necessitates not only mechanistic understanding of prenatal substance exposure, but also social and contextual understanding of situations involving infant withdrawal (Raffaeli et al.). Considering neonatal withdrawal syndromes can arise from both prescribed and illicit maternal substance exposure, each case must be assessed and treated according to individual patient need (Alic). The proceeding research aims to compile knowledge regarding the biological processes of infant withdrawal. By outlining the current state of knowledge, gaps in research and care can be found and ameliorated to provide better outcomes for infants and their families. This work is not, in any way, intended to provide or influence medical advice or guidance. Please consult licensed healthcare professionals for all medical or health-related concerns.

Works Cited

Alic, Margaret. "Neonatal Abstinence Syndrome." *The Gale Encyclopedia of Mental Health*, edited by Brigham Narins, 4th ed., vol. 3, Gale, 2019, pp. 1114-1118. *Gale Health and Wellness*, https://go-gale-com.ezproxy1.library.arizona.edu/ps/i.do?p=HWRC&u=uarizona_main&id=GALE%7CCX2491200339&v=2.1&it=r. Accessed 17 Apr. 2020.

"Chapter 2 Impact of Substance Abuse on Families." *Substance Abuse Treatment and Family Therapy,* Center for Substance Abuse Treatment, Treatment Improvement Protocol (TIP) Series, no. 39, 2004, NCBI Bookshelf, www.ncbi.nlm.nih.gov/books/NBK64258/. Accessed 13 Feb. 2020.

"Data Overview." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 19 Mar. 2020, www.cdc.gov/drugoverdose/data/index.html.

"Dr. Feelgood: Dealer or Healer? (2016)." *IMDb*, www.imdb.com/title/tt5192362/. Accessed 13 Feb. 2020.

"Management of Substance Abuse: Facts and Figures." *World Health Organization,* WHO, www.who.int/substance_abuse/facts/en/. Accessed 17 April 2020.

Nachtwey, James. "The Opioid Diaries." *TIME*, time.com/james-nachtwey-opioid-addiction-america/. Accessed 13 Feb. 2020.

"Neonatal Abstinence Syndrome | Cincinnati Children's." *YouTube*, uploaded by Cincinnati Children's, 3 Mar. 2017, www.youtube.com/watch?v=yr-kLlwNexs. Accessed 13 Feb. 2020.

"Our National Crisis." *The Opioid Diaries* | *TIME*, time.com/opioid-addiction-epidemic-in-america. Accessed 13 Feb. 2020.

"Overdose Death Rates." *National Institute on Drug Abuse*, NIDA*,* Mar. 2020, www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed 17 April 2020.

Raffaeli, Genny, et al. "Neonatal Abstinence Syndrome: Update on Diagnostic and Therapeutic Strategies." *Pharmacotherapy*, vol. 37, no. 7, 2017, pp. 814–823, https://doi-org.ezproxy4.library.arizona.edu/10.1002/phar.1954.

"Substance Abuse." *Healthy People 2020*, Office of Disease Prevention and Health Promotion www.healthypeople.gov/2020/topics-objectives/topic/substance-abuse. Accessed 05 May 2020.

"Substance Use in Women: Substance Use While Pregnant and Breastfeeding." *National Institute on Drug Abuse,* NIDA, April 2020, www.drugabuse.gov/publications/substance-use-in-women/substance-use-while-pregnant-breastfeeding. Accessed 17 April. 2020.

"Understanding the Epidemic." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 19 Mar. 2020, www.cdc.gov/drugoverdose/epidemic/index.html. Accessed 17 April 2020.

Wexelblatt, Scott L., et al. "Opioid Neonatal Abstinence Syndrome: An Overview." *Clinical Pharmacology and Therapeutics*, vol. 103, no. 6, pp. 979–981, doi:10.1002/cpt.958.

Wilkerson, Richard Gentry, et al. “The Opioid Epidemic in the United States.” *Emergency Medicine Clinics of North America*, vol. 34, no. 2, 2016, pp. e1–e23. doi:10.1016/j.emc.2015.11.002. Accessed 13 Feb. 2020.

“Withdrawal State.” *World Health Organization*, World Health Organization, www.who.int/substance_abuse/terminology/withdrawal/en/.

Opioids and Opiates

Opioid-related death is a worldwide tragedy (Knoppert). “The Opioid Epidemic” encompasses the devastating effects of opioid misuse and overuse (“What Is the U.S.”). Opioid overdose claimed over 33,000 lives during 2015 in the United States (Skolnick). Both prescription opioid analgesics and illegal varieties have played a role in the public health crisis that causes over 100 deaths every day (Skolnick; Mahase; “America’s Drug Overdose”).

Opioids medications can alleviate various types of pain, from short-term to long-term conditions (Hagemeier). Postoperative pain and pain resulting from cancer are among the conditions treated with opioids (Grewal and Huecker). In addition to pain management, opioids are also used to treat diarrhea and cough, with medications such as loperamide and codeine, respectively (Grewal and Huecker). In general, “opioid” refers to chemicals that act at opioid receptors in the body (Wilkerson et al.). Opioids originating from the poppy plant are called “opiates” (Wilkerson et al.). Opiates include codeine, heroin, and morphine, while opioids also include synthetic varieties such as carfentanil, acetylfentanyl, and fentanyl (Wilkerson et al; Grewal and Huecker; “Synthetic Opioid”; “What Are Opioids?”). Other commonly known opioid varieties include oxycodone, tramadol, levorphanol, and hydrocodone (Trescot et al.). Some opioids can be prescribed medicinally, such as morphine, whereas others, such as heroin, are only available illegally in the United States (Wilkerson et al; Trescot et al; Hagemeier). Opioids can be introduced to the body via numerous methods including ingestion, intravenous or intramuscular injection, rectal and topical application (Grewal and Huecker).

Opioids function biologically through opioid receptors found naturally in the human body, primarily throughout the nervous system (Trescot et al.). Opioids function similarly to endogenously produced endorphins (Trescot et al.). Three types of opioid receptors can be found throughout the nervous system: mu (μ), kappa (κ), and delta (∂) (Trescot et al.). Mu receptors are located in the brain and come in several subtypes that, when stimulated, promote subjective feelings of pain relief and elation, as well as physical changes including slowed breathing and sedation (Trescot et al.). Activation of opioid receptors can lead to the release of cAMP-inhibiting proteins and inhibition of voltage-dependent calcium channels (Trescot et al.). When these calcium channels are inhibited, cells do not release pain-stimulating neurotransmitters such as "glutamate, substance P, and calcitonin gene-related peptide" (Chahl; Trescot et al.). Opioids are thus able to stop transmission of pain signaling (Trescot et al.; Al-Hasani and Bruchas). Opioids are also known to encourage pleasure pathways within the brain by preventing GABA release (Al-Hasani and Bruchas; Trescot et al). Since GABA acts as an inhibitory neurotransmitter, preventing its release leads to increased stimulation of its target neurons (Sherwood 87). Thus, prevention of GABA release in the ventral tegmental area (VTA) leads to an increase in dopamine signaling pathways, inducing happiness and euphoric emotions (Trescot et al.). Al-Hasani and Bruchas summarize the effects of opioid substances on the human brain: "While μ opioids continue to be some of the most effective analgesics, they are also efficacious mood enhancers and cause activation of central dopamine reward pathways that modulate euphoria" (Al-Hasani and Bruchas). Overall, opioids lead to positive subjective emotion and relief from pain (Trescot et al; Al-Hasani and Bruchas).

In addition to immediate effects of analgesia and euphoric mood, the class of substances is also well-known for initiating physical and physiological dependence when taken long-term (Al-Hasani and Bruchas; Chan and Lutfy). According to the Centers for Disease Control and Prevention, the DSM-5 defines Opioid Use Disorder "as a problematic pattern of opioid use leading to clinically significant impairment or distress" ("Module 5"). Long-term effects of opioid use include tolerance and dependence (Jamison and Mao). Where tolerance is defined as requiring higher quantities of a substance to feel the same subjective effects, dependence refers to when withdrawal symptoms precipitate after cessation of substance use (Jamison and Mao). Opioid use disorder, tolerance, and substance dependence are interconnected conditions with varying biological underpinnings (Jamison and Mao; Wang et al.). For a start, tolerance is thought to occur upon repeated exposure to opioids, which can lead to irregular behavior of molecular receptors (Wang et al.). In particular, cyclic AMP (cAMP) and protein kinase A (PKA) have been implicated in opioid addictive mechanisms (Chan and Lutfy). Opioid receptors inhibit adenylyl cyclase, causing less cAMP to accumulate within a cell, which decreases activity of PKA (Chan and Lutfy). Opioid use has been found to increase activity of the adenylyl cyclase pathway after chronic exposure (Chan and Lutfy). Moreover, opioids have been found to affect certain areas of the brain (Kim et al.). Increased production of dopamine, particularly in the Ventral Tegmental Area (VTA), has been linked to subjective feelings of reward (Kim et al.). In animal studies, VTA neurons reduced in size after long-term opioid exposure, potentially altering this reward system (Kim et al.). Cannabinoid receptor type 1 proteins have also been implicated in brain alterations from opioid exposure (Kim et al.). The amygdala may contribute to different pathways associated with opioid use disorders, and the hippocampus is thought to induce various mechanisms of learned behavior (Kim et al.). Glutamate signaling in various regions may also be altered through substance use (Wang et al.). Numerous studies have found interrelated brain structural changes as a result of opioid use over long periods of time (Wang et al.; Kim et al.).

As a result of physiological changes, the cessation of opioid use after long-term exposure leads to withdrawal effects (Jamison and Mao; Wang et al). Adult withdrawal can manifest with behavioral and psychological symptoms, including anxiety and irritability (Wang et al.). Physical pain can include musculoskeletal aches and abdominal pain (Wang et al.). Other symptoms, such as nasal congestion, yawning, lacrimation, and sweating are also common (Wang et al.). Withdrawal may also precipitate gastrointestinal irregularities including diarrhea (Wang et al.). Opioid withdrawal is a severe clinical condition and can be life-threatening (Shah and Huecker).

Withdrawal effects can also occur in infants after prenatal exposure to opioids (Alic). Since opioid substances have the ability to cross the placenta, maternal use can lead to fetal exposure (Alic;

Raffaeli et al.). Both maternal use of prescription and non-prescription opioid varieties, ranging from methadone to codeine to heroin, can precipitate withdrawal in newborns (Alic; Raffaeli et al.). As opioids can lead to tolerance and dependence, neonates can experience withdrawal symptoms after birth due to cessation of opioid exposure (Jamison and Mao; Mcqueen and Murphy-Oikonen; Alic). Specific molecular pathways leading to infant withdrawal, while not fully known, have been proposed to involve changes in neurotransmission and opioid receptor levels (Raffaeli et al.). Infant opioid withdrawal is termed Neonatal Abstinence Syndrome (NAS), a condition that has increased in incidence by 500% in the United States between 2000 and 2017 (Alic).

NAS is well-documented in medical literature (Mcqueen and Murphy-Oikonen). Dr. Loretta Finnegan began to publish some of the first assessments of NAS in the 1970s, which emphasize the importance of care and treatment for newborns and their mothers (Mcqueen and Murphy-Oikonen; Finnegan). Since then, knowledge of the condition has grown immensely (Mcqueen and Murphy-Oikonen). However, considering "opioids are the most common illicit substance for which pregnant women seek treatment," research into NAS and its treatment remains critical to promoting public health (Sanlorenzo et al.). Specifically, many researchers advocate for the standardization of procedures regarding NAS diagnosis and treatment (Mcqueen and Murphy-Oikonen; Sanlorenzo et al.). Neonatal Abstinence Syndrome presents many unique considerations, and new research findings continue to illuminate the importance of promoting mother and infant bonding (Mcqueen and Murphy-Oikonen).

Neonatal Abstinence Syndrome displays numerous variable signs and symptoms, generally within the first several days of life (Alic; Soraisham). Physical signs include an increased level of nervous system and gastrointestinal activity (Sanlorenzo et al.). Neurologically, infants may experience muscle tremors, shaking, heightened reflex sensitivity, and seizures (Alic). Vomiting and diarrhea are among some of the gastrointestinal symptoms, as well, which can lead to dehydration (Alic; Soraisham). Infants experiencing NAS may also present with a fever, and elevated heart and respiratory rates (Alic; Soraisham). Irregularities in feeding, sleeping, and weight have also been reported (Alic; Soraisham). Infant behavioral indicators of withdrawal can include skin picking, implacable crying, agitation, and excessive mouth movement such as sucking motions and yawning (Alic; Soraisham). Skin mottling and sneezing are yet additional signs of infant withdrawal (Alic). NAS expression varies widely, and severity of associated conditions and symptoms depend largely on the individual case and context (Jansson and Patrick). Factors such as genetic differences, comorbid infection, level of prenatal care, maternal stress, duration and chemical of exposure can all alter NAS presentation (Alic; Jansson and Patrick). Several genetic traits have been associated with NAS severity, including single nucleotide polymorphisms in OPRM1 and COMT genes, which code for the mu opioid receptor and catechol-o-methyltransferase genes, respectively (Sanlorenzo et al.). In addition to prenatal opioid exposure, maternal use of medications such as SSRIs, gabapentin, nicotine, and benzodiazepines has been found to play a role in the expression of NAS (Sanlorenzo et al.; Mcqueen and Murphy-Oikonen).

Diagnosis of neonatal abstinence syndrome is generally reliant on patient history, or infant toxicology screens such as urine, hair, or meconium testing (Alic; Mcqueen and Murphy-Oikonen). When infants present symptoms indicative of withdrawal, healthcare works can use various assessment systems to determine severity and course of action (Jansson and Patrick). NAS diagnostic tools can help physicians gauge treatment plans, especially relative to pharmacological intervention strategies (Alic; Sanlorenzo et al.; Jansson and Patrick). The Finnegan Abstinence Scoring System and its derivatives are widely used and measure the severity of withdrawal symptoms based on observational analysis (Raffaeli et al.). However, one 2018 review notes that the Finnegan scoring model may not actually lead to better results in cases of NAS (Sanlorenzo et al.). Instead, the study notes promising results from a scale used by Grossman et al. in which NAS severity was assessed based on various infant behaviors including normalcy of sleeping and feeding (Sanlorenzo et al.). Similarly, one *Pediatric Clinics of North America* review discussed the success of "Eat, Sleep, Console" protocols in limiting hospital stays for infants experiencing NAS (Jansson and Patrick). The article also emphasized the importance of maternal involvement in treatment decisions (Jansson and Patrick). Overall, many publications note that the tools used to evaluate NAS represent an area of neonatal care that can be further improved (Sanlorenzo et al.; Mcqueen and Murphy-Oikonen).

