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# Prenatal Nicotine Exposure as a Teratogen in Neurological Pathways

By Monica Grover

## *Author Note*

This paper was prepared for HONR 200, Section 702, taught by Professor Mary Boyes in fall 2014.

## *Abstract*

Attention-deficit/hyperactivity disorder (ADHD) is the most heritable and commonly diagnosed childhood psychiatric disorder with 4% of all children being diagnosed with this disorder. Prenatal smoking has been found to be a risk factor for ADHD, a disorder that has been believed to be linked to the fluctuation of dopamine levels. Prenatal nicotine exposure in the second trimester influences dopaminergic neurological pathways by altering dopamine release levels. The altered dopamine levels make the fetus brain more sensitive to the nicotine, causing the nicotine exposure to be more dangerous in causing ADHD symptoms. Prenatal nicotine exposure alters the neurological pathway of the neurotransmitters, ACh and dopamine, not only in the fetus but later in adolescence too. When nicotine enters the body, it is distributed quickly through the bloodstream and into the Central Nervous System (CNS). Cigarette smoke interferes with customary placental function, and therefore the flow of nutrients and oxygen. The nAChRs increases the amount of dopamine released in the synaptic area. Functional changes in DRD4 receptors and in dopamine transporter number caused by genetic variations and prenatal smoking exposure results in changes in dopamine release; however, the relationship between prenatal nicotine exposure and ADHD symptoms was not changed by sociodemographic factors. Interventions should be set-up in order to urge women to quit smoking during their pregnancy. The present study has health significance in that the research will urge pregnant women to be cautious of smoking through proposed interventions.

## *Introduction*

Although the Center for Disease Control states that there is a decline in women who smoke during pregnancy since the 1990s, smoking during pregnancy continues to be a major health concern. The Centers for Disease Control and Prevention also reported that 12.3% of mothers who gave birth in 1999 smoked. LaGasse et al. (2003) point out that unlike other substances of abuse like cocaine and alcohol, cigarettes are usually smoked on a daily basis. Prenatal smoking is also responsible for 20-30% of infants born with low-birth weights. Cigarette smoke interferes with customary placental function because it decreases uterine blood flow, and therefore the flow of nutrients and oxygen, decreases by 38% (LaGasse et al., 1319). Secondly, “in utero, nicotine targets nicotinic acetylcholine receptors in the fetal brain to change the pattern of cell proliferation and differentiation” (1320) which leads to cell loss and neuronal damage.

Blood holds many nutrients, oxygen, and iron that supply the brain which is necessary for healthy brain function. A thirty eight percent decrease in these nutrients is very drastic and is linked to not only low birth rates but also the fetus' neurobehavior. The lack of normal blood flow can impact neurological pathways. Nicotine reduces this blood flow which restricts the

amount of nutrients, oxygen, and iron that supplies the fetus' brain. When nicotine enters the body, it is distributed quickly through the bloodstream, and it can cross the blood-brain barrier to enter the central nervous system (CNS). Blood-Siegfried, J., & Rende, E. (2010) claim that cigarette smoke is made up of over 4000 compounds; nicotine, in particular, is the likely candidate for causing prenatal damage. Smoking during pregnancy is the cause for 161,000 prenatal deaths and 4800 infant deaths in the United States each year (145). Over half of these deaths are associated with sudden infant death syndrome (SIDS).

Berg-Nielsen et al. (2012) claim that prenatal smoking has been found to be a risk factor for "attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), poor cognitive functioning, antisocial problems, aggression, delinquency, substance abuse, and internalizing problems" (Berg-Nielsen et al., 635). Bohlin and Rodriguez (2005) claim that ADHD is the most commonly diagnosed childhood psychiatric disorder, as 4% children have the disorder (247).

Bohlin and Rodriguez further state that nicotine has been found to cause dysfunction of the dopaminergic system in a similar manner of those with ADHD. Specifically, previous work on rodents showed that the neurological damage, such as increased emotionality and different dopaminergic functions, depend on the time of nicotine exposure. Disturbances and alterations in structural brain anatomy have shown to develop from environmental stress during pregnancy. All these effects are long-term, which follow the infant to adulthood.

