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Developmental toxicity of nicotine: A transdisciplinary synthesis and implications for emerging tobacco products

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Abstract

While the health risks associated with adult cigarette smoking have been well described, effects of nicotine exposure during periods of developmental vulnerability are often overlooked. Using MEDLINE and PubMed literature searches, books, reports and expert opinion, a transdisciplinary group of scientists reviewed human and animal research on the health effects of exposure to nicotine during pregnancy and adolescence. A synthesis of this research supports that nicotine contributes critically to adverse effects of gestational tobacco exposure, including reduced pulmonary function, auditory processing defects, impaired infant cardiorespiratory function, and may contribute to cognitive and behavioral deficits in later life. Nicotine exposure during adolescence is associated with deficits in working memory, attention, and auditory processing, as well as increased impulsivity and anxiety. Finally, recent animal studies suggest that nicotine has a priming effect that increases addiction liability for other drugs. The evidence that nicotine adversely affects fetal and adolescent development is sufficient to warrant public health measures to protect pregnant women, children, and adolescents from nicotine exposure.

Keywords

nicotine; electronic nicotine delivery systems; priority/special populations

1. Background

After decades of declining cigarette sales, cigarette companies expanded their product lines to include a range of nicotine-containing products with varying levels of toxicity, including smokeless tobacco in the 1990s, and electronic cigarettes and other types of electronic nicotine delivery systems (ENDS) in the early 2000s. Some tobacco companies have also added nicotine replacement therapy (NRT) pharmaceuticals.(1-3) Electronic cigarettes– devices which create an aerosol for inhalation by heating a liquid solution that typically contains propylene glycol and/or glycerin, flavorings, and nicotine–have experienced rapid growth since their introduction into the US market.(4-6) However, their arrival has also

engendered debate in the public health community.(7, 8) Those concerned about the risks from electronic cigarettes to individual and population level health note that electronic cigarettes could perpetuate conventional cigarette use in smokers who use both products instead of quitting cigarettes completely, and that adolescent users of these products could progress to conventional cigarette use.(4, 9, 10) In contrast, others contend that electronic cigarettes have lower toxicity than conventional cigarettes, higher consumer appeal than NRT, and that their use may lead to cessation or to a reduction in toxicant exposure, thereby reducing the burden of tobacco-related death and disease.(11)

A key assertion advanced by those in favor of wide access to electronic cigarettes is that nicotine exposure presents a minimal health risk for most adult tobacco users.(12) This is based, in part, on longitudinal studies of adults exposed to nicotine from smokeless tobacco or NRT, which found lowered risk for myocardial infarction, stroke, and lung cancer compared with risk in cigarette smokers.(13-16) However, this assertion has important limitations. Electronic cigarette use is not limited to adults or to conventional cigarette smokers.(17) Use has increased dramatically in high school and middle school students since 2011, (5) and in 2014, twice as many youth used electronic cigarettes alone as in combination with cigarettes.(18) Furthermore, as will be presented here, conclusions about the risks of nicotine exposure based on studies in adults cannot be extrapolated to adolescents or pregnant women and their fetuses, because these populations have health risks unique to their particular stages of development. Nevertheless, discussions of the potential adverse health effects of nicotine among pregnant women and adolescents are often absent from discussions related to the public health impact of electronic cigarettes.

In May of 2015, scientists from varied disciplines were convened by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to review the scientific literature on the health effects of nicotine exposure during periods of developmental vulnerability. In this expert review, meeting participants used MEDLINE and PubMed literature searches, books, reports, and expert opinion to summarize and synthesize relevant epidemiological, clinical, and preclinical research on the health effects of exposure to tobacco and nicotine pregnancy and adolescence. Electronic cigarettes were introduced to markets relatively recently, and their effects on health outcomes in pregnant women and adolescents have not been directly assessed. In addition, there are no published studies of developmental outcomes using animal models nicotine exposure from electronic cigarettes. Therefore, the authors draw on studies of other forms of tobacco exposure (cigarettes and smokeless tobacco) in humans and conventional nicotine exposure in animals. While there is evidence from animal models that gestational nicotine exposure also affects several organ systems, including renal, hematopoietic, adipose and endocrine,(19-23) we focused on the central nervous and pulmonary systems, which are the most established and clearest targets of nicotine. In addition, shorter-term studies of exposures to electronic cigarette-derived aerosols in adult mouse models demonstrate that electronic cigarettes can produce pulmonary and behavioral effects similar to those seen with conventional nicotine exposures. (24-27)

The implications of the increasing use of nicotine-containing products, specifically electronic cigarettes, for pregnant women and adolescents are discussed, and potential strategies for minimizing exposure in these populations are presented.