Patient care for infants with Neonatal Abstinence Syndrome can involve pharmacological and non-pharmacological interventions (Alic; Jansson and Patrick; Mcqueen and Murphy-Oikonen). Management strategies that do not involve medication are deemed “non-pharmacological” interventions, which primarily require a safe and calm environment for the neonate (Raffaeli et al.). Treatment involves creating a calm atmosphere with minimal sounds and soft lighting for the infants to receive care and support throughout the course of the symptoms (Raffaeli et al.). A special emphasis is placed on promoting bonding between the mother and child, by receiving care in the same room and breastfeeding, when these options are feasible and safe for the mother and infant (Raffaeli et al.). Other ways to promote calmness in infants includes music therapy and sensory stimuli such as swaddling, swaying, and holding (Alic). Additionally, infants with NAS are very carefully transitioned between states of sleep and wakefulness to avoid sudden disruption (Jansson and Patrick). Special care is also taken in feeding, such as by using formulas high in calories to promote growth and development (Alic; Raffaeli et al.).

In addition to the described non-pharmacological treatment methods, pharmacological interventions are also employed in the treatment of NAS (Raffaeli et al.). Medical literature reveals that opioids, including morphine and methadone, are often used in healthcare settings to mitigate infant withdrawal symptoms (Raffaeli et al.). Recent studies, however, suggest buprenorphine treatment to improve NAS outcomes (Raffaeli et al.). Raffaeli et al. notes that phenobarbital is used to reduce seizure activity, and clonidine is used lessen severity of nervous symptoms, as well (Raffaeli et al). Physicians may use pharmacological intervention in addition to nonpharmacological approaches, especially when infants present with severe symptoms including seizures (Raffaeli et al.).

One *Neuropathology of Drug Addictions and Substance Misuse* publication details the specific context of maternal codeine use, noting the immense prevalence of codeine exposure during pregnancy (Soraisham). Codeine is often prescribed to pregnant women for its analgesic properties (Soraisham). However, fetal exposure to the medication can lead to neonatal abstinence syndrome (Soraisham). Particular take-aways include the need for parental education and risk-benefit analysis to ensure that patients can decide clearly the course of action they wish to take (Soraisham). Both managing patient pain and decreasing risks of potential side-effects for the infant are critical and require thorough consideration; hence, the article encouraged counseling options for these situations (Soraisham).

Infants experiencing Neonatal Abstinence Syndrome require special care and gentle treatment (Alic; Soraisham; Raffaeli et al.). Treatment of NAS entails providing a caring, supportive, restful environment in which infants can cope and family ties can be nurtured (Alic; Mcqueen and Murphy-Oikonen). Most notably, recent articles truly encourage bonding between mothers and their babies, as research has shown that situations in which both mother and infant have the opportunity to room together demonstrate better medical outcomes (Alic; Sanlorenzo et al.). Infants experiencing Neonatal Abstinence Syndrome clearly need care, support, patience, and kindness from their caretakers (Alic).

Works Cited

Al-Hasani, Ream, and Michael R. Bruchas. “Molecular Mechanisms of Opioid Receptor-Dependent Signaling and Behavior.” *Anesthesiology*, vol. 115, Dec. 2011, pp. 1363–1381., doi:10.1097/aln.0b013e318238bba6.

Alic, Margaret. "Neonatal Abstinence Syndrome." *The Gale Encyclopedia of Mental Health*, edited by Brigham Narins, 4th ed., vol. 3, Gale, 2019, pp. 1114-1118. *Gale Health and Wellness*, https://link-gale-com.ezproxy1.library.arizona.edu/apps/doc/CX2491200339/HWRC?u=uarizona_main&sid=HWRC&xid=e5ab297c. Accessed 19 Apr. 2020.

“America's Drug Overdose Epidemic: Data to Action.” *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 8 Jan. 2020, www.cdc.gov/injury/features/prescription-drug-overdose/index.html. Accessed 19 Apr. 2020.

Chahl, Loris A. “Experimental and Clinical Pharmacology: Opioids - Mechanisms of Action.” *Australian Prescriber*, vol. 19, no. 3, 1 Jan. 1996, pp. 63–65., doi:10.18773/austprescr.1996.063.

Chan, Patrick, and Kabirullah Lutfy. “Chapter 7-- Molecular Changes in Opioid Addiction: The Role of Adenylyl Cyclase and CAMP/PKA System.” *Progress in Molecular Biology and Translational*

Science The Molecular Basis of Drug Addiction, vol. 137, 2016, pp. 203–227., doi:10.1016/bs.pmbts.2015.10.005.

Finnegan, Loretta. "Pathophysiological and Behavioral Effects of the Transplacental Transfer of Narcotic Drugs to Fetuses and Neonates of Narcotic Dependent Mothers." *Bulletin on Narcotics*, vol. 31, no. 3-4, Jan. 1971, pp. 1–58. *ResearchGate*, www.researchgate.net/publication/22743844_Pathophysiological_and_behavioral_effects_of_the_transplacental_transfer_of_narcotic_drugs_to_fetuses_and_neonates_of_narcotic_dependent_mothers. Accessed 19 Apr. 2020.

Grewal, Neelam and Martin R. Huecker. "Opioid." *StatPearls [Internet]*. StatPearls Publishing LLC, Jan. 2020, https://www.ncbi.nlm.nih.gov/books/NBK551720/.

Hagemeier, Nicholas E. "Introduction to the Opioid Epidemic: The Economic Burden on the Healthcare System and Impact on Quality of Life." *American Journal of Managed Care*, 11 May 2018, www.ajmc.com/journals/supplement/2018/combating-opioid-epidemic/intro-opioid-epidemic-economic-burden-on-healthcare-system-impact-quality-of-life. Accessed 18 Apr. 2020.

Jamison, Robert N., and Jianren Mao. "Opioid Analgesics." *Mayo Clinic Proceedings*, vol. 90, no. 7, 2015, pp. 957–968., doi:10.1016/j.mayocp.2015.04.010.

Jansson, Lauren M, and Stephen W Patrick. "Neonatal Abstinence Syndrome." *The Pediatric Clinics of North America*, vol. 66, no. 2, 1 Apr. 2019, pp. 353–367.

Kim, Juhwan, et al. "Brain Reward Circuits in Morphine Addiction." *Molecules and Cells*, vol. 39, no. 9, Sept. 2016, pp. 645–653., doi:10.14348/molcells.2016.0137.

Knoppert, David. "The Worldwide Opioid Epidemic." *Pediatric Drugs*, vol. 13, no. 5, 2011, pp. 277–279., doi:10.2165/11592700-000000000-00000.

Mahase, Elisabeth. "Most Fatal Opioid Overdoses Are Not Caused by Prescription Drugs, US Study Finds." BMJ, Nov. 2019, p. l5993., doi:10.1136/bmj.l5993.

Mcqueen, Karen, and Jodie Murphy-Oikonen. "Neonatal Abstinence Syndrome." *New England Journal of Medicine*, vol. 375, no. 25, 2016, pp. 2468–2479., doi:10.1056/nejmra1600879.

"Module 5: Assessing and Addressing Opioid Use Disorder (OUD)." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, www.cdc.gov/drugoverdose/training/oud/accessible/index.html. Accessed 19 Apr. 2020.

Raffaeli, Genny, et al. "Neonatal Abstinence Syndrome: Update on Diagnostic and Therapeutic Strategies." *Pharmacotherapy*, vol. 37, no. 7, 2017, pp. 814–823, https://doi-org.ezproxy4.library.arizona.edu/10.1002/phar.1954.

Sanlorenzo, Lauren A., et al. "Neonatal Abstinence Syndrome: An Update." *Current Opinion in Pediatrics*, vol. 30, no. 2, 2018, pp. 182–186., doi:10.1097/mop.0000000000000589.

Shah, Mansi and Martin R. Huecker. "Opioid Withdrawal." *StatPearls [Internet]*. StatPearls Publishing LLC, Jan. 2020, https://www.ncbi.nlm.nih.gov/books/NBK526012/. Accessed 19 Apr. 2020.

Sherwood, Lauralee. *Fundamentals of Human Physiology*. 4th ed., Cengage Learning, 2010.

Skolnick, Phil. "The Opioid Epidemic: Crisis and Solutions." *Annual Review of Pharmacology and Toxicology*, vol. 58, no. 1, Jan. 2018, pp. 143–159., doi:10.1146/annurev-pharmtox-010617-05253.

Soraisham, Amuchou Singh. "Chapter 37 - Maternal Codeine and Its Effect on the Fetus and Neonate: A Focus on Pharmacogenomics, Neuropathology, and Withdrawal." *Neuropathology of Drug Addictions and Substance Misuse Volume 3: General Processes and Mechanisms, Prescription Medications, Caffeine and Areca, Polydrug Misuse, Emerging Addictions and Non-Drug Addictions*, Elsevier Inc, 2016, pp. 392–398., doi: 10.1016/B978-0-12-800634-4.00037-8.

"Synthetic Opioid Overdose Data." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 19 Mar. 2020, www.cdc.gov/drugoverdose/data/fentanyl.html. Accessed 18 Apr. 2020.

Trescot, Andrea M., et al. "Opioid Pharmacology." *Pain Physician*, vol. 11, no. 2S, 2008, pp. S133–S153, www.painphysicianjournal.com/current/pdf?article=OTg3&journal=42. Accessed 19 Apr. 2020.

Wang, Shao-Cheng, et al. "Opioid Addiction, Genetic Susceptibility, and Medical Treatments: A Review." *International Journal of Molecular Sciences*, vol. 20, no. 17, 2 Sept. 2019, p. 4294., doi:10.3390/ijms20174294.

"What Are Opioids?" *HHS.gov*, U.S. Department of Health and Human Services, 15 May 2018, www.hhs.gov/opioids/prevention/index.html. Accessed 18 Apr. 2020.

"What Is the U.S. Opioid Epidemic?" *HHS.gov*, U.S. Department of Health and Human Services, 4 Sept. 2019, www.hhs.gov/opioids/about-the-epidemic/index.html. Accessed 18 Apr. 2020.

Wilkerson, Richard Gentry et al. "The Opioid Epidemic in the United States." *Emergency Medicine Clinics of North America*, vol. 34, no. 2, 1 May 2016, pp. e1–e23, doi:10.1016/j.emc.2015.11.002.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) emerged as a pharmaceutical therapy for clinical depression in the 1980s (Joshi; Hillhouse and Porter; Weitzel and Jiwanlal). SSRIs quickly increased in demand, with over 92 million prescriptions in 2000 alone (Weitzel and Jiwanlal). SSRIs include fluoxetine, citalopram, escitalopram, fluvoxamine, sertraline, vilazodone, and paroxetine ("Selective Serotonin Reuptake Inhibitors (SSRIs) Information"). Selective serotonin reuptake inhibitors function mechanistically by increasing the amount of serotonin in neuronal synapses through prevention of reuptake processes, though each individual medication may function slightly differently ("Escitalopram"; Hiemke and Härtter; "Vilazodone"). For instance, Vilazodone is also known to exhibit partial-agonist activity on certain serotonin receptors ("Vilazodone"). Numerous psychiatric conditions are currently treated with these medications, such as clinical depression, obsessive-compulsive disorder, eating disorders, premenstrual dysphoric disorders, generalized anxiety disorder and bipolar I depression ("Vilazodone"; Hiemke and Härtter; "Escitalopram"; "Fluoxetine"). A specific variation of SSRI may be preferred for particular cases or conditions ("Escitalopram"; "Vilazodone"; "Fluoxetine."). Hiemke and Härtter note that SSRIs are markedly safer than tricyclic antidepressants due to decreased risk of nervous and cardiovascular system toxicity (Hiemke and Härtter). Due to the prevalence of SSRI use, it is important to understand the effects and considerations for SSRI use during pregnancy (Weitzel and Jiwanlal; “Fluoxetine”; “Citalopram”; Susser et al.).

On a cellular level, selective serotonin reuptake inhibitors increase the amount of serotonin contained in neuronal synapses (“Selective Serotonin Reuptake Inhibitors (SSRIs)”; “Citalopram”). SSRIs increase the concentration of serotonin by forming a blockade at reuptake transporters on neuronal membranes (“Selective Serotonin Reuptake Inhibitors (SSRIs)”; Hiemke and Härtter). These transporters usually function to intake serotonin from the synaptic cleft and return the neurotransmitters to the presynaptic neuron (Hensler). When this action is blocked, such as by SSRIs, serotonin remains in the synapse (Ciccarelli and White 54). SSRIs selectively prohibit serotonin reuptake, minimally interfering with other neurotransmitters such as dopamine or norepinephrine (Hiemke and Härtter). Different SSRIs display a different degree of selectivity, however (Hiemke and Härtter). For instance, Paroxetine and Sertraline are known to impact acetylcholine and dopamine receptors, respectively, as well as inhibit serotonin reuptake (Hiemke and Härtter). The method by which SSRIs exert antidepressant effects has not yet been clearly defined, though the “monoaminergic hypothesis of depression” proposes that SSRIs lessen depressive symptoms by altering dysregulated norepinephrine and serotonin signaling in those with depression (Joshi; “Fluoxetine”).

Though substance use disorders arising from prescription medication is not uncommon, SSRI dependency is rare (Evans and Sullivan). According to a 2014 review, literature regarding SSRI use disorders are exceedingly scarce, with only seven case reports detailing misuse of fluoxetine (Evans and Sullivan). Reasons for misuse included psychological effect and hunger suppression (Evans and Sullivan). Overall, data shows that SSRI dependency is very infrequent (Evans and Sullivan). However, exposure to SSRI antidepressants has been found to alter neuroanatomy and brain activity and structure (Dusi et al.; Bellani et al.). Several studies report citalopram to decrease amygdala activity and reboxetine to increase amygdala activity in healthy subjects (Bellani et al.). In subjects with major depressive disorder, fluoxetine was found to increase the metabolism of certain brain regions, including parts of the frontal cortex, when compared to placebo controls (Bellani et al.). Numerous other studies found that participants demonstrated altered brain activity patterns, as observed through fMRI tests, PET scans, and other biometric techniques, after taking SSRI medications over varying lengths of time (Bellani et al.). The results found in these studies demonstrate not only different aspects of SSRI biochemistry, but also the intricacies involved in human brain function (Bellani et al.).