The dopaminergic system consists of neurological pathways in the brain that transfer the neurotransmitter dopamine from one region of the brain to another. On a smaller cellular scale, dopamine travels from the synapse to the cytosol. Nicotine alters the amount of dopamine released by up-regulating or deregulating the amount of dopamine released into the cytosol which can cause ADHD symptoms. The altered levels of dopamine also factor into leading to ADHD symptoms.

The most important physiologic characteristic of nicotine is its ability to stimulate the nicotinic acetylcholine receptors (nAChRs). Nicotine is a direct stimulant of the nAChR and dopamine receptors. The result of the stimulation of nAChRs during brain development alters the proliferation, maturation, and differentiation of brain cells. Additionally, dopamine regulates blood pressure and suppresses inappropriate behavioral impulses, making dopamine a key factor in controlling ADHD. Blood-Siegfried and Rende claim that "children with a specific polymorphism (genetic variation) in the dopamine transporter and exposure to maternal smoking have a significantly higher incidence of hyperactivity impulsivity than children without this combination of environmental and genetic risk" (147).

Falk et al. lists behaviors of ADHD such as hyperactivity and aggressiveness that is associated with prenatal tobacco use, but does not make the association. Other behaviors include cognitive disturbances and dependence of nicotine and alcohol later in life. On the contrary, although many factors such as stress and socio-demographic status are associated with prenatal smoking, prenatal smoking is independently linked with an increased risk for symptoms of ADHD in children. The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA) is widely used by scientists, doctors, and mental health professionals to make a diagnosis of ADHD.

According to "Symptoms and Diagnostic Criteria", the DSM-5 classifies three categories of symptoms of ADHD: Inattentive presentation, hyperactive-Impulsive presentation, and combined presentation. In order to be diagnosed with ADHD, children must have six or more of the nine characteristics and older teens or adults must have at least five of the nine characteristics.

In the present study, it was concluded that prenatal nicotine exposure in the second trimester causes an up-regulation in dopaminergic neurological pathways and alters dopamine release levels. The altered dopamine levels make the fetus brain more sensitive to the nicotine, causing the nicotine exposure to increase the severity of ADHD symptoms.

#### *Prenatal Nicotine Exposure as an Independent Factor*

According to Berg-Nielsen et al., “studies on the effect of prenatal nicotine exposure on rodents and primates support a teratological effect of nicotine on the developing brain, especially the hippocampus and areas in the prefrontal cortex. However, the possibility also exists that prenatal smoking may be a proxy for other environmental effects (e.g., low socio-economic status)” (642). The habit of smoking can develop from a variety of personal backgrounds. Smoking, similarly, can cause a lot of personal problems to arise such as low socio-economic status. The cause and effects are arranged in a cycle. The theme of epigenetics remains as prenatal smoking is considered an environmental effect. Nicotine travels through the placenta of the mother which as a result can damage the fetus brain. Clear relationships have not been made between ODD and ADHD and neither environmental or genetics can be eliminated. The teratological effect of nicotine has not been fully understood by the research world in regards to brain regions and biological processes.

Kahn et al. states that “Specifically, we found that the DAT polymorphism was only associated with child hyperactivity-impulsivity and oppositional symptoms among children who were also exposed to maternal prenatal smoking. Although the underlying cause of ADHD has long been recognized to be multifactorial, the current study represents a first step in ascertaining how genes and environmental exposure may interact to influence child behavior.” (108). Hyperactivity, impulsivity, and oppositional symptoms are all common symptoms of ADHD. The present study incorporates the importance of integrating environmental factors in genetic studies of ADHD. A polymorphism in the 3'-untranslated region of the DAT gene exists in which a base pair sequence is repeated from 3 to 11 times. The DAT allele alone nor prenatal smoking alone show a high correlation of ADHD behaviors; however, when together, the correlation is very high. Factors such as the aforementioned environmental factors may function as catalysts with prenatal smoking. Thus, the theme of epigenetics and that the dopamine neurological pathway is the other factor that leads to ADHD. Prenatal smoking alone will not lead to ADHD, but instead, the likelihood of ADHD will increase when prenatal smoking is present with a catalyst.