2. Tobacco use and nicotine exposure during pregnancy

2.1 Pregnancy outcomes

Maternal cigarette smoking during pregnancy is causally associated with a number of adverse pregnancy outcomes, including ectopic pregnancy, fetal growth restriction, preterm birth, placental abruption, and orofacial cleft defects.(15) Despite high awareness that smoking increases the risk of pregnancy complications,(28) over 10% of U.S. women smoke cigarettes during pregnancy, exposing more than 400,000 fetuses each year.(29) Tobacco smoke contains thousands of chemicals, many of which could contribute to adverse outcomes.(30) However, studies of pregnant women who are exposed to nicotine without products of combustion through the use of smokeless tobacco products can provide insight into the potential role of nicotine. These studies have found associations with preterm birth, stillbirth, and orofacial cleft defects,(15, 31-35) but no clear association with fetal growth restriction.(36-39) In agreement with the latter finding, animal models utilizing nicotine alone do not demonstrate any consistent effect on fetal growth at exposures modeling those in typical smokers.(40-42) Together, these findings provide evidence that nicotine and other tobacco smoke components produce distinctive adverse pregnancy outcomes.

2.2 Fetal brain development

During development, neurotransmitters control and coordinate the cellular and architectural assembly of the central nervous system.(43, 44) At the appropriate developmental phase, stimulation of neurotransmitter receptors regulates brain assembly by (1) promoting cell replication; (2) initiating differentiation; (3) initiating and then terminating axonogenesis and synaptogenesis; (4) regulating cell death; and (5) promoting cell migration to specific brain regions.

Acetylcholine plays a critical role in brain maturation via activation of nicotinic acetylcholine receptors (nAChRs). These receptors are a structurally diverse family of ligand-gated ion channels which regulate synaptic plasticity and brain development. Nicotine crosses the placenta(45) and specifically binds to nAChRs in the fetal brain.(46, 47) Since nAChRs are functional at early stages of brain development, their early activation and/or desensitization by nicotine can lead to long-term developmental disruption.(48-50) Even first-trimester exposure can induce disruption of brain development at both cellular and structural levels.(51) Although the structural features may appear grossly normal by early adulthood,(52) a detailed analysis of synaptic architecture shows long-lasting alterations (layer thinning, loss of neuropil, glial “scarring”), particularly in the hippocampus and somatosensory cortex areas that are critical for attention and cognitive function.(52-54) Thus, from a morphological standpoint, nicotine is a subtle neuroteratogen. However, its functional consequences exceed the visible evidence of disrupted development.

In developing rats exposed prenatally to nicotine at plasma levels comparable to those in human active smokers, standard biomarkers of cell injury indicate apoptosis, reductions in the numbers of neuronal cells, truncation of axonogenesis, and deficient synaptogenesis. (55-58) Neuronal damage and cell loss involving the activation of genes associated with apoptosis intensify in the postnatal period despite the discontinuation of nicotine exposure. (57, 59, 60) The developmental context is critical for evoking damage, since nicotine-induced apoptosis in the immature brain is distinct from its effect in the mature brain. (61, 62) For example, hippocampal progenitor cells show nicotine-induced apoptosis only during early differentiation. (63) Furthermore, the delayed-onset changes that occur when nicotine is no longer present in the system indicate that nicotine changes the entire trajectory of brain development so that adverse effects can emerge later in life, after a period of apparent normality. This is particularly important for patterns of synaptic activity that display initial deficits in the early postnatal period, but tend to recover by juvenile stages, only to show a reemergence of hypoactivity in adolescence, (59, 64-66) at which point there is a persistent deficit in nAChR function. (67-70)

To characterize the involvement of nAChRs in regulating brain development during the third trimester human fetal period, studies examined the effects of nicotine exposure during the functionally-equivalent early postnatal period in rats and found altered thalamocortical maturation, resulting in subsequent impairment of cognitive behaviors. (67, 71, 72) The hippocampus and cerebellum, which are both late maturing structures, also exhibited unique regulation by nAChRs, (73-76) and consequently, postnatal nicotine exposure disrupted morphological assembly of these regions. (77, 78) Thus, animal studies indicate that nicotine exposure can negatively impact all stages of fetal brain development. Indeed, it is estimated that nicotine is responsible for as much as 36%-46% of the overall impact of tobacco smoke on the development of brain circuitry in animal models. (79)

It is important to note that the adverse effects of nicotine on brain development occur at exposure levels that do not compromise somatic growth. (64) Maternal cigarette smoking is strongly associated with intrauterine growth retardation, a well-recognized predictor of poor perinatal outcomes. (15) However, because nicotine targets the fetal brain, damage can be present, even when birth weight is normal. This reflects the specific actions of nicotine on nAChRs that modulate neuronal development, in contrast to non-specific fetal insults, which typically spare brain development at the expense of fetal somatic growth. (64, 80, 81)