As evidenced by the brain studies, selective serotonin reuptake inhibitors can induce biological changes in individuals who take these medications (Bellani et al.). After stopping long-term medication use, physiological processes in the body must readjust to new chemical conditions, which can potentially lead to withdrawal symptoms (Ciccarelli and White 161-162). Cessation of SSRI use can lead to "Discontinuation Syndrome," the clinical diagnosis for SSRI-induced withdrawal symptoms (Horowitz and Taylor). Symptoms can mimic those indicative of the initial condition, such as anxiety or depression, and therefore may go unrecognized or prompt the resumption of medication use (Horowitz and Taylor). However, physicians can use different criteria to distinguish between withdrawal and development or resumption of a psychiatric condition, including manifestation of physical symptoms and timing of condition appearance (Horowitz and Taylor). Symptoms of Discontinuation Syndrome range in severity and can present in numerous different ways (Horowitz and Taylor). Physical, mental, and sensory symptoms may occur (Horowitz and Taylor; Jha et al.). Physical symptoms include increased heart rate and blood pressure, fatigue, headache, gastrointestinal irregularities, loss of balance, dizziness, and diaphoresis (Horowitz and Taylor; Jha et al.). Mental withdrawal effects have been reported to include sadness, stress, anxiety, and confusion (Horowitz and Taylor). Withdrawal can also manifest through crying, loss of appetite, sleep disturbances, as well as alterations to perception, such as "shock-like sensations" (Horowitz and Taylor). "Discontinuation Syndrome" is thought to result from adjustment to both decreased serotonin levels and decreased production of nervous system pathway proteins after reuptake is no longer inhibited (Jha et al.). Though different articles present disparate rates of discontinuation syndrome, one 2019 study found that, on average, about half of SSRI users experience a form of withdrawal (Horowitz and Taylor).

As selective serotonin reuptake inhibitors can induce discontinuation syndrome in adults, neonates born after prolonged in-utero exposure to SSRIs may also experience withdrawal effects (Alehan et al.). One 2008 case study reported that a newborn experienced withdrawal-like symptoms including increased muscle tone and tension, after prenatal fluoxetine exposure (Alehan et al.). After ruling out numerous other potential underlying causes, including genetic and infectious conditions, the physicians attributed abnormal neonatal presentation to fluoxetine withdrawal (Alehan et al.). Symptoms were severe and long-lasting, requiring treatment at the neonatal intensive care unit (NICU) for over a month (Alehan et al.). The physicians supported the infant's diagnosis of fluoxetine withdrawal with information from medical literature detailing neonatal symptoms associated with SSRI use during pregnancy (Alehan et al.). Documented neonatal symptoms include muscle movement irregularities, such as "tremor, hypertonicity… shivering, restlessness, and convulsions," and behavioral irregularities related to crying and eating patterns (Alehan et al.). However, these symptoms do not conclusively result from either fluoxetine withdrawal or serotonin toxicity, two similarly presenting conditions (Alehan et al.; Koren and Nordeng). Since the infant did not present with a high fever characteristic of toxicity, the authors suppose that the condition represented a withdrawal syndrome (Alehan et al.). The study concludes by urging healthcare workers to be prepared for neonatal symptoms subsequent to maternal SSRI exposure (Alehan et al.).

In addition to the case study, numerous articles detail the occurrence of withdrawal-like symptoms in neonates after prenatal SSRI exposure (Alehan et al.; Koren and Nordeng; Ornoy). Due to the high prevalence of depression in reproductive-age women, SSRI use during pregnancy is widespread and necessitates consideration of potential risks (Koren and Nordeng; Susser et al.). Infants can experience "Neonatal Adaptation Syndrome," the clinical condition of neonatal symptoms after in utero SSRI exposure (Koren and Nordeng; "Perinatal Services BC"). This condition has been found to affect up to 30% of neonates exposed in-utero (Koren and Nordeng). Prenatal SSRI use has been associated with more severe neonatal adaptation symptoms when the exposure occurs during later stages of pregnancy (Moulsdale and Hermann). Selective norepinephrine reuptake inhibitor (SNRI) exposure has been found to incite effects analogous to those resulting from SSRIs (Koren and Nordeng; Moulsdale and Hermann). Though some literature attributes the condition to SSRI withdrawal, data also suggests that neonatal adaptation symptoms may result from overexcitation of serotonin pathways ("Perinatal Services BC"; Moulsdale and Hermann).

Infants experiencing Neonatal Adaptation Syndrome may present with respiratory failure, thus researchers emphasize the importance of monitoring potentially exposed infants (Koren and Nordeng). Other descriptions of neonatal symptoms after SSRI exposure align with the Alehan et al. case study, including neurological symptoms, homeostatic irregularities, irregular feeding, and muscle tremors or convulsions (Alehan et al.; Moulsdale and Hermann). Neonates have also reportedly experienced seizures, irregular sleeping, digestion problems, and low blood glucose levels (Moulsdale and Hermann). Despite potentially severe respiratory issues, neonates with adaptation symptoms generally spend less than a week in the neonatal intensive care unit (NICU) (Koren and Nordeng). One 2014 study found that only 3% of exposed neonates experienced severe withdrawal symptoms based on the Finnegan scoring (Forsberg et al.). However, the study found irregularly low blood sugar levels to remain a common concern for infants prenatally exposed to SSRIs (Forsberg et al.). In general, Neonatal Adaptation Syndrome manifests without severe symptoms and resolves within several days to weeks (Moulsdale and Hermann; Susser et al.). In fact, as of 2013, no infant deaths had been reported due to neonatal adaptation syndrome ("Perinatal Services BC").

Currently, care for neonates with the potential to develop Neonatal Adaptation Syndrome involves careful monitoring and symptom evaluation ("Perinatal Services BC"). If symptoms appear, some management strategies include environmental regulation and treatment in the NICU if needed ("Perinatal Services BC"). Relaxing, calming environmental conditions with minimal light and sound stimulation are used to ease symptoms ("Perinatal Services BC"). According to Perinatal Services BC, severe symptoms, including respiratory failure, may require intervention in the NICU (Perinatal Services BC"). Neonatal care also encompasses education of families regarding the potential effects of in utero SSRI/SNRI exposure ("Perinatal Services BC"). Despite potential neonatal symptoms, several sources argue that continuation of SSRI/SNRI treatment may be the best treatment option for some patients (Koren and Nordeng; "Perinatal Services BC"). Considering unmanaged depression or other psychological conditions can also lead to complications for both the mother and the neonate, SSRI/SNRI use during pregnancy may be indicated in certain circumstances (Koren and Nordeng; Perinatal Services BC). Thus, physicians and their patients must carefully consider potential options and weigh potential positive and negative ramifications of all treatment routes (Koren and Nordeng; "Perinatal Services BC").

Works Cited

Alehan, Füsun, et al. "Prolonged Neonatal Complications after in Utero Exposure to Fluoxetine." *The Journal of Maternal-Fetal and Neonatal Medicine*, vol. 21, no. 12, Taylor & Francis, 11 Jun. 2008, pp. 921–923, doi:10.1080/14767050802266899.

Bellani, Marcella, et al. "The Effects of Antidepressants on Human Brain as Detected by Imaging Studies. Focus on Major Depression." *Progress in Neuropsychopharmacology & Biological Psychiatry*, vol. 35, no. 7, 15 Aug. 2011, pp. 1544–1552, doi:10.1016/j.pnpbp.2010.11.040.

Ciccarelli, Saundra K., and J. Noland White. *Psychology*. 5th ed., Pearson, 2017.

"Citalopram." *DrugBank*, https://www.drugbank.ca/drugs/DB00215. Accessed 25 Jan. 2020.

Dusi, Nicola, et al. "Brain Structural Effects of Antidepressant Treatment in Major Depression." *Current Neuropharmacology*, vol. 13, no. 4, Bentham Science Publishers Ltd., Sept. 2015, pp. 458–465, doi:10.2174/1570159x1304150831121909.

"Escitalopram." *DrugBank,* https://www.drugbank.ca/drugs/DB01175. Accessed 25 Jan. 2020.

Evans, Elizabeth, and Maria Sullivan. "Abuse and Misuse of Antidepressants." *Substance Abuse and Rehabilitation*, vol. 5, 2014, pp. 107–120. doi:10.2147/SAR.S37917.

"Fluoxetine." *DrugBank*. https://www.drugbank.ca/drugs/DB00472. Accessed 25 Jan. 2020.

Forsberg, Lisa, et al. "Neonatal Adaptation in Infants Prenatally Exposed to Antidepressants- Clinical Monitoring Using Neonatal Abstinence Score." *PLoS ONE*, vol. 9, no. 11, Public Library of Science, 3 Nov. 2014, p. e111327, doi:10.1371/journal.pone.0111327.

Hensler, Julie G. “Serotonin in Mood and Emotion.” *Handbook of Behavioral Neuroscience*, vol. 21, Elsevier Science & Technology, 2010, pp. 367–378. doi: 10.1016/S1569-7339(10)70090-4

Hiemke, Christoph, and Sebastian Härtter. “Pharmacokinetics of Selective Serotonin Reuptake Inhibitors.” *Pharmacology and Therapeutics*, vol. 85, no. 1, Jan. 2000, pp. 11–28, doi:10.1016/S0163-7258(99)00048-0.

Hillhouse, Todd M., and Joseph H. Porter. “A Brief History of the Development of Antidepressant Drugs: From Monoamines to Glutamate.” *Experimental and Clinical Psychopharmacology*, vol. 23, no. 1, Feb. 2015, pp. 1–21., doi:10.1037/a0038550.

Horowitz, Mark Abie, and David Taylor. “Tapering of SSRI Treatment to Mitigate Withdrawal Symptoms.” *The Lancet Psychiatry*, vol. 6, no. 6, Elsevier Ltd, 1 June 2019, pp. 538–546, doi:10.1016/S2215-0366(19)30032-X.

Jha, Manish K., et al. “When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips.” *American Journal of Psychiatry*, vol. 175, no. 12, American Psychiatric Association, 1 Dec. 2018, pp. 1176–1184, doi:10.1176/appi.ajp.2018.18060692.

Joshi, Amol. “Selective Serotonin Re-Uptake Inhibitors: An Overview.” *Psychiatria Danubina*, vol. 30, Medicinska Naklada Zagreb, 2018, pp. S605–S609.

Koren, Gideon, and Hedvig Nordeng. “Antidepressant Use during Pregnancy: The Benefit-Risk Ratio.” *American Journal of Obstetrics and Gynecology*, vol. 207, no. 3, Mosby, Sept. 2012, pp. 157–163, doi:10.1016/j.ajog.2012.02.009.

Moulsdale, Wendy, and Susan Hermann. “In Utero Exposure to Selective Serotonin Reuptake Inhibitors: Evidence for Poor Neonatal Adaptation.” *Newborn and Infant Nursing Reviews*, vol. 8, no. 3, Sept. 2008, pp. 123–130, doi:10.1053/j.nainr.2008.06.006.

Ornoy, Asher. “Neurobehavioral Risks of SSRIs in Pregnancy: Comparing Human and Animal Data.” *Reproductive Toxicology*, vol. 72, Elsevier Inc., 1 Sept. 2017, pp. 191–200, doi:10.1016/j.reprotox.2017.05.003.

"Perinatal Services BC Antidepressant Use During Pregnancy: Considerations for the Newborn Exposed to SSRIs/SNRIs." *Perinatal Services BC*, 2013, www.perinatalservicesbc.ca/Documents/Guidelines-Standards/Newborn/AntidepressantUseExposedNewbornGuideline.pdf

"Selective Serotonin Reuptake Inhibitors (SSRIs) Information." *U.S. Food and Drug Administration*, FDA, www.fda.gov/drugs/information-drug-class/selective-serotonin-reuptake-inhibitors-ssris-information. Accessed 25 Jan. 2020.

"Selective Serotonin Reuptake Inhibitors (SSRIs)." *Mayo Clinic*, Mayo Foundation for Medical Education and Research, 17 Sept. 2019, www.mayoclinic.org/diseases-conditions/depression/in-depth/ssris/art-20044825. Accessed 20 April 2020.

Susser, Leah C., et al. "Selective Serotonin Reuptake Inhibitors for Depression in Pregnancy." *American Journal of Obstetrics and Gynecology*, vol. 215, no. 6, Mosby Inc., Dec. 2016, pp. 722–30, doi:10.1016/j.ajog.2016.07.011.

"Vilazodone." *DrugBank*, https://www.drugbank.ca/drugs/DB06684. Accessed 25 Jan. 2020.

Weitzel, Cathy, and Shiloh Jiwanlal. "SSRIs." *RN*, vol. 64, no.8, Aug. 2001, pp. 43. *Gale Academic OneFile,* https://go-gale-com.ezproxy3.library.arizona.edu/ps/i.do?id=GALE%7CA77614421&v=2.1&u=uarizona_main&it=r&p=AONE&sw=w. Accessed 20 April 2020.

Nicotine

Nicotine is a well-known addictive compound innately produced by the tobacco plant ("Nicotine" [*PubChem Database*]; "Cigarettes"). Nicotine can be introduced to the body through inhalation of smoke or snuff, physical contact with a patch, or oral absorption from gum or chew ("Nicotine" [*PubChem Database*]; "Nicotine" [*DrugBank*]; "Cigarettes"; Kuhn, et al. 216-218). In addition to tobacco-related nicotine exposure (such as cigarettes, cigars, and chewing tobacco), vape and e-cigarette devices use an electric heater to deliver nicotine in a vaporized, tobaccoless smoke (Breland et al.; Kuhn, et al. 232;

Devito and Krishnan-Sarin). In all its multitudinous forms, nicotine can become physiologically and psychologically addictive, leading to cravings, withdrawal, and disruption in everyday life (Kuhn, et al. 232; West). A 2006 study by Hughes et al. even concluded that, though many who use nicotine are not considered dependent, "nicotine dependence is one of the most common mental disorders" as defined by both the Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD) (Hughes et al.). Yearly, only three smoking cessation efforts are successful for every 100 individuals who smoke nicotine-containing tobacco products (Benowitz). Considering its prevalence and potential deleterious consequences, nicotine dependence proves to be a widespread health concern (Jackson, et al.).