In the study conducted by Berg-Nielsen et al., “Smoking during pregnancy and psychiatric disorders in preschoolers,” published in 2012 in the journal of European Child and Adolescent Psychiatry, three tests were used to analyze parental mental disorder and alcohol addiction symptoms, including the Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory, and the Alcohol Use Disorders Identification Test (AUDIT). A series of questions regarding home conditions, taking into account occupation, marital status, descent, number of children, and questions regarding possible complications during pregnancy followed the tests. These questions could be simply answered with a yes or no response or a scale rating that was provided (638). Kahn et al. also explored other possible environmental predictors to ADHD such as “household income (at 24 months), maternal education, maternal race, prenatal smoke exposure, and sex of the child were not significantly different between those children included and those not included in the study.” However, postnatal household nicotine exposure was associated with higher scores (108). Kahn et al. went in depth in gathering data to ensure that there were no major predictors that could also lead to ADHD symptoms. Household income,

education, race, prenatal smoke exposure, and sex of the child are all factors that can increase the likelihood of the mother smoking. In addition, all of these predictors can be associated with mental illnesses. Rodriguez and Bohlin noticed that the sex of the child was significant. These predictors can also be catalysts in the development of ADHD such as DAT polymorphism. A cofactor found by Bohlin and Rodriguez is stress. "One, because smokers tend to smoke more under stress and perceived stress increases the likelihood of continued smoking during pregnancy, it is necessary to study smoking and stress together." (247). Smoking becomes a cycle for users. Certain socioeconomic, cultural, and emotional backgrounds can cause an increase in chance of a person to smoke. Smoking as a result can also cause these same socioeconomic, cultural, and emotional backgrounds. However, Berg-Nielsen et al. and Henderson et al. both found that socioeconomic, education, and various other factors are not significant. Smokers tend to smoke more under stressful conditions which increases the amount of smoking during pregnancy. Prenatal smoking can lead to ADHD symptoms but in an independent manner.

Similar to the study conducted by Kahn et al., one of the main findings of the study conducted by Berg-Neilson was that a wide range of variables were controlled which did not affect the results. Berg-Neilson et al. further explain that "the overall objective of this study was to determine whether smoking during pregnancy is related to psychiatric disorders in 4-year-olds while controlling for a wide range of potential confounding variables (i.e. parental anxiety, depression, personality disorders, drug abuse, and socio-economic characteristics)" (635). Recent studies involving prenatal nicotine exposure follow the fetus from the first trimester until birth. However, Berg-Nielsen et al. studied four year olds in order to observe the behavioral changes more clearly over time. Berg-Nielsen found that when a wide range of variables were controlled, results were not affected.

Henderson et al. in "Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype" also included various similar confounding variables in their research. However, the factors were found to be insignificant. Because of this insignificance, prenatal smoking during pregnancy is the independent variable in causing ADHD symptoms (1326). Bohlin and Rodriguez studied the independent effects of prenatal smoking and stress (247). Furthermore, the child's age at follow-up, maternal civil status, presence of father figure, and income were found to be unrelated to ADHD symptoms. Multiple regression analyses showed that both smoking and stress independently contributed to the change in ADHD symptoms for the sample in both boys and girls. The relationship between prenatal nicotine exposure and stress and ADHD symptoms was not changed by sociodemographic factors (250).

### *Symptoms of ADHD*

Nicotine-exposed infants are more hypertonic, stressed, and show abstinence signs in the central nervous system, visual area, and gastrointestinal in comparison to unexposed newborns. According to the Centers for Disease Control and Prevention, symptoms of ADHD must be present for over six months for diagnosis. LaGasse et al. in "Smoking during pregnancy and newborn neurobehavior" state that infants exposed to tobacco were more "excitable and hypertonic, required more handling and showed more stress/abstinence signs, specifically in the central nervous system (CNS), gastrointestinal, and visual areas" (1317). Berg-Neilson et al. clarifies the rating for ADHD symptoms as "For example, a typical rating scale item for ADHD is "can't sit still, restless or hyperactive". The informant (in this case, the parent) must determine the definition of "restless", the intensity of restlessness, how long the behaviour endures, and how often the behaviour occurs before characterising a child as "restless" (642). In previous studies about ADHD, typically the informant is either a parent or teacher of the subject. Discrepancies can arise due to bias in evaluating the child. Bias is inevitable when using an

interview style procedure. These behaviors are included in the DSM guide and are typically the symptoms observed with altered dopamine levels. Prenatal nicotine exposure alters dopamine levels when nicotine binds to receptors in the brain, causing these ADHD symptoms to arise.