The effects of isolated nicotine exposure on human fetal brain development have not been studied directly. However, maternal cigarette smoking has measurable effects on brain structure that are consistent with animal models that evaluated nicotine alone. Imaging studies found that fetuses exposed to maternal smoking had decreased transcerebellar and lateral ventricle diameter/width (ultrasound) and decreased overall brain volume (MRI) compared with unexposed fetuses, as well as smaller frontal lobe and cerebellar volumes in infancy. (82-84) Imaging studies of offspring in later life also found differences in the brains of exposed offspring, including reduced cerebral cortical gray matter, reduced subcortical gray matter volumes in the amygdala, thalamus, and pallidum, and reduced volume in the corpus callosum. (85-90) In a study of 6- to 8-year-old children prenatally exposed to maternal smoking, the authors found reduced brain volume, smaller cortical gray and white

matter volumes, and thinning of the superior frontal, superior parietal, lateral occipital, and precentral cortices compared with age- and gender-matched unexposed children.(91) Taken together, studies of tobacco exposure in human fetuses are in agreement with those of nicotine exposure in animals, and in particular, those which documented disruption of brain development independent of effects on fetal growth.(83, 89, 91) The structural alterations seen in human studies are paralleled by functional changes in the fetus. Studies using real-time fetal monitoring(92-95) found greater rates of maladaptive response to the non-stress test (a clinical index of fetal well-being)(96), including reduced heart rate variability, increased mouth and self-touch movements, and impaired recognition of maternal voice in fetuses of smokers compared with those of nonsmokers.(97-99)

2.3 Perinatal mortality and sudden infant death syndrome

Maternal smoking during pregnancy increases the risk of perinatal mortality (which includes both stillbirth and neonatal death) by 20-30%,(100) and of sudden infant death syndrome (SIDS) 2.4 to 3-fold.(101) Maternal smokeless tobacco use in pregnancy is associated with a 1.6 to 2.6-fold increase in stillbirth.(31, 33)

Maternal smoking is thought to increase perinatal mortality and SIDS risk in part through its effects on fetal and infant stress responses. Human parturition is associated with an extended period of hypoxia, and the fetus and newborn possess unique adaptive responses that maintain cardiovascular function during this period. These responses center around circulatory adjustments that ensure adequate perfusion of the brain and heart, and require autonomous secretion of catecholamines from the adrenal medulla (102), as well as a myocardium that is adapted to function in a low oxygen environment.(103, 104) Prenatal nicotine exposure leads to severe reduction or loss of the adrenomedullary component, along with a reduced cardiac response to adrenergic stimulation, resulting in brain injury or death during a hypoxic episode that would ordinarily not be harmful.(59, 60, 105) Although animal studies provide the primary evidence for this mechanism, the same deficiency in adrenomedullary function in response to hypoxia has been identified in the offspring of smokers at birth.(106) The loss of cardiovascular adaptation caused by maternal smoking affects the fetus during delivery, when hypoxic events can evoke stillbirth or birth asphyxia, as well as during infancy, when hypoxic events can result in SIDS.(107)

Additional contributions of maternal smoking to SIDS risk likely entail effects on central cardiorespiratory control and arousal. Maturation of sleep architecture and sleep during the first year of life includes changes in both respiratory and cardiovascular control.(108) Infants, especially those born preterm, are at increased risk for cardiorespiratory disturbances, apnea, and hypoxemia during sleep, events for which arousal is an important protective response. Failure of this response mechanism could contribute to SIDS risk.(109-111) Maternal smoking and smokeless tobacco use during pregnancy are associated with increased risk of neonatal apnea, while maternal smoking is also associated with a decreased arousal response.(109, 112-118) The administration of nicotine to pregnant ewes can evoke the same deficit in newborn lambs.(119) In addition, there is evidence that prenatal nicotine exposure damages brainstem circuits that are responsible for mounting

appropriate respiratory responses to neonatal hypoxia, which could contribute to additional SIDS risk.(120, 121)

2.4 Infant stress response

Maternal smoking during pregnancy in humans leads to alterations in behavior and stress responsiveness in newborns, in addition to the specific effects on hypoxic stress discussed above. Specifically, studies of the immediate neonatal period (postnatal days 1-5) revealed increased signs of abstinence/withdrawal, hypertonicity, irritability, and excitability in tobacco-exposed neonates, with a clear dose-response relationship to nicotine exposure. (122-126) Studies later in the neonatal period (10-30 days) found continued or emerging behavioral effects on self-regulation, attention, need for external soothing or handling, and arousal—all potentially portending longer-term effects on attention and regulation.(127-129) Several studies also found alterations in stress responses in exposed infants. For example, the stress hormone, cortisol, was increased in the cord blood of newborns of smoking mothers,(130-132) and infants aged 1-7 months showed altered cortisol response to stress. (133-135) There is extensive scientific literature on the long-term neurobehavioral deficits associated with early life exposure to prolonged stress and/or excessive glucocorticoid hormones (reviewed by Maccari et al, 2003).(136) Similarly, animal studies found evidence that prenatal nicotine exposure disrupts stress hormone regulation in offspring.(137-139) For example, in one study, adult male rats with gestational exposure to nicotine showed abnormal neuroendocrine responses to stress.(137)