Nicotine both increases activity of the central nervous system and induces subjective feelings of reward ("Nicotine" [*PubChem Database*]; "Nicotine" [*DrugBank*]). Nicotine binds to specific nicotinic cholinergic receptors in the brain, inducing an action potential that leads to release of the neurotransmitter dopamine ("Nicotine" [*DrugBank*]; Benowitz). Dopamine signaling is known to promote feelings of satisfaction, playing a role in dependence and habit formation ("Nicotine" [*DrugBank*]; Benowitz). Though the nicotinic cholinergic pathway is typically initiated by acetylcholine, Nicotine can act as an agonist to promote dopamine signaling (Benowitz; "Nicotine" [*DrugBank*]). Nicotine-induced feelings of reward and gratification are thought to arise through limbic system pathways, particularly intercommunication between the ventral tegmental area (VTA) and the nucleus accumbens (NA) (Nestle; Benowitz). Since both brain regions are associated with pleasure and motivation, this pathway influences perceived reward after drug exposure (Benowitz). Nicotine can also influence release of other neurotransmitters and hormones, such as GABA and glutamate (Benowitz). Nicotine thus can exert numerous physiological and psychological effects (Benowitz).

Prolonged nicotine exposure can alter neurobiology (Benowitz). Dopamine and GABA signaling in the brain have been found to undergo various changes after continued nicotine use (Benowitz). In particular, certain receptors can become "desensitized" to the agonistic activity of nicotine when high quantities are continually supplied to cells (Benowitz). In response to desensitization, neurons increase expression of these receptors (Benowitz; Govind et al.). When nicotine is no longer supplied, for instance from smoking cessation, the receptors regain sensitivity (Benowitz). When nicotine is unavailable, vacant receptors can lead to withdrawal symptoms and thus may contribute to tolerance and dependence (Benowitz). Additionally, nicotine is known to alter signaling in the amygdala in animal models (Huang, et al.). Though nicotine amplifies addiction-related dopamine signaling in the mesolimbic portion of the brain, the chemical is thought to be less addictive than other substances due to its concurrent effect on inhibitory neurotransmission through the neurotransmitter GABA (Picciotto and Mineur; Benowitz). Overall, the biochemical effects of nicotine use are thought to lead to development of substance dependence, as well as induce withdrawal symptoms after cessation of use (Benowitz; Picciotto and Mineur).

Nicotine withdrawal symptoms can manifest physically, behaviorally, and mentally (McLaughlin et al.; Jackson et al.). Certain symptoms may involve emotional changes, such as elevated stress levels, inability to feel pleasure, and increased pain sensitivity (Benowitz; McLaughlin et al.). Feelings of anger and depression are also common (Picciotto and Mineur; Benowitz; McLaughlin et al.). Physical symptoms can include musculoskeletal and gastrointestinal disturbances, as well as decreased heartrate (McLaughlin et al.). Nicotine withdrawal can also induce changes to mental state, including difficulty with focus, sleep, or rest (McLaughlin et al.). According to studies, when withdrawal symptoms emerge, physical and mental discomfort often prompts resumption of substance use (Benowitz; Jackson et al.). Social and psychological signals may also lead to continued use (Benowitz). For instance, social situations may incite memories related to nicotine exposure (Benowitz). Notably, nicotine withdrawal can present differently, in symptoms and severity, depending on the individual (Jackson; McLaughlin et al.).

Since nicotine has been shown to elicit withdrawal symptoms in adults, studies have investigated potential withdrawal effects in infants after prenatal exposure (Godding et al.; Hurt et al.). Embryonic development of nicotinic cholinergic receptors, as well as nicotine’s ability to cross the placenta, have been cited as two ways that nicotine may potentially impact the developing fetus, though effects are not entirely known (Godding et al; Frøisland). Additionally, in-utero exposure has been found to induce fetal blood nicotine levels higher than corresponding maternal levels (Godding et al; Frøisland). Though there are varying conclusions related to the existence of an infant nicotine withdrawal syndrome, several studies do support the potential for such a syndrome (Stroud et al.; Vagnarelli et al.; Godding et al.).

Studies have aimed to determine the legitimacy of an infant withdrawal syndrome as a result of prenatal nicotine exposure (Godding et al.). One such study by Godding et al. compared presentation of two parallel groups of infants: one group prenatally exposed and one group unexposed to nicotine (Godding et al.). Neurological function, including arousal, muscle tone, reflex response, and movement were assessed for both groups and compared (Godding et al.). The healthcare team also evaluated withdrawal symptoms for all infants using Finnegan Scoring (Godding et al.). The study found statistically significant differences in neurological development between the groups on the first, second, and fifth day after birth (Godding et al.). Though the exposed group demonstrated lower neurological scores on these days, the group's scores did increase as the study progressed (Godding et al). Moreover, withdrawal scores on the first, second, and fourth days after birth were found to be significantly higher in exposed vs unexposed infants (Godding et al.). The researchers ultimately found that "withdrawal symptoms occur in newborns exposed to heavy maternal smoking during pregnancy" (Godding et al.). Another study also monitored infants prenatally exposed to nicotine, but observed infants within the timeframe of 10 to 27 days after birth (Stroud et al.). The *Journal of Pediatrics* study by Stroud et al. observed nervous system and behavioral development in exposed infants and parallel matched unexposed infants (Stroud et al.). Though the study found differences in neurobehavioral presentation between the two groups, the study did not find withdrawal-like symptoms in these infants (Stroud et al.). Researchers noted that, since the study observed infants over a week after birth, absence of withdrawal symptoms may support previous studies' proposals of neonatal nicotine withdrawal (Stroud et al.). Both the Godding et al. and Stroud et al. studies were relatively small, with less than 40 and less 60 total infants, respectively (Godding et al.; Stroud et al.).

In addition to prenatal nicotine exposure via maternal smoking, exposure can also occur through maternal use of *Iqmik* (Hurt et al.). *Iqmik* is "a mixture of leaf tobacco and ash," that has also been implicated in neonatal withdrawal symptoms (Hurt et al.). A 2005 study by Hurt et al. found cord tissue samples after *Iqmik* exposure to have an almost twofold increase nicotine and cotinine concentrations when compared to cord samples after exposure to other tobacco products (Hurt et al.). Cotinine, a byproduct of the body's nicotine metabolism, is used to estimate nicotine exposure in humans ("Cotinine Factsheet"). After assessing Lipsitz withdrawal scores of infants exposed to *Iqmik*, infants exposed to other forms of tobacco, and unexposed infants, researchers concluded that neurobehavioral symptoms were found in both tobacco-exposed groups (Hurt et al.). Limitations of the study, such as the non-double-blind structure, may have skewed or hindered results (Hurt et al.). Additionally, the study did not find a positive correlation between symptom severity and nicotine dosage, leading the authors to neither confirm nor deny a true withdrawal syndrome (Hurt et al.).

Infant neurobehavioral symptoms subsequent to prenatal nicotine exposure have also been documented in several case studies (Vagnarelli et al.; Frøisland). In one case, an infant began to exhibit withdrawal-like symptoms two days after birth (Vagnarelli et al.). The infant displayed nervous and muscular system symptoms, such as tremors and spasms (Vagnarelli et al.). The infant also presented with increased excitability and crying (Vagnarelli et al.). After blood and tissue sampling laboratory tests, including exams to test nervous system functioning, physicians found no underlying pathologies (Vagnarelli et al.). The only abnormal finding was significantly increased cotinine levels in breast milk after delivery, and hair samples of both the mother and child (Vagnarelli et al.). High levels of cotinine indicated consistent nicotine exposure during both the prenatal and perinatal periods (Vagnarelli et al.). Vagnarelli et al. estimated an intake of about 30-40 cigarettes per day during pregnancy, based on nicotine and cotinine concentration data from previous studies (Vagnarelli et al.). After two weeks of hospital surveillance and care, the infant was able to return home (Vagnarelli et al.). The infant experienced "residual rare tremors" for several weeks after birth, though other aspects of development progressed normally (Vagnarelli et al.). The study attributed varying levels of nicotine in breast milk, as a result of smoking cessation attempts, to contribute to the infant's withdrawal symptoms (Vagnarelli et al.). In a similar 2017 case study, an infant presented with an implacable cry, increased muscle tone, and hypersensitivity to auditory and visual stimuli (Frøisland). Laboratory tests revealed no abnormal results, except for high nicotine and cotinine levels in infant tissue samples (Frøisland). The infant's symptoms were attributed to withdrawal after prenatal exposure to nicotine (Frøisland). The mother reported using 'snus,' a form of oral nicotine, over ten times daily during gestation, leading to fetal exposure (Frøisland). The study emphasized the importance of educating individuals about nicotine during pregnancy, particularly non-smoking methods of exposure (Frøisland).

Several commonalities emerge throughout the varying studies of neonatal withdrawal. Firstly, studies tend to utilize the Finnegan Withdrawal Score, or the Lipsitz Scale, both of which are based on assessment of opiate withdrawal (Vagnarelli et al.; Godding et al.; Hurt et al.; Frøisland). This presents a potential issue in assessing other types of substance withdrawal (Hurt et al.; Vagnarelli et al.). One study recommended the use of both an "acoustic cry analysis" and NNNS, the NICU Network Neurobehavioral Scale (NNNS) which assesses nervous system function in newborns, to more accurately define withdrawal symptoms in cases of neonatal exposure (Hurt et al.; "NICU Network Neurobehavioral"). The judgement criteria for withdrawal symptoms is important for accurate assessment of patient condition (Hurt et al.; Vagnarelli et al.).

Studies have demonstrated different neurobehavioral presentation in infants prenatally exposed to nicotine than unexposed infants (Hurt et al.; Godding et al.). While some articles note these differences as evidence of a withdrawal syndrome, others hesitate to define the symptoms as withdrawal (Vagnarelli et al.; Godding et al.; Hurt et al.). It has been noted, however, that prenatal nicotine exposure does not present as clinically severe as other withdrawal syndromes such as those induced by in utero opioid exposure (Godding et al.). Research presented by the Godding et al. study sheds new light on the issue, since the authors concluded that "data strongly suggest that nicotine withdrawal symptoms, even discrete, are present in newborns of [heavy smoker] mothers" (Godding et al.). Overall, nicotine use during pregnancy presents many unique considerations that should be thoroughly studied and compassionately addressed (Hurt et al.; "Smoking, Pregnancy, and Babies").

Works Cited

Benowitz, Neal L. “Nicotine Addiction.” *The New England Journal of Medicine*, Edited by Robert S. Schwartz, vol. 362, no. 24, 17 June 2010, pp. 2295–2303., doi:10.1056/nejmra0809890.

Breland, Alison, et al. “Electronic Cigarettes: What Are They and What Do They Do?” *Annals of the New York Academy of Sciences*, vol. 1394, no. 1, 15 Jan. 2016, pp. 5–30., doi:10.1111/nyas.12977.

“Cigarettes and Other Tobacco Products.” *NIDA*, National Institute on Drug Abuse, Jan. 2020, https://www.drugabuse.gov/publications/drugfacts/cigarettes-other-tobacco-products. Accessed 28 April 2020.

“Cotinine Factsheet | National Biomonitoring Program | CDC.” *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, https://www.cdc.gov/biomonitoring/Cotinine_FactSheet.html. Accessed 30 April 2020.

Devito, Elise E., and Suchitra Krishnan-Sarin. “E-Cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure.” *Current Neuropharmacology*, vol. 16, no. 4, 1 May 2018, pp. 438–459., doi:10.2174/1570159x15666171016164430.

Frøisland, Dag Helge. “Nicotine Withdrawal Syndrome in a Newborn Baby after Maternal Use of Oral Applied Moist Tobacco (Snus), Should Result in Greater Awareness to the Use of Snus among Pregnant Women.” *Acta Paediatrica*, vol. 106, no. 9, 16 May 2017, pp. 1531., doi:10.1111/apa.13913.

Godding, Veronique, et al. “Does *In Utero* Exposure to Heavy Maternal Smoking Induce Nicotine Withdrawal Symptoms in Neonates?” *Pediatric Research*, vol. 55, no. 4, 1 Apr. 2004, pp. 645–651., https://doi-org.ezproxy2.library.arizona.edu/10.1203/01.PDR.0000112099.88740.4E

Govind, Anitha P., et al. “Nicotine-Induced Upregulation of Nicotinic Receptors: Underlying Mechanisms and Relevance to Nicotine Addiction.” *Biochemical Pharmacology*, vol. 78, no. 7, 1 October 2009, pp. 756–765., doi:10.1016/j.bcp.2009.06.011.

Huang, Yan-You, et al. “Chronic Nicotine Exposure Induces a Long-Lasting and Pathway-Specific Facilitation of LTP in the Amygdala.” *Learning & Memory*, vol. 15, no. 8, Aug, 2008, pp. 603–610., doi:10.1101/lm.975308.

Hughes, John R., et al. “Prevalence of DSM/ICD-Defined Nicotine Dependence.” *Drug and Alcohol Dependence*, vol. 85, no. 2, 8 Nov. 2006, pp. 91–102., doi:10.1016/j.drugalcdep.2006.04.004.

Hurt, Richard D, et al. “Iqmik – A Form of Smokeless Tobacco Used by Pregnant Alaska Natives: Nicotine Exposure in Their Neonates.” *The Journal of Maternal-Fetal & Neonatal Medicine*, vol. 17, no. 4, 2005, pp. 281–289., doi:10.1080/14767050500123731.

Jackson, K.J., et al. “New Mechanisms and Perspectives in Nicotine Withdrawal.” *Neuropharmacology*, vol. 96, pt. B, Sept. 2015, pp. 223–234., doi: 10.1016/j.neuropharm.2014.11.009.