Falk et al. in “Smoking during early pregnancy affects the expression pattern of both nicotinic and muscarinic acetylcholine receptors in human first trimester brainstem and cerebellum” list behaviors of ADHD such as “hyperactivity, aggressiveness and tendency to seek conflicts, depression and anxiety” that is associated with prenatal tobacco use, but do not associate these symptoms to ADHD. Other behaviors include cognitive disturbances, learning and attention deficits, and dependence of nicotine and alcohol later in life (389). The symptoms, hyperactivity, aggressiveness, and tendency to seek conflicts, are really common behaviors for ADHD. However, Falk et al. did not make this connection which demonstrates that although there are links between nicotine exposure and ADHD and brain dysfunction, not many connections have been made among the three variables. Furthermore, Falk et al. stated that nicotine exposure may increase the chances of the child smoking later in life. This presents a possibility that prenatal smoking establishes a never-ending cycle.

In the study of Bohlin and Rodriguez, ADHD symptoms were measured using the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) instead of a measuring scale of behavior. Bohlin and Rodriguez in the article “Are maternal smoking and stress during pregnancy related to ADHD symptoms in children?” argue that previous studies found that anxiety in late pregnancy predicted hyperactivity and inattention symptoms in 4-year-old boys and later in 8-year-old boys and girls (p. 247).

According to Henderson et al., the DSM-IV number for ADHD symptoms was significantly higher in the offspring who were exposed to prenatal smoking than in those who were not (4.2 versus 3.4) (1322). Forssberg et al. claim that the mean DSM-IV score for the symptoms of ADHD was  $35 \pm 7$  (p. 235). Furthermore, Bohlin and Rodriguez further clarify that children who meet six out of nine symptoms are said to have ADHD (p. 248). In contrast, LaGasse et al. used the The NICU Network Neurobehavioral Scale (NNNS) instead of the DSM-IV and found that dose-response relationships showed higher maternal salivary cotinine values related to more stress/abstinence signs ( $r = .530$ ) including CNS ( $r = .532$ ) and visual stress ( $r = .688$ ) and higher excitability scores ( $r = .617$ ). Cigarettes per day during pregnancy was related to more stress/abstinence signs ( $r = .582$ ) including CNS ( $r = .561$ ) and visual stress ( $r = .640$ ) (1323).

Although the diagnosis of ADHD is met with six of nine symptoms, the severity of each symptom increased with nicotine exposure. Prenatal nicotine exposure triggered clear symptoms of ADHD as listed in the DSM-IV. Higher  $r$  values show a higher dose-response relationship between maternal smoking and ADHD symptoms.

According to LaGasse et al., results showed that infants exposed to tobacco were more “excitable and hypertonic, required more handling and showed more stress/abstinence signs, specifically in the central nervous system (CNS), gastrointestinal, and visual areas” (1317). The  $r$  values showed a slight correlation between maternal cotinine values and signs of stress, visual stress, and excitability. In the NNNS scale used by LaGasse et al., the exam assesses neurologic, behavioral, and stress/abstinence neurobehavioral function. The neurologic part tests active and passive tone, embryonic reflexes, and questions that reflect the integrity of the central nervous system (CNS) and maturity of the infant. “The NNNS items are scored using the following summary scales: Habituation, Attention, Arousal, Regulation, Number of Handling Procedures, Quality of Movement, Excitability, Lethargy, Number of Nonoptimal Reflexes, Number of Asymmetric Reflexes, Hypertonicity, Hypotonicity, and Stress/Abstinence. The Stress/Abstinence scale is further divided into the following subscores: physiologic, autonomic,

CNS, skin, visual, gastrointestinal, and state” (1320). According to LaGasse et al., infants in the smoking group showed more excitability, asymmetrical reflexes, and hypertonia than infants in the nonsmoking group.