Kuhn, Cynthia, et al. *Buzzed: The Straight Facts about the Most Used and Abused Drugs from Alcohol to Ecstasy*. 5th Ed, W.W. Norton, 2019.

McLaughlin, Ian, et al. “Nicotine Withdrawal.” *Current Topics in Behavioral Neurosciences*, vol. 24, 19 Aug. 2015, pp. 99–123., doi:10.1007/978-3-319-13482-6_4.

Nestle, Eric J. “Is There a Common Molecular Pathway for Addiction?” *Nature Neuroscience*, vol. 8, no. 11, Nature Publishing Group, Nov. 2005, pp. 1445+. *Gale Academic OneFile*, https://link-gale-com.ezproxy2.library.arizona.edu/apps/doc/A185538544/AONE?u=uarizona_main&sid=AONE&xid=b2a880f2., doi: 10.1038/nn1578. Accessed 30 Apr. 2020

“Nicotine.” *DrugBank*, https://www.drugbank.ca/drugs/DB00184. Accessed 24 April 2020.

“Nicotine” *National Center for Biotechnology Information PubChem Database*, U.S. National Library of Medicine, https://pubchem.ncbi.nlm.nih.gov/compound/89594, Nicotine CID=89594. Accessed 24 April 2020.

“NICU Network Neurobehavioral Scale (NNNS.)” *Brown Center for the Study of Children at Risk,* Brown University, www.brown.edu/research/projects/children-at-risk/about.

Picciotto, Marina R., and Yann S. Mineur. “Molecules and Circuits Involved in Nicotine Addiction: The Many Faces of Smoking.” *Neuropharmacology*, vol. 76, pt. B, Jan. 2014, pp. 545–553., doi:10.1016/j.neuropharm.2013.04.028.

"Smoking, Pregnancy, and Babies." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 23 Mar. 2020, www.cdc.gov/tobacco/campaign/tips/diseases/pregnancy.html. Accessed 05 May 2020.

Stroud, Laura R, et al. "Maternal Smoking during Pregnancy and Newborn Neurobehavior: Effects at 10 to 27 Days." *The Journal of Pediatrics*, vol. 154, no. 1, Jan. 2009, pp. 10–16. doi: 10.1016/j.jpeds.2008.07.048

Vagnarelli, Federica, et al. "TDM Grand Rounds: Neonatal Nicotine Withdrawal Syndrome in an Infant Prenatally and Postnatally Exposed to Heavy Cigarette Smoke." *Therapeutic Drug Monitoring*, vol. 28, no. 5, 2006, pp. 585–588., doi:10.1097/01.ftd.0000245391.56176.ad.

West, Robert. "Defining and Assessing Nicotine Dependence in Humans." *Novartis Foundation Symposia: Understanding Nicotine and Tobacco Addiction*, Edited by Gregory Bock and Jamie Goode, vol. 275, 13 Apr. 2006, pp. 36–58., doi:10.1002/9780470029237.ch4.

Cocaine and Crack-Cocaine

Cocaine is a chemical derived from the coca plant that acts to stimulate the nervous system ("Cocaine" [*NIDA*]; "Cocaine" [*DrugBank*]; Kuhn, et al. 286). The substance has documented use in medical practice as an anesthetic and in recreational settings to increase alertness, pleasure, and energy level ("Cocaine" [*DrugBank*]); "Cocaine" [*NIDA*]). Cocaine is generally inhaled as a crushed powder, intravenously injected as a solution, absorbed through oral tissue, or smoked in the form of 'crack'-- a "rock crystal" form of the substance ("Cocaine" [*NIDA*]). Behavioral and psychological effects of cocaine vary significantly, resulting in mood changes from increased pleasure to frustration, paranoia and anger ("Cocaine" [*NIDA*]). In 2014 alone, about 18 million people worldwide used a form of cocaine (Butler, et al.). One *Drug and Alcohol Dependence* article even estimated that 7.4 million individuals had a form of cocaine-use disorder in 2013 (Butler, et al.). In the United States, a recent increase in cocaine use has been suggested based on survey data, drug export information, and rate of cocaine-related death (John and

Wu). Cocaine exposure can lead to severe effects including strokes, seizures, cardiovascular damage and death (*Salem Health*).

Cocaine produces a reward response in the brain by influencing communication between the ventral tegmental area (VTA) and nucleus accumbens (NA), two brain regions involved in reward, motivation, and behavior (Cooper et al.; Scofield et al.). Mechanistically, cocaine increases nervous system activity by inhibiting neuronal reuptake of dopamine (Sherwood 90). Reuptake inhibition causes dopamine accumulation in the synapse, increasing neuron firing (Sherwood 90). Cocaine-induced dopamine signaling to the NA reinforces behaviors by producing feelings of reward (Cooper et al.). Cooper et al. explains that the activity of this brain circuit is thought to incite continued use of the pleasurable stimulus (cocaine), despite concurrent harmful outcomes (Cooper et al.).

Not only does cocaine induce immediate effects, but prolonged cocaine use can also alter neurological function (Cooper et al.; Sherwood 90). Biologically, consistent provocation of the dopamine pathway can lead to receptor downregulation, the underlying mechanism of tolerance (Sherwood 90). Cocaine has also been shown to alter the cellular communication through changes to growth factor, GTPase, glutamate, and brain-derived neurotrophic factor signaling (Cooper et al). Additionally, cocaine can restructure pleasure pathways in the brain through neuroplasticity, the ability of neuronal pathways to adjust to stimuli, which may be involved in the development of cocaine use disorder (Cooper et al.; Shaffer). Specific neurons in the NA also create “silent synapses”, which indicates a shift in receptor expression; cocaine withdrawal is associated with reversal of this shift, and subsequent desire for continued drug use (Cooper et al.). This process is thought to play a role in withdrawal (Cooper et al.).

After prolonged cocaine exposure, cessation of use can lead to a state of withdrawal (Sofuoglu et al.). Withdrawal symptoms can present both psychologically and physiologically (Sofuoglu et al.). Psychological symptoms include depression, disrupted sleep, and other mood changes such as frustration (Sofuoglu et al.). Lethargy, hunger, and changes to cognitive-motor function can also result (Sofuoglu et al.). Cocaine withdrawal often leads to depression, which is attributed to drug-induced alteration of norepinephrine, dopamine, and serotonin signaling (Sofuoglu et al.). Strong cravings for cocaine also tend to accompany withdrawal symptoms (Sofuoglu et al.). Symptom severity can vary depending on the individual (Sofuoglu et al.).

According to a 1998 *Pediatrics* publication, neurobehavioral symptoms in infants after maternal cocaine exposure were attributed to the direct effects of cocaine, as opposed to substance withdrawal (Committee on Drugs). The article noted symptom timing to support this notion (Committee on Drugs). Since prenatal cocaine exposure has been linked to neurological and behavioral symptoms in newborns, withdrawal scales have been used to measure severity (Committee on Drugs). However, one study noted that score differences between infants prenatally exposed and unexposed to cocaine were only found in non-blinded studies, indicating potential assessment bias (Committee on Drugs). Furthermore, a 1995 study found that both unexposed and cocaine-exposed newborns scored similarly on several nervous system metrics, but differently on behavioral scales (King et al). Infants with prenatal exposure were found to have heightened reflex responses, increased sucking motions, and more "jitteriness" than unexposed newborns, though no differences in medical intervention were needed between groups (King et al.). On the basis of these behavioral differences, the study did not rule out the possibility of a neonatal cocaine withdrawal (King et al.). Notably, the study was structured so all evaluators were blinded to infant exposure status (King et al). One 1990 publication discusses symptoms of intrauterine cocaine exposure including abnormal feeding, irritability, and altered patterns of sleep (Hansen).

More recently, a 2005 meta-analysis from the Archives of Gynecology and Obstetrics, analyzed various health concerns related to intrauterine cocaine exposure (dos Santos et al.). The study noted that cocaine and its related products (i.e. crack-cocaine) can reach the fetus during development through placental exposure (dos Santos et al.). Additionally, the review discussed agitation, emesis, elevated temperature, and seizures as common symptoms in newborns exposed to cocaine in utero (dos Santos et al.). The authors posit that these symptoms align with cocaine withdrawal effects and altered neurotransmission (dos Santos et al.).

One analysis assessed the impact of cocaine on infant behavior during early days of life (Eyler et al.). The researchers investigated inconsistencies in previous literature regarding whether neurobehavioral differences in infants prenatally exposed to cocaine result from direct substance toxicity, withdrawal after birth, or long-term consequences of intrauterine cocaine exposure (Eyler et al.). Each potential effect is carefully defined: “acute toxicity” refers to the direct effect of cocaine on the newborn, “withdrawal effects” refer to symptoms that arise from cessation of substance exposure after birth, and “nontransient” effects refer to long-term differences in various neurobehavioral metrics as a result of prenatal substance exposure (Eyler et al.). By comparing infant urine concentration of cocaine metabolites, timing after birth, and symptomatic presentation, the researchers assessed how cocaine exposure related to infant symptoms (Eyler et al.). Infants were observed for reflex response, muscle movement, and ability to self-regulate among other neurobehavioral criteria (Eyler et al.). The study did not find definitive evidence for “acute toxicity,” or “withdrawal effects” (Eyler et al.). Though data revealed that prenatal cocaine exposure impacts infant neurological and behavioral presentation, symptoms could not be attributed to any specific effect category (Eyler et al.).

Overall, prenatal cocaine exposure can induce a variety of conditions after birth, including neurological symptoms such as seizures, irritability, and heightened reflex responses (dos Santos et al.; King et al.). Though some articles attribute these symptoms to a likely withdrawal syndrome, others claim the effects may result from the direct effect of cocaine remaining in the infant’s body (dos Santos et al.; Committee on Drugs; Eyler et al.). More research regarding neonatal cocaine exposure is therefore needed to address these points of difference (Eyler et al.).

Works Cited

Butler, Ainslie J., et al. “Health Outcomes Associated with Crack-Cocaine Use: Systematic Review and Meta-Analyses.” *Drug and Alcohol Dependence*, vol. 180, 1 Nov. 2017, pp. 401–416., doi:10.1016/j.drugalcdep.2017.08.036.

"Cocaine." *NIDA,* National Institute on Drug Abuse, 13 Jul. 2018, https://www.drugabuse.gov/publications/drugfacts/cocaine. Accessed 2 May 2020.

“Cocaine.” *DrugBank*, www.drugbank.ca/drugs/DB00907. Accessed 3 May 2020.

Committee on Drugs. “Neonatal Drug Withdrawal.” *Pediatrics*, vol. 101, no. 6, American Academy of Pediatrics, pp. 1079-1088. https://pediatrics.aappublications.org/content/101/6/1079. Accessed 3 May 2020.

Cooper, Sarah, et al. “Reward Circuitry in Addiction.” *Neurotherapeutics*, vol. 14, no. 3, 2017, pp. 687–697., doi:10.1007/s13311-017-0525-z.

dos Santos, Jucilene, et al. “Maternal, Fetal and Neonatal Consequences Associated with the Use of Crack Cocaine during the Gestational Period: a Systematic Review and Meta-Analysis.” Archives of Gynecology and Obstetrics, vol. 298, 27 Jun. 2018, pp. 487–503, https://doi-org.ezproxy2.library.arizona.edu/10.1007/s00404-018-4833-2.

Eyler, Fonda Davis, et al. “Newborn Evaluations of Toxicity and Withdrawal Related to Prenatal Cocaine Exposure.” *Neurotoxicology and Teratology*, vol. 23, no. 5, 2001, pp. 399–411., doi:10.1016/s0892-0362(01)00166-0.

Hansen, Robin L. "Diagnosis, treatment, and follow-up of newborns addicted to cocaine." *The Western Journal of Medicine*, vol. 153, no. 6, BMJ Publishing Group Ltd., Dec. 1990, p. 646. *Gale Academic OneFile*, https://link-gale-com.ezproxy3.library.arizona.edu/apps/doc/A9347184/AONE?u=uarizona_main&sid=AONE&xid=78ac1842. Accessed 3 May 2020.

John, William S., and Li-Tzy Wu. “Trends and Correlates of Cocaine Use and Cocaine Use Disorder in the United States from 2011 to 2015.” *Drug and Alcohol Dependence*, vol. 180, 1 Nov. 2017, pp. 376–384., doi:10.1016/j.drugalcdep.2017.08.031.

King, Terri A., et al. "Neurologic manifestations of in utero cocaine exposure in near-term and term infants." *Pediatrics*, vol. 96, no. 2, American Academy of Pediatrics, Aug. 1995, p. 259-264. *Gale Academic OneFile*, https://link-gale-com.ezproxy3.library.arizona.edu/apps/doc/A17407727/AONE?u=uarizona_main&sid=AONE&xid=f6d90230. Accessed 3 May 2020.

Kuhn, Cynthia, et al. *Buzzed: The Straight Facts about the Most Used and Abused Drugs from Alcohol to Ecstasy*. 5th Ed, W.W. Norton, 2019.

Salem Health: Addictions and Substance Abuse (2-Volume Set), edited by Robin Kamienny Montvilo, Salem Press, 2012. ProQuest Ebook Central, https://ebookcentral.proquest.com/lib/uaz/detail.action?docID=3400531.

Scofield, M. D., et al. "The Nucleus Accumbens: Mechanisms of Addiction across Drug Classes Reflect the Importance of Glutamate Homeostasis." *Pharmacological Reviews*, vol. 68, no. 3, 2016, pp. 816–871., doi:10.1124/pr.116.012484.

Shaffer, Joyce. "Neuroplasticity and Clinical Practice: Building Brain Power for Health." *Frontiers in Psychology*, vol. 7, 2016, doi:10.3389/fpsyg.2016.01118.

Sherwood, Lauralee. *Fundamentals of Human Physiology*. 4th ed., Cengage Learning, 2010.

Sofuoglu, Mehmet, et al. "The Effect of Individual Cocaine Withdrawal Symptoms on Outcomes in Cocaine Users." *Addictive Behaviors*, vol. 30, no. 6, July 2005, pp. 1125–1134., doi:10.1016/j.addbeh.2004.10.010.