### *nAChR Receptors*

Prenatal nicotine exposure increases the binding of nicotine receptors which alters the normal developmental pattern of the acetylcholine system in human fetal brain. The stimulation of neural nicotine acetylcholine receptors (nAChR) increases synaptic dopamine release in striatal and cortical regions. Bohlin and Rodriguez state that nicotine has been found to cause dysfunction of the dopaminergic system in a similar manner of those with ADHD (p. 246). More specifically, according to Henderson et al., the stimulation of neural nicotine acetylcholine receptors (nAChR) increases synaptic dopamine release in striatal and cortical regions (p. 1320). Falk et. al state that “The density of [3H]-nicotine binding sites in human brainstem at midgestation is significantly higher compared with brainstem from early infancy” (390). ACh receptors are most prominent in the second trimester which is three to six months. Midgestation, however, is about five to eight weeks. Thus, the results of this study may be inconsistent due to this short time frame. In addition, ACh receptors are more prominent in infants than in adults. In the study, Falk et al. show that ACh receptor levels are significantly higher in midgestation and then higher in the second trimester. Thus, there is a discrepancy in the amount of ACh receptors from midgestation to adulthood. Further research should be done on the differences of ACh concentrations from midgestation to infancy and then adulthood. Also, as the density of nicotine binding sites increases, the fetus becomes more sensitive to nicotine. Falk et. al. focused on the brainstem while other studies mostly focused on the cerebellum.

Additionally, Falk et al. further state that “nAChRs are up-regulated in response to long term exposure to agonists. Studies in postmortem human brain have revealed increased number of nAChRs in brains of smokers compared with non-smokers” (390). The postmortem human brain tissue was obtained from aborted fetuses. Law et al. obtained similar results in which receptors are up-regulated, but Falk et al. instead focused on ACh receptors and not nicotine receptors. Since the receptors increase in the brains of smokers, the brains become more sensitive to nicotine and therefore, yield more aggressive and compulsory behaviors. Agonists include nicotine and other harmful substances in cigarette smoke. This may indicate that an increase in ACh receptors may correlate with an increase in nicotine receptors. An increase in density of nicotine binding sites results in the fetus becoming more sensitive to nicotine. This may yield ADHD symptoms.

Forsberg et al. in “Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: Association between striatal dopamine markers and motor hyperactivity” claim that recent research focused on the correlation of the dopaminergic system and ADHD used single photon emission tomography (SPET) and positron emission tomography (PET) (231). The study conducted by Gold et al. examined the changes in neuronal nicotinic acetylcholine receptors (nAChRs) in the cerebral cortex, thalamus, and striatum of male rats caused by prenatal exposure of nicotine from gestational day 3 to postnatal day 10 (PN10). Nicotine exposure in adolescents caused up-regulation of binding in all three regions (88).

According to Gold et al., “Prenatal nicotine exposure may lead to changes that subsequently affect the expression and function of nAChRs in the adolescent brain that have been re-exposed to nicotine, contributing to an altered biological response and an increased susceptibility for addiction” (89). Gold et al. claims that prenatal smoking contributes to ADHD symptoms. Constant nicotine exposure in adult rats has been shown to dramatically alter both numbers

and function of nAChRs.

Forsberg et al. claim that the levels of dopamine can either increase or decrease depending on the brain region. Therefore, it is thought that there exists abnormal regulation of presynaptic biological markers of dopaminergic transmission in subjects with ADHD (231). Gold et al. states that prenatal nicotine exposure activates nAChRs at inappropriate times and at increased levels which causes changes in development (89). Gold et al. also argues that constant nicotine exposure in adult rats has been shown to dramatically alter both numbers and function of nAChRs. While nicotine also up-regulates nAChRs in adolescent rats, this effect is greatly reduced compared to that in adults (91). Dopamine levels are crucial because it controls attentiveness and behavioral symptoms. An increase in dopamine levels can be as damaging as a decline.

According to Falk et al., the nicotinic acetylcholine receptors (nAChRs) have subtypes that form functional receptors in the thalamus, hippocampus, and cortex, and are expressed more during the first trimester than in adult brains. Binding sites and mRNA for different subunits of nAChRs are evident in the fetal brain from the 4–5 weeks of gestation (394). Falk et al. claim that the gene expression pattern of both nicotinic receptor subunits were changed after smoking in all three regions of the brain. Falk et al. further states that “this research study demonstrates that smoking during the first trimester influences the expression of nAChRs and mAChRs in the human brainstem and cerebellum of the fetus” (395). These changes in receptor expression and regulation can create disturbances in the fetus later in life.