Amphetamines and Methamphetamine

Amphetamine and related compounds stimulate the central nervous, leading to increased energy level, concentration, and attentiveness (*Drugs of Abuse*; "Metamfetamine"; Kuhn et al. 297). Types of amphetamines include dextroamphetamine, methamphetamine, and others (*Drugs of Abuse*; "Metamfetamine"). Administration of amphetamines typically occurs in the form of pills that are ingested or powder that is dissolved and subsequently injected (*Drugs of Abuse*; Shannon 213). Methamphetamine can also be inhaled as powder or smoked as "ice," a crystal form of the substance (Shannon 213; *Drugs of Abuse*). While methamphetamine can have legal uses in medicine, the substance is commonly used in illegal contexts (Shannon 213; *Drugs of Abuse*). Amphetamine has a complex history ("Amphetamine"; Heal et al.). Today, the substance is prescribed for pharmacological treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy, among other conditions (Kuhn et al. 297;

"Amphetamine"). Dextroamphetamine, an active ingredient in Adderall, is an amphetamine variation also used in ADHD treatment (*Drugs of Abuse*; "Dextroamphetamine"). Due to central nervous system effects, amphetamine and related substances can result in tachycardia, hypertension, increased body temperature, sleeping difficulties, and eventual profound lack of energy (Shannon; *Drugs of Abuse*).

Amphetamine structurally resembles catecholamines, such as norepinephrine, endogenously synthesized by the body (Heal et al.). Amphetamines activate sympathetic nervous activity through several different molecular mechanisms, all which increase the availability of neurotransmitters in the synaptic cleft (Heal et al.). Firstly, amphetamine enters the cells through monoamine reuptake transporters, increasing neurotransmitter presence in the synapse (Heal et al.; Stix). Once in the cell, the molecule alters the functionality of neurotransmitter reuptake machinery, resulting in increased cellular excretion of dopamine and other neurotransmitters into the synaptic cleft (Heal et al.; Stix). Amphetamines can also act to inhibit the reuptake machinery and the enzyme MAO involved in chemical breakdown, both of which result in higher levels of neurotransmitters in the neuronal synapse (Heal et al.). Through these processes, amphetamine increases norepinephrine and dopamine signaling in the brain (Heal et al.). Amphetamines lead to increased dopamine signaling, particularly in the mesolimbic pathway of the brain, inciting subjective feelings of reward (Adinoff). Methamphetamine is structurally similar to amphetamine, with an additional methyl group that enhances the chemical's effects (Zorick et al.).

Prolonged amphetamine exposure has been linked to numerous neurological differences (Chang et al.; Harro). Altered neurotransmission, specifically dopamine and serotonin signaling processes, occurs with continued use of amphetamines (Chang et al.). One article by Chang et al. found fewer dopamine D2 receptors in the brains of those exposed to methamphetamines, which the authors noted as potentially indicative of methamphetamine-mediated alterations to neurotransmission, though this remains uncertain (Chang et al.). Additionally, the study revealed structural differences within the brains of individuals chronically exposed to amphetamines (Chang et al.). MRI and PET imaging technology displayed a notable change in striatum size, as well as a decrease in certain metabolite (N-acetylaparate and creatine) levels in those with long-term methamphetamine exposure (Chang et al.). The article notes "increasing evidence of the involvement of the dorsal striatum in addiction," providing one aspect in which the differences in brain structure and metabolism detected in the study may coincide with formation of a substance use disorder (Chang et al.). Other documented brain changes include restructuring of the prefrontal cortex and the corpus callosum, as well as altered interneural communication (Oei et al.).

Amphetamine withdrawal occurs in about 87% of individuals after cessation of persistent use (*Management of Substance*). Symptoms include emotional, physical, and mental disturbances: frustration, irritability, lethargy, strong desire to continue drug use, sleep pattern disruptions or excessive desire for sleep, upsetting dreams and increased hunger (Harro; *Management of Substance*; Zorick et al.). Anhedonia, anxiety, and depression are among the psychological symptoms of withdrawal (*Management of Substance*). Though symptom severity fluctuates between individuals, amphetamine withdrawal is generally not considered to be life-threatening (Zorick et al.; Harro). In cases of methamphetamine withdrawal, some psychological effects may persist for several days, whereas substance cravings have been found to continue for over a month (Zorick et al.).

Since amphetamine use occurs in numerous contexts, prenatal exposure may vary significantly depending on the situation (Oei et al.). Expectant mothers may use amphetamines therapeutically or recreationally (Oei et al.). However, of the varying methods of exposure, "the major concern… is about those who use illegal forms of amphetamines," according to a 2012 *Nature* article (Oei et al.). Heightened concern is credited, in part, to coexisting prenatal health concerns common in cases of illicit amphetamine use, including potentially unsafe habitation and inadequate medical care during pregnancy (Oei et al.). Since maternal amphetamine use has increased, it is important to gather research regarding the effects of in utero amphetamine exposure on newborns (Oei et al.; Smith et al.). However, publications note limited research regarding different aspects of methamphetamine use disorders during pregnancy (Wells et al.; Oei et al.; Smith et al.).

Fetal exposure to maternal amphetamine occurs through placental exchange (Oei et al.). Level of exposure can be determined by the amount of breakdown products measured "in the umbilical cord, the placenta, or the amniotic fluid" (Oei et al.). According to Oei et al., amphetamine-specific withdrawal scoring systems have not yet been delineated; thus, infants undergoing amphetamine withdrawal may not be properly diagnosed, which could prevent adequate patient care (Oei et al.). Similar to adult withdrawal symptoms, amphetamine-exposed neonates have been shown to exhibit fatigue, as well as sleep and feeding irregularities (Harro; Oei et al.). Rapid respiratory rate and irritability are other symptoms identified subsequent to in-utero exposure (Oei et al.). After prenatal methamphetamine exposure, infants can also present with neurobehavioral symptoms including decreased activity level, decreased motor function, and increased stress (Oei et al.). Where some reports have not explicitly defined symptoms as resulting from withdrawal, others have specifically noted neonatal "withdrawal symptoms" (Wouldes and Lester; "Chapter 3"; Oei et al.).

Importantly, several studies found that neonatal symptoms after amphetamine exposure were generally treatable (Oei et al.; Smith et al). For instance, in a study of 173 infants exposed to amphetamines in utero, "none of the amphetamine-exposed infants required pharmacological treatment and most recovered within 1 week" (Oei et al.). A 2003 study in the *Journal of Developmental & Behavioral Pediatrics* found similar results, since only 1 of every 25 exposed infants needed medication to treat their symptoms (Smith et al.). In this study, methamphetamine-exposed and unexposed infants were matched, and various neurobehavioral symptoms were compared, including infant muscle movement, lacrimation, perspiration, respiration, and feeding (Smith et al.). Though only a small proportion of infants experienced symptoms of significant withdrawal, the study did not entirely reject a withdrawal syndrome altogether (Smith et al.). Studies have shown neurobehavioral effects in infants prenatally exposed to methamphetamine, potentially related to neurotoxicity or withdrawal (Smith et al.; Oei et al.).

Overall, methamphetamine and amphetamine use during pregnancy may present special considerations for newborns (Oei et al). Symptomatic presentation in infants has not been definitively characterized as a withdrawal syndrome in all publications, however, several studies do attribute neonatal effects to potential amphetamine withdrawal (Wouldes and Lester; Smith et al; "Chapter 3"; Oei et al.). Many researchers note the importance of continuing research in this area to more thoroughly understand the biology involved in maternal amphetamine use (Oei et al.; Wells et al.).

Works Cited

Adinoff, Bryon. “Neurobiologic Processes in Drug Reward and Addiction.” *Harvard Review of Psychiatry*, vol. 12, no. 6, Nov./Dec. 2004, pp. 305–320., doi:10.1080/10673220490910844.

“Amphetamine.” *DrugBank*, www.drugbank.ca/drugs/DB00182. Accessed 03 May 2020.

Chang, Linda, et al. “Structural and Metabolic Brain Changes in the Striatum Associated with Methamphetamine Abuse.” *Addiction*, vol. 102, no. s1, 27 Feb. 2007, pp. 16–32., doi:10.1111/j.1360-0443.2006.01782.x.

“Chapter 3: Physiological Effects of Alcohol, Drugs, and Tobacco on Women.” *Substance Abuse Treatment: Addressing the Specific Needs of Women* in Treatment Improvement Protocol (TIP) Series, no. 51, 2009, Rockville MD, Substance Abuse and Mental Health Services Administration (US), https://www.ncbi.nlm.nih.gov/books/NBK83244/.

“Dextroamphetamine.” *DrugBank*, www.drugbank.ca/drugs/DB01576. Accessed 03 May 2020.

Drugs of Abuse | A DEA Resource Guide: 2017 Edition. Drug Enforcement Administration, U.S. Department of Justice, 2017, https://www.dea.gov/sites/default/files/sites/getsmartaboutdrugs.com/files/publications/DoA_2017Ed_Updated_6.16.17.pdf#page=50. Accessed 03 May 2020.

Harro, Jaanus. “Neuropsychiatric Adverse Effects of Amphetamine and Methamphetamine.” *International Review of Neurobiology*, vol. 120, 2015, pp. 179–204., doi:10.1016/bs.irn.2015.02.004.

Heal, David J, et al. “Amphetamine, Past and Present – a Pharmacological and Clinical Perspective.” *Journal of Psychopharmacology*, vol. 27, no. 6, Jun. 2013, pp. 479–496., doi:10.1177/0269881113482532.

Kuhn, Cynthia, et al. *Buzzed: The Straight Facts about the Most Used and Abused Drugs from Alcohol to Ecstasy*. 5th Ed, W.W. Norton, 2019.

Management of Substance Dependence Review Series: Systematic Review of Treatment for Amphetamine-Related Disorders. Department of Mental Health and Substance Dependence, World Health Organization, 2001, apps.who.int/iris/bitstream/handle/10665/42445/WHO_MSD_MSB_01.5.pdf;jsessionid=688CDF106DFBCF06B706D9A8C3E60F49?sequence=1.

"Metamfetamine." *DrugBank*, www.drugbank.ca/drugs/DB01577. Accessed 03 May 2020.

Oei, J L, et al. "Amphetamines, the Pregnant Woman and Her Children: a Review." *Journal of Perinatology*, vol. 32, 31 May 2012, pp. 737–747., doi:10.1038/jp.2012.59.

Shannon, Joyce Brennfleck. *Drug Abuse Sourcebook: Basic Consumer Health Information about the Abuse of Cocaine, Club Drugs, Hallucinogens, Heroin, Inhalants, Marijuana, and Other Illicit Substances, Prescription Medications, and Over-the-Counter Medicines...* 3rd ed., Omnigraphics, 2010.

Shannon, Joyce Brennfleck. *Drug Abuse Sourcebook: Basic Consumer Health Information about the Abuse of Cocaine, Club Drugs, Hallucinogens, Heroin, Inhalants, Marijuana, and Other Illicit Substances, Prescription Medications, and Over-the-Counter Medicines...* 3rd ed., Omnigraphics, 2010.

Smith, Lynne, et al. "Effects of Prenatal Methamphetamine Exposure on Fetal Growth and Drug Withdrawal Symptoms in Infants Born at Term." *Journal of Developmental & Behavioral Pediatrics*, vol. 24, no. 1, Feb. 2003, pp. 17-23, Journals@ Ovid Full Text, http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovftf&NEWS=N&AN=00004703-200302000-00006. Accessed 04 May. 2020.

Stix, Gary. "Turbocharging the Brain." *Scientific American*, vol. 301, no. 4, Oct. 2009, pp. 46–55., doi:10.1038/scientificamerican1009-46.

Wells, Charlotte et al. “Withdrawal Management and Treatment of Crystal Methamphetamine Addiction in Pregnancy: A Review of Clinical Effectiveness and Guidelines” *CADTH Rapid Response Report: Summary with Critical Appraisal*, Canadian Agency for Drugs and Technologies in Health, 17 Jun. 2019, Ottawa ON, https://www.ncbi.nlm.nih.gov/books/NBK546255/. Accessed 04 May 2020.

Wouldes, Trecia A., and Barry M. Lester. “Stimulants: How Big Is the Problem and What Are the Effects of Prenatal Exposure?” *Seminars in Fetal and Neonatal Medicine*, vol. 24, no. 2, Apr. 2019, pp. 155–160., doi:10.1016/j.siny.2019.01.011.

Zorick, Todd et al. “Withdrawal Symptoms in Abstinent Methamphetamine-Dependent Subjects.” *Addiction (Abingdon, England)*, vol. 105, no. 10, 2010, pp. 1809-1818. doi:10.1111/j.1360-0443.2010.03066.x

Conclusion

Prenatal substance exposure is a multifaceted aspect of healthcare (Raffaeli et al.). Infants exposed to different substances in utero may experience withdrawal effects after birth, manifesting in various ways including irregular sleeping, feeding, and muscle movements, among other symptoms (“Substance Use in Women”). Though Neonatal Abstinence Syndrome resulting from opioid exposure remains at the forefront of the conversation surrounding withdrawal symptoms in newborns, some evidence suggests that similar syndromes may result from prenatal exposure to other substances (“Substance Use in Women”). Infant withdrawal effects from nonopioid substances have been studied, but different research has been found to reach incongruent or ambiguous verdicts regarding the underlying mechanistic cause of symptoms (Koren and Nordeng; Hurt et al.; Eyler et al; Smith et al.). For instance, selective serotonin reuptake inhibitors (SSRIs) have been found to induce Neonatal Adaptation Syndrome, a condition which has been attributed to SSRI withdrawal in some research, and serotonin toxicity in other studies (Koren and Nordeng; “Perinatal Services BC”). Nicotine has also been shown to precipitate neurobehavioral symptoms in infants after birth, though different researchers have found varying results regarding a specific withdrawal syndrome (Godding et al.). Research related to infant withdrawal after in utero cocaine exposure also varies, with some authors suggesting a withdrawal-like syndrome, and others attributing effects directly to drug toxicity (dos Santos et al; Committee on Drugs). Likewise, methamphetamine and amphetamine exposure during pregnancy has been shown to produce symptoms in newborns, with some publications discussing these symptoms as a true "withdrawal" syndrome, and others remaining less certain (Oei et al.; "Chapter 3"; Wouldes and Lester). Therefore, much remains to be learned about the effects of various substances exposures in utero (Oei et al; Wouldes and Lester).