The study conducted by Gold et al. in “Prenatal exposure of rats to nicotine causes persistent alterations of nicotinic cholinergic receptors” examined the changes in neuronal nicotinic acetylcholine receptors (nAChRs) in the cerebral cortex, thalamus, and striatum of male rats caused by prenatal exposure of nicotine from gestational day 3 to postnatal day 10 (PN10) (95). According to LaGasse et al., “Fetal nicotine exposure upregulates nicotinic cholinergic receptor binding sites, causing abnormalities in the development of synaptic activity. The end result is cell loss and ultimately, neuronal damage” (1319). Kahn et al. and Falk et al. also note the role of acetylcholine receptors. Nicotine targets ACh receptors that change the amount of cells being produced. Nicotine exposure creates more nicotine cholinergic receptor binding sites that cause abnormalities. Upregulation is when there is an increase in the number of receptors on the surface of target cells which make them more sensitive to a substance. This upregulation makes the fetus brain more sensitive to the nicotine, causing the nicotine exposure to be more dangerous in causing ADHD symptoms. Gold et al. argues that nicotine exposure in adolescents decreased the amount of nicotine-stimulated dopamine release in the striatum and that prenatal nicotine exposure causes alterations in nAChRs and in their regulation by nicotine that continues in adolescence (p. 94). A fluctuation in the number of receptors and therefore, the sensitivity to nicotine can increase the severity of ADHD symptoms.

### *DAT Allele*

Child hyperactivity-impulsivity and oppositional behaviors, symptoms of ADHD, were increased among children who are homozygous for the dopamine transporter 10-repeat allele (DAT) but only when those children were also exposed to maternal prenatal smoking. Altered dopamine signaling changes motor hyperactivity and is considered as a potential endophenotype, a phenotype with clear genetic connection, of ADHD. According to the Genetic Science Learning Center, “epigenetics is the study of these chemical reactions and the factors that influence them.” According to Berg-Nielsen et al., although ADHD is highly heritable, the environmental effect of smoking is a major factor; both genetic and the teratological effects of nicotine contribute to the relationship between prenatal smoking and behavioral disorders (636). The study conducted by Forsberg et al. examined the dopamine transporter (DAT) and dopamine



D2 receptor (D2R) binding in adolescents with ADHD to search for its relationship with cognitive functions as well as locomotor hyperactivity. DAT is a protein that spans over the whole membrane that pumps the neurotransmitter, dopamine, out of the synapse back into cytosol (229).

According to Forssberg et al., the psychostimulants methylphenidate and amphetamine, both increase the internal synaptic dopamine concentration through inhibition of the dopamine transporter (DAT) which is shown in healthy adults and subjects with ADHD. Different alleles of DAT, dopamine D4 receptor, and D2 receptor genes have all been associated with ADHD symptoms and also have responded to treatment with methylphenidate (230).

Henderson et al., ADHD is a result of a complex combination of genetics and environmental interactions. “The main findings of the current study are that gene–environment interactions modulate the risk for the ADHD-combined subtype, whether defined by DSM-IV or population-based criteria” (1325). The strength of the associations between polymorphisms of the DAT1 or DRD4 genes and ADHD combined subtype were increased with prenatal smoking exposure. Forssberg et al states that “The lower BP values for DAT in the midbrain suggest that dopamine signaling in subjects with ADHD is altered” (229). Gold et al. found similar results in that prenatal exposure to nicotine causes alterations in nAChRs and in their regulation by nicotine that persists into adolescence (94).

Nicotine exposure increases the amount of nAChRs which increases the amount of dopamine released from the synapse to the cytosol. The nAChRs increases the amount of dopamine released in the synaptic area which has been shown to cause ADHD symptoms. Functional changes in DRD4 receptors and in dopamine transporter number caused by genetic variations and prenatal smoking exposure results in changes in dopamine release. This release of dopamine is sensitive to nicotine and both interact to cause ADHD symptoms.