One recurring concern, mentioned by numerous studies, was the lack of diagnostic measuring tools for nonopioid infant withdrawal (Godding et al.; Oei et al.; Eyler et al.). Finnegan scoring and other diagnostic systems formulated for neonatal opioid withdrawal have been used to assess infant symptoms after prenatal exposure to substances from cocaine to nicotine, amphetamines, and SSRIs (Eyler et al.; Godding et al.; Oei et al.; Forsberg et al.). The use of opioid withdrawal scales for nonopioid exposures was noted as a limitation to current research and medical practice (Godding et al.; Oei et al). Moreover, the efficacy of the Finnegan scoring system has been questioned even in assessment of neonatal opioid withdrawal, with one study noting the potential for other symptom metrics to improve outcomes (Sanlorenzo et al.). Overall, researchers note that infant withdrawal assessments may be skewed when nonopioid substances are judged according to metrics designed for opioid exposures only (Oei et al.; Godding et al.). One notable study of neonatal nicotine exposure recommended the use of the NICU Network Neurobehavioral Scale (NNNS) to observe and identify withdrawal symptoms in cases of nonopioid exposure (Hurt et al.). The NNNS has been used in a variety of contexts, measuring the effects of in utero exposure to numerous substances (Tronick and Lester). One recent 2019 study mentions the NNNS the measurement tool for cocaine and methamphetamine related symptoms, for instance (Wouldes and Lester). Publications have encouraged development of improved evaluation measurements, particularly for nonopioid exposures, and standardization of evaluation procedures for neonatal withdrawal symptoms (Oei et al.; Mcqueen and Murphy-Oikonen).

Numerous studies note the importance of continuing research in this field of study, to better understand the effects of maternal substance use (Oei et al.; Eyler et al.; Wouldes and Lester; Raffaeli et al.). Literature details the need for careful, high-quality studies to obtain accurate information related to prenatal drug exposure (Raffaeli et al.; Eyler et al.). Some researchers reference a lack of literature regarding a specific aspect of prenatal substance exposure; for instance, one report found a gap in research related to crystal methamphetamine use during pregnancy (Wells et al.). Other publications emphasize more depth and breadth of research or encourage more studies with larger sample sizes (Raffaeli et al.; Hurt et al.). Researchers also highlight the importance of studies with a blinded design, to ensure accurate infant evaluations (Eyler et al.; Committee on Drugs). Still other studies emphasize the need for additional research into treatment methods for neonatal withdrawal symptoms (Sanlorenzo, et al.). In a myriad of ways, authors in the area of prenatal substance exposure underscore the importance of continued research in the field (Eyler et al.; Sanlorenzo, et al.; Oei et al).

All mothers and newborns should receive care and consideration. Every pregnancy is different, with varying circumstances, expectations, and challenges. I hope this paper provides a basic overview of important research related to prenatal substance exposure and neonatal withdrawal effects. Though neonatal substance exposure is but one tiny aspect of the vast field of biology and medicine, it deserves thorough research, attention, and care.

Table 1

Substance	Key Mechanism(s) of Action	Key Neurological Findings Associated with Long-Term Use	Withdrawal Symptoms	Information on Infant Withdrawal
Opioids	• Analgesia: prevents release of pain-stimulating neurotransmitters (Chahl; Trescot et al) • Euphoria: prevents release of GABA,	• Increased adenylyl cyclase activity (Chan and Lutfy) • Changes in amygdala, hippocampus (Kim et al.)	• Physical: musculoskeletal, abdominal pain, crying, sweating (Wang et al.) • Psychological: anxiety, agitation (Wang et al.)	• Classified as Neonatal Abstinence Syndrome (Alic; Mcqueen and Murphy-Oikonen) • Nervous system and GI symptoms of varying severity (Sanlorenzo et al.;

	leading to increased dopaminergic activity (Trescot et al)	• Altered dopamine signaling (Kim et al.)		Jansson and Patrick)
Selective Serotonin Reuptake Inhibitors (SSRIs)	• Mediation of psychiatric symptoms: prevention of serotonin reuptake to increase levels of the serotonin neurotransmitter in the synaptic cleft (Ciccarelli and White 54)	• Dependency very infrequent (Evans and Sullivan) • Structural brain changes vary depending on a variety of factors, including SSRI used (Bellani et al.)	• Physical: tachycardia, headache, fatigue, GI symptoms, sweating, dizziness (Horowitz and Taylor) • Psychological: anxiety, confusion, depression (Horowitz and Taylor)	• Clinically known as Neonatal Adaptation Syndrome (Koren and Nordeng; “Perinatal Services BC”) • Neurological symptoms, homeostatis regulation difficulties, changes in feeding (Moulsdale and Hermann)
Nicotine	• Agonist activity at nicotinic cholinergic receptors (Benowitz; “Nicotine” [DrugBank]) • Reward and gratification arise through limbic system pathways, particularly affecting the ventral tegmental area (VTA) and the nucleus accumbens (NA) (Nestle; Benowitz)	• Upregulation and desensitization of nicotinic cholinergic receptors (Benowitz) • Changes in dopamine signaling (Picciotto and Mineur) • Amygdala implicated (Huang et al.)	• Anger, depression, inability to feel pleasure, increased pain response (Picciotto and Mineur; Benowitz; McLaughlin et al.) • Difficulty with rest, sleep, and focus (McLaughlin et al.)	• Case-studies show potential effects in infants prenatally exposed to significant amounts of nicotine (Vagnarelli et al.; Frøisland) • Small-scale studies support neurobehavioral differences in nicotine-exposed vs unexposed infants within the first several days of life (Godding et al.; Hurt et al.)
Cocaine	• Dopamine reuptake inhibitor (Sherwood 90) • Increases neuronal activity from VTA to NA by extra dopamine in the synapse (Cooper et al.; Sherwood 90)	• Downregulation of dopamine receptors leads to tolerance (Sherwood 90) • Neuroplasticity effects can restructure pleasure pathways (Cooper et al.)	• Depression and mood changes (Sofuoglu et al.) • Changes to cognitive-motor function (Sofuoglu et al.) • Lethargy and cocaine cravings (Sofuoglu et al.)	• Neurobehavioral symptoms present in infants prenatally exposed to cocaine include seizures, irritability, heightened reflex responses, emesis (King et al.; dos Santos et al.) • Varied conclusions in different studies

				regarding whether or not a true withdrawal syndrome exists (Eyler et al.).
Methamphetamine/ Amphetamines	• Altered functionality of neurotransmitter reuptake machinery, increasing cellular excretion of dopamine (Heal et al.; Stix) • Increased dopamine signaling in the mesolimbic pathway (Adinoff)	• Changes to dopamine and serotonin signaling (Chang et al.) • Potential restructuring of prefrontal cortex and corpus callosum (Oei et al.)	• Frustration, irritability, lethargy, strong desire to continue drug use, changes to sleep and dreams, hunger (Harro; *Management of Substance*; Zorick et al.) • Depression (*Management of Substance*)	• Conflicting reports regarding whether or not neonatal symptoms after subsequent maternal amphetamine exposure (Wouldes and Lester; “Chapter 3”; Oei et al) • Symptoms after neonatal amphetamine exposure include fatigue, sleep and feeding irregularities (Harro; Oei et al.)

Table 1 gives a brief summary of the concepts discussed throughout the paper.

Works Cited

Adinoff, Bryon. “Neurobiologic Processes in Drug Reward and Addiction.” *Harvard Review of Psychiatry*, vol. 12, no. 6, Nov./Dec. 2004, pp. 305–320., doi:10.1080/10673220490910844.

Alic, Margaret. "Neonatal Abstinence Syndrome." *The Gale Encyclopedia of Mental Health*, edited by Brigham Narins, 4th ed., vol. 3, Gale, 2019, pp. 1114-1118. *Gale Health and Wellness*, https://go-gale-com.ezproxy1.library.arizona.edu/ps/i.do?p=HWRC&u=uarizona_main&id=GALE%7CCX2491200339&v=2.1&it=r. Accessed 17 Apr. 2020.

Bellani, Marcella, et al. “The Effects of Antidepressants on Human Brain as Detected by Imaging Studies. Focus on Major Depression.” *Progress in Neuropsychopharmacology & Biological Psychiatry*, vol. 35, no. 7, 15 Aug. 2011, pp. 1544–1552, doi:10.1016/j.pnpbp.2010.11.040.

Benowitz, Neal L. “Nicotine Addiction.” *The New England Journal of Medicine*, Edited by Robert S. Schwartz, vol. 362, no. 24, 17 June 2010, pp. 2295–2303., doi:10.1056/nejmra0809890.

Chahl, Loris A. “Experimental and Clinical Pharmacology: Opioids - Mechanisms of Action.” *Australian Prescriber*, vol. 19, no. 3, 1 Jan. 1996, pp. 63–65., doi:10.18773/austprescr.1996.063.

Chan, Patrick, and Kabirullah Lutfy. “Chapter 7-- Molecular Changes in Opioid Addiction: The Role of Adenylyl Cyclase and CAMP/PKA System.” *Progress in Molecular Biology and Translational Science The Molecular Basis of Drug Addiction*, vol. 137, 2016, pp. 203–227., doi:10.1016/bs.pmbts.2015.10.005.

Chang, Linda, et al. “Structural and Metabolic Brain Changes in the Striatum Associated with Methamphetamine Abuse.” *Addiction*, vol. 102, no. s1, 27 Feb. 2007, pp. 16–32., doi:10.1111/j.1360-0443.2006.01782.x.

“Chapter 3: Physiological Effects of Alcohol, Drugs, and Tobacco on Women.” *Substance Abuse Treatment: Addressing the Specific Needs of Women* in Treatment Improvement Protocol (TIP) Series, no. 51, 2009, Rockville MD, Substance Abuse and Mental Health Services Administration (US), https://www.ncbi.nlm.nih.gov/books/NBK83244/.

Ciccarelli, Saundra K., and J. Noland White. *Psychology*. 5th ed., Pearson, 2017.

Committee on Drugs. “Neonatal Drug Withdrawal.” *Pediatrics*, vol. 101, no. 6, American Academy of Pediatrics, pp. 1079-1088. https://pediatrics.aappublications.org/content/101/6/1079. Accessed 3 May 2020.

Cooper, Sarah, et al. “Reward Circuitry in Addiction.” *Neurotherapeutics*, vol. 14, no. 3, 2017, pp. 687–697., doi:10.1007/s13311-017-0525-z.

dos Santos, Jucilene, et al. “Maternal, Fetal and Neonatal Consequences Associated with the Use of Crack Cocaine during the Gestational Period: a Systematic Review and Meta-Analysis.” Archives of Gynecology and Obstetrics, vol. 298, 27 Jun. 2018, pp. 487–503, https://doi-org.ezproxy2.library.arizona.edu/10.1007/s00404-018-4833-2.

Evans, Elizabeth, and Maria Sullivan. “Abuse and Misuse of Antidepressants.” *Substance Abuse and Rehabilitation*, vol. 5, 2014, pp. 107–120. doi:10.2147/SAR.S37917.

Eyler, Fonda Davis, et al. “Newborn Evaluations of Toxicity and Withdrawal Related to Prenatal Cocaine Exposure.” *Neurotoxicology and Teratology*, vol. 23, no. 5, 2001, pp. 399–411., doi:10.1016/s0892-0362(01)00166-0.

Forsberg, Lisa, et al. “Neonatal Adaptation in Infants Prenatally Exposed to Antidepressants- Clinical Monitoring Using Neonatal Abstinence Score.” *PLoS ONE*, vol. 9, no. 11, Public Library of Science, 3 Nov. 2014, p. e111327, doi:10.1371/journal.pone.0111327.

Frøisland, Dag Helge. “Nicotine Withdrawal Syndrome in a Newborn Baby after Maternal Use of Oral Applied Moist Tobacco (Snus), Should Result in Greater Awareness to the Use of Snus among Pregnant Women.” *Acta Paediatrica*, vol. 106, no. 9, 16 May 2017, pp. 1531., doi:10.1111/apa.13913.

Godding, Veronique, et al. “Does *In Utero* Exposure to Heavy Maternal Smoking Induce Nicotine Withdrawal Symptoms in Neonates?” *Pediatric Research*, vol. 55, no. 4, 1 Apr. 2004, pp. 645–651., https://doi-org.ezproxy2.library.arizona.edu/10.1203/01.PDR.0000112099.88740.4E

Harro, Jaanus. “Neuropsychiatric Adverse Effects of Amphetamine and Methamphetamine.” *International Review of Neurobiology*, vol. 120, 2015, pp. 179–204., doi:10.1016/bs.irn.2015.02.004.

Heal, David J, et al. “Amphetamine, Past and Present – a Pharmacological and Clinical Perspective.” *Journal of Psychopharmacology*, vol. 27, no. 6, Jun. 2013, pp. 479–496., doi:10.1177/0269881113482532.

Horowitz, Mark Abie, and David Taylor. “Tapering of SSRI Treatment to Mitigate Withdrawal Symptoms.” *The Lancet Psychiatry*, vol. 6, no. 6, Elsevier Ltd, 1 June 2019, pp. 538–546, doi:10.1016/S2215-0366(19)30032-X.

Huang, Yan-You, et al. “Chronic Nicotine Exposure Induces a Long-Lasting and Pathway-Specific Facilitation of LTP in the Amygdala.” *Learning & Memory*, vol. 15, no. 8, Aug, 2008, pp. 603–610., doi:10.1101/lm.975308.

Hurt, Richard D, et al. “Iqmik – A Form of Smokeless Tobacco Used by Pregnant Alaska Natives: Nicotine Exposure in Their Neonates.” *The Journal of Maternal-Fetal & Neonatal Medicine*, vol. 17, no. 4, 2005, pp. 281–289., doi:10.1080/14767050500123731.

Hurt, Richard D, et al. “Iqmik – A Form of Smokeless Tobacco Used by Pregnant Alaska Natives: Nicotine Exposure in Their Neonates.” *The Journal of Maternal-Fetal & Neonatal Medicine*, vol. 17, no. 4, 2005, pp. 281–289., doi:10.1080/14767050500123731.

Jansson, Lauren M, and Stephen W Patrick. “Neonatal Abstinence Syndrome.” *The Pediatric Clinics of North America*, vol. 66, no. 2, 1 Apr. 2019, pp. 353–367.

Kim, Juhwan, et al. “Brain Reward Circuits in Morphine Addiction.” *Molecules and Cells*, vol. 39, no. 9, Sept. 2016, pp. 645–653., doi:10.14348/molcells.2016.0137.

King, Terri A., et al. "Neurologic manifestations of in utero cocaine exposure in near-term and term infants." *Pediatrics*, vol. 96, no. 2, American Academy of Pediatrics, Aug. 1995, p. 259-264. *Gale Academic OneFile*, https://link-gale-com.ezproxy3.library.arizona.edu/apps/doc/A17407727/AONE?u=uarizona_main&sid=AONE&xid=f6d90230. Accessed 3 May 2020.

Koren, Gideon, and Hedvig Nordeng. “Antidepressant Use during Pregnancy: The Benefit-Risk Ratio.” *American Journal of Obstetrics and Gynecology*, vol. 207, no. 3, Mosby, Sept. 2012, pp. 157–163, doi:10.1016/j.ajog.2012.02.009.

Management of Substance Dependence Review Series: Systematic Review of Treatment for Amphetamine-Related Disorders. Department of Mental Health and Substance Dependence, World Health Organization, 2001, apps.who.int/iris/bitstream/handle/10665/42445/WHO_MSD_MSB_01.5.pdf;jsessionid=688CDF106DFBCF06B706D9A8C3E60F49?sequence=1.

McLaughlin, Ian, et al. “Nicotine Withdrawal.” *Current Topics in Behavioral Neurosciences*, vol. 24, 19 Aug. 2015, pp. 99–123., doi:10.1007/978-3-319-13482-6_4.

Mcqueen, Karen, and Jodie Murphy-Oikonen. “Neonatal Abstinence Syndrome.” *New England Journal of Medicine*, vol. 375, no. 25, 2016, pp. 2468–2479., doi:10.1056/nejmra1600879.

Moulsdale, Wendy, and Susan Hermann. “In Utero Exposure to Selective Serotonin Reuptake Inhibitors: Evidence for Poor Neonatal Adaptation.” *Newborn and Infant Nursing Reviews*, vol. 8, no. 3, Sept. 2008, pp. 123–130, doi:10.1053/j.nainr.2008.06.006.

Nestle, Eric J. “Is There a Common Molecular Pathway for Addiction?” *Nature Neuroscience*, vol. 8, no. 11, Nature Publishing Group, Nov. 2005, pp. 1445+. *Gale Academic OneFile*, https://link-gale-com.ezproxy2.library.arizona.edu/apps/doc/A185538544/AONE?u=uarizona_main&sid=AONE&xid=b2a880f2., doi: 10.1038/nn1578. Accessed 30 Apr. 2020.

“Nicotine.” *DrugBank*, https://www.drugbank.ca/drugs/DB00184. Accessed 24 April 2020.

“NICU Network Neurobehavioral Scale (NNNS.)” *Brown Center for the Study of Children at Risk,* Brown University, www.brown.edu/research/projects/children-at-risk/about.

Oei, J L, et al. “Amphetamines, the Pregnant Woman and Her Children: a Review.” *Journal of Perinatology*, vol. 32, 31 May 2012, pp. 737–747., doi:10.1038/jp.2012.59.

“Perinatal Services BC Antidepressant Use During Pregnancy: Considerations for the Newborn Exposed to SSRIs/SNRIs.” *Perinatal Services BC*, 2013, www.perinatalservicesbc.ca/Documents/Guidelines-Standards/Newborn/AntidepressantUseExposedNewbornGuideline.pdf

Picciotto, Marina R., and Yann S. Mineur. “Molecules and Circuits Involved in Nicotine Addiction: The Many Faces of Smoking.” *Neuropharmacology*, vol. 76, pt. B, Jan. 2014, pp. 545–553., doi:10.1016/j.neuropharm.2013.04.028.

Raffaeli, Genny, et al. “Neonatal Abstinence Syndrome: Update on Diagnostic and Therapeutic Strategies.” *Pharmacotherapy*, vol. 37, no. 7, 2017, pp. 814–823, https://doi-org.ezproxy4.library.arizona.edu/10.1002/phar.1954.

Sanlorenzo, Lauren A., et al. “Neonatal Abstinence Syndrome: An Update.” *Current Opinion in Pediatrics*, vol. 30, no. 2, 2018, pp. 182–186., doi:10.1097/mop.0000000000000589.

Sherwood, Lauralee. *Fundamentals of Human Physiology*. 4th ed., Cengage Learning, 2010.

Smith, Lynne, et al. “Effects of Prenatal Methamphetamine Exposure on Fetal Growth and Drug Withdrawal Symptoms in Infants Born at Term.” *Journal of Developmental & Behavioral Pediatrics*, vol. 24, no. 1, Feb. 2003, pp. 17-23, Journals@ Ovid Full Text, http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovftf&NEWS=N&AN=00004703-200302000-00006. Accessed 04 May. 2020.

Sofuoglu, Mehmet, et al. “The Effect of Individual Cocaine Withdrawal Symptoms on Outcomes in Cocaine Users.” *Addictive Behaviors*, vol. 30, no. 6, July 2005, pp. 1125–1134., doi:10.1016/j.addbeh.2004.10.010.

Stix, Gary. “Turbocharging the Brain.” *Scientific American*, vol. 301, no. 4, Oct. 2009, pp. 46–55., doi:10.1038/scientificamerican1009-46.

“Substance Use in Women: Substance Use While Pregnant and Breastfeeding.” *National Institute on Drug Abuse,* NIDA, April 2020, www.drugabuse.gov/publications/substance-use-in-women/substance-use-while-pregnant-breastfeeding. Accessed 17 April. 2020.

Trescot, Andrea M., et al. “Opioid Pharmacology.” *Pain Physician*, vol. 11, no. 2S, 2008, pp. S133–S153, www.painphysicianjournal.com/current/pdf?article=OTg3&journal=42. Accessed 19 Apr. 2020.

Tronick, Ed, and Barry M. Lester. “Grandchild of the NBAS: The NICU Network Neurobehavioral Scale (NNNS).” *Journal of Child and Adolescent Psychiatric Nursing*, vol. 26, no. 3, 2013, pp. 193–203., doi:10.1111/jcap.12042.

Vagnarelli, Federica, et al. “TDM Grand Rounds: Neonatal Nicotine Withdrawal Syndrome in an Infant Prenatally and Postnatally Exposed to Heavy Cigarette Smoke.” *Therapeutic Drug Monitoring*, vol. 28, no. 5, 2006, pp. 585–588., doi:10.1097/01.ftd.0000245391.56176.ad.

Wang, Shao-Cheng, et al. “Opioid Addiction, Genetic Susceptibility, and Medical Treatments: A Review.” *International Journal of Molecular Sciences*, vol. 20, no. 17, 2 Sept. 2019, p. 4294., doi:10.3390/ijms20174294.

Wells, Charlotte et al. “Withdrawal Management and Treatment of Crystal Methamphetamine Addiction in Pregnancy: A Review of Clinical Effectiveness and Guidelines” *CADTH Rapid Response Report: Summary with Critical Appraisal*, Canadian Agency for Drugs and Technologies in Health, 17 Jun. 2019, Ottawa ON, https://www.ncbi.nlm.nih.gov/books/NBK546255/. Accessed 04 May 2020.

Wouldes, Trecia A., and Barry M. Lester. “Stimulants: How Big Is the Problem and What Are the Effects of Prenatal Exposure?” *Seminars in Fetal and Neonatal Medicine*, vol. 24, no. 2, Apr. 2019, pp. 155–160., doi:10.1016/j.siny.2019.01.011.

Zorick, Todd et al. “Withdrawal Symptoms in Abstinent Methamphetamine-Dependent Subjects.” *Addiction (Abingdon, England)*, vol. 105, no. 10, 2010, pp. 1809-1818. doi:10.1111/j.1360-0443.2010.03066.x

Appendix

Neurons are nervous system cells that function as messengers, transmitting information from one region to another through a series of electrochemical pulses termed *action potentials* (Cicarelli and White 46-48). A basic mechanism for neuronal message transmission can be described as follows:

> Neurons are arranged such that the “end” of one neuron is closely associated with the “front” of another (Sherwood 91; Cicarelli and White 46-47). To send a chemical signal, the first neuron, or *presynaptic* neuron, releases specific chemicals into the interneuron space, or *synapse* (Cicarelli and White 50-53). The chemicals released into the synapse are detected by the next neuron, or *postsynaptic* neuron (Cicarelli and White 50-53). Detection usually occurs by specific receptors on the cell membrane, that bind to these messenger chemicals (Cicarelli and White 51). The messenger chemicals are termed *neurotransmitters* and, when bound to cellular receptors, induce

an electrochemical gradient within the cell (Cicarelli and White 50-51). This electrochemical gradient, or *action potential*, travels down the entire neuron, leading to the release of neurotransmitters (Cicarelli and White 48-51). These neurotransmitters are detected by the next neuron's receptors, and the chain of action potentials can continue to send signals throughout the body (Cicarelli and White 51).

Agonists are chemicals that, when introduced, produce an effect similar to a chemical innately made in the body ("Agonist"). *Antagonists* are chemicals that, when introduced, hinder the effects of a chemical innately made in the body ("Antagonist").

Additionally, the brain is the organ most physiologically and psychologically relevant to this paper. The brain can be divided into two regions: (1) the brain stem and cerebellum, and (2) the forebrain (Sherwood 112). The forebrain can be further described as two interrelated portions, the limbic system and the cerebrum (Cicarelli and White 76-78; Sherwood 112-115). Parts of the cerebrum, however, are involved in limbic system functioning—no region functions independently of the others (Sherwood 124). Please note that this list is not exhaustive, but rather intended to provide a general overview of function.

Table 2: Regions and Overview of Function of the *Brain Stem and Cerebellum*

Brain Region	**Overview of Function**
Medulla	• Automatic mechanical bodily processes including respiration and heartbeat (Cicarelli and White 73; Sherwood 113) • Other functions include swallowing and digestive action (Cicarelli and White 73; Sherwood 113)
Pons	• Transmission of information from the body to the forebrain (Cicarelli and White 74; Sherwood 112) • Involved in movement and state of consciousness regulation (Cicarelli and White 74)
Reticular Formation	• Involved in maintaining wakefulness and identifying sensory changes (Cicarelli and White 74)
Cerebellum	• Critical to proprioception and movement (Cicarelli and White 75; Sherwood 113)

The brainstem is critical to automatic body processes needed for life (Sherwood 113).

Table 3: Regions and Overview of Function of the *Forebrain: Limbic System*

Brain Region	**Overview of Function**
Hypothalamus	• Maintains drive for basic activities, including eating, sleeping, and drinking (Cicarelli and White 76) • Involved in adjusting automatic respiratory and circulatory function (Sherwood 124)
Thalamus	• Filters and transmits sensory information (Sherwood 123) • Involved in relaying signals to other areas of the brain (Cicarelli and White 76; Sherwood 123)
Hippocampus	• Involved in learning and the creation and processing of memories (Cicarelli and White 77; Sherwood 111)
Amygdala	• Critical to inducing and processing fear (Cicarelli and White 77; Sherwood 124)

The brain's limbic system consists of multiple brain structures working together to regulate emotion and behavior, as well as produce appropriate physiological responses to perceived stimuli (Sherwood 124). The limbic system exerts immense control over processes of learning and emotional response, particularly involving behavior associated with reproduction and survival (Sherwood 124).

Nearby these brain structures lies the Ventral Tegmental Area (VTA), a structure beneath the cerebrum that plays a significant role in pathways involved in substance use disorders (Hanlon, et al.). The VTA is known to release dopamine, a neurotransmitter, to other regions of the brain (Hanlon, et al.). Another region, the Nucleus Accumbens (NA) has implications in similar pathways, as well (Catterall). In particular, excitation of the NA has been associated with cravings (Hanlon et al.). Dopamine has been found to modulate NA activity (Catterall). Communication between the NA and VTA regions is known as the "mesolimbic circuit" (Hanlon et al.).

Table 4: Regions and Overview of Function of the *Forebrain: Cerebrum*

Brain Region	**Overview of Function**
Occipital Lobes	• Processes visual information and stimuli (Cicarelli and White 78-79)
Frontal Lobes	• Motor control and movement (Cicarelli and White 79) • Critical thinking, thought processing, imagination, emotional integration, memory, attitude, and personality (Cicarelli and White 79; Sherwood 115)
Parietal Lobes	• Involved in perception, particularly sensations of touch (Sherwood 115) • Processes physical pain and pressure, as well as environmental stimuli such as temperature (Sherwood 115)
Temporal Lobes	• Processes auditory information and stimuli (Cicarelli and White 79)
Basal Nuclei	• Plays a role in movement and muscle control (Sherwood 114-115)

The forebrain is considered to be responsible for sensory perception, higher processing and critical thinking (Cicarelli and White 78-79; Sherwood 115). Overall, the brain is a multifaceted organ with significant implications in addiction medicine (Catterall).

Works Cited

"Agonist." *Merriam-Webster*, Merriam-Webster, www.merriam-webster.com/dictionary/agonist. Accessed 29 April 2020.

"Antagonist." *Merriam-Webster*, Merriam-Webster, www.merriam-webster.com/dictionary/antagonist. Accessed 19 April 2020.

Catterall, W.A. "Neuromodulation of Sodium Channels." *Encyclopedia of Neuroscience*, 2009, pp. 513–519.

Ciccarelli, Saundra K., and J. Noland White. *Psychology*. 5th ed., Pearson, 2017.

Hanlon, C. A., et al. "Chapter 6 -- Biomarkers for Success: Using Neuroimaging to Predict Relapse and Develop Brain Stimulation Treatments for Cocaine-Dependent Individuals." *International Review of Neurobiology*, vol. 129, 2016, pp. 125–156. Doi: 10.1016/bs.irn.2016.06.006.

Sherwood, Lauralee. *Fundamentals of Human Physiology*. 4th ed., Cengage Learning, 2010.