In the study of Kahn et al. in “Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors” (107) the 480 allele was proposed to be an ADHD risk factor when coupled with prenatal smoking. On the contrary, Henderson et al. state that “Interestingly, the association found in this study with the dopamine transporter gene is with the 440 allele rather than the 480 allele, which usually is considered the risk allele in candidate-gene studies of ADHD” (1327). The 480 allele was proposed to be an ADHD risk factor when coupled with prenatal smoking in the study of Kahn et al. (2003). There are two genotypes of this allele that are associated with the dopamine transporter gene. Kahn et al. (2003) found that children with the DAT 480/480 homozygous genotype who were exposed to prenatal smoking had significantly elevated hyperactive–impulsive and oppositional scores on the Conners’ Parent Rating Scale Revised-Long Version. Although prenatal smoking has been shown to independently result in ADHD symptoms, the role of genetics can also change the release of dopamine. The dopamine transporter gene regulates the amount of dopamine released into the cytosol which as a result can lead to ADHD symptoms.

According to Forssberg et al. “The findings, suggesting higher dopa decarboxylase activity, and our results showing lower DAT binding might suggest altered presynaptic regulation of dopaminergic transmission in ADHD. This is in line with experimental animal models of ADHD showing downregulation in midbrain dopaminergic neurotransmission in relation to the reduced DAT gene expression” (235). LaGasee et al. claim that an upregulation in ACh receptors makes the fetus more sensitive to nicotine (1323). However, Forresberg et al. found a deregulation of dopamine. The neurotransmitter, dopamine, is a calming chemical. High amounts of dopamine can cause a loss of focus in patients. ADHD symptoms include inattentiveness which can be caused by too little or too much dopamine. Due to this fluctuation, the synapse

must regulate the amount of dopamine that can be released into the cytosol. As mentioned in Falk's source, prenatal nicotine exposure upregulates nicotine receptors which enhances stimulated release of dopamine (393).

Kahn et al. claim that the gene for the dopamine transporter (DAT) is the site of response for psychostimulants like methylphenidate. Psychostimulants are psychoactive drugs that prompt temporary improvements in either mental or physical functions or both. Examples of these functions may include higher alertness, wakefulness, and locomotion (108). Bohlin and Rodriguez also state that "Nicotine has been found to cause dysfunction of the dopaminergic system, which is consistent with observations that children with ADHD also have a similar dysfunction" (247). Nicotine has been found to cause an abnormal increase of dopamine. Symptoms of an increase in dopamine have been present in ADHD subjects. The dopaminergic system consists of neurological pathways in the brain that transfer the neurotransmitter dopamine from one region of the brain to another. The mapping of this pathway can be compared between children with ADHD and children whose mother smoked during pregnancy.

### *Conclusion*

Long-lasting and frequent nicotine exposure has been known to cause up-regulation of both ACh and dopamine. The increase in ACh and dopamine has been shown to cause ADHD symptoms. Up-regulation is the process in which there is an increased response to a stimulus such as nicotine. The number of receptors increases, causing an increase in sensitivity to nicotine. However, a point that deviates from the present research questions is if the ACh and dopamine receptors can become tolerant to the nicotine with too much exposure. Gold et al. claims that "Furthermore, while chronic exposure to nicotine often causes receptor up-regulation, it also can lead to receptor desensitization and tolerance, which could be an explanation of the dissociation between results of binding and functional assay" (95).

Further research should be conducted to discover other major neurotransmitters that are regulated differently due to nicotine exposure. Interventions for pregnant women and young girls throughout the world to stress the dangers of smoking could decrease the amount of women who smoke during pregnancy. Furthermore, according to Blood-Siegfried and Rende both self-report and past recall of smoking status during pregnancy introduces a significant concern of an underreporting bias. Research in prenatal smoking has health significance in that the research will urge pregnant women to be cautious of smoking. Prenatal nicotine exposure alters the neurological pathway of the neurotransmitter, ACh, not only in the fetus but later in adolescence too. The child is more inclined to smoke, which leads to additional health concerns later in life.. The use of interventions through either patient navigators or videos through a tablet during routine medical visits could be utilized in a potential experiment to test the use of interventions in percentage of women who smoke during pregnancy.

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