2.5 Auditory processing

A number of studies have examined maternal smoking and infant auditory processing. (140-143) Healthy newborn infants of non-smoking mothers discriminated among a greater number of syllables whereas healthy newborns of smokers began the discrimination process at least 150 msec later and differentiated fewer stimuli.(144) Effects on auditory processing may persist beyond infancy; an increased risk of low-frequency hearing loss has been documented in adolescent offspring of women who smoked during pregnancy.(145) Animal research supports that nicotine adversely affects auditory processing.(71, 146) Exposure of rats to nicotine in the second postnatal week, corresponding to the third trimester of human fetal brain development,(147) disrupted the development of glutamate synapses in the auditory cortex, which has been associated with long-term deficits in auditory processing and learning.(67, 71)

2.6 Outcomes in childhood and adolescence

Numerous studies have addressed the long-term consequences of maternal smoking during pregnancy on offspring behavior. The most consistent associations are with externalizing and disruptive behaviors, such as conduct disorder (antisocial personality disorder in adults) and oppositional defiant disorder, from infancy through adulthood, as well as the precursors of these behaviors.(148, 149) However, a major limitation of traditional approaches to studies of prenatal tobacco exposure and behavioral outcomes has been the inability to fully control for potential confounding factors, particularly family environment and genetic factors.(150) More recently, high quality, prospective studies using multimethod exposure measurement and propensity score modeling have delineated a coherent pattern of disruptive behavior

associated with prenatal tobacco exposure, beginning in early childhood.(151, 152) For example, adoption studies provide support for an independent effect of maternal smoking during pregnancy on externalizing behaviors.(151) A recent sibling study that included detailed exposure data and careful control for family-level effects found modest, but statistically significant associations between tobacco exposure and conduct disorder symptoms and oppositional defiant disorder symptoms.(153) Both associations were similar in magnitude to contributions from genetics and family environment described in prior work. These studies add evidence supporting a role for prenatal tobacco exposure in increased risk for externalizing behaviors.

Associations have also been described between maternal smoking during pregnancy and offspring internalizing behaviors (anxiety and depression), attention deficit hyperactivity disorder (ADHD), and impairments in learning and memory, but are less consistent than for externalizing behaviors.(150, 154-176) These inconsistencies illustrate the difficulty in determining cause-and-effect relationships for different outcomes in diverse human populations with multiple confounders and risk factors for neurobehavioral deficits, especially when the associated behavior may not emerge for years after the injurious exposure.

Animal models have been used to assess the role of prenatal nicotine exposure on developmental and long-term behavioral outcomes. Reflex behaviors characterize the development of sensory and motor systems in the brain, and rodent studies suggest that prenatal nicotine exposure delays maturation of reflexes, including negative geotaxis and surface righting (measures of limb coordination and locomotor development), as well as causing long-lasting alterations in filtering auditory information. (146, 177-179) However, these findings are not entirely consistent; some studies found normal reflex development in exposed animals (reviewed by Sobrian and Holson 2011).(180) Activity levels have also been studied using rodent models, again with inconsistent results, perhaps reflecting differences in the developmental exposure period and the method of nicotine administration, or, in some cases, lack of sufficient statistical power in the experimental design.(180)

In contrast, there is greater consistency among animal studies examining the effects of prenatal nicotine exposure on cognitive development, suggestive of global impairments in learning and memory.(181-190) These effects appear to be dose dependent and sensitive to factors such as sex and timing of exposure. Research suggests that these deficits reflect effects on nAChR modulation of long-term potentiation in the hippocampus.(187) Adverse outcomes on affective behavior have also been identified, including learned helplessness, fear trace conditioning, and anhedonia.(191, 192) Combined gestational/neonatal exposure is associated with increased anxiety levels, poor adaptation in a new environment, and decreased novelty-seeking.(181, 193, 194)

2.7 Pulmonary outcomes

Maternal smoking during pregnancy has adverse effects outside the central nervous system, most notably on lung development, causing lifelong decreases in pulmonary function. (195-199) At birth, and prior to any significant postnatal exposure to tobacco smoke, infants born to smokers show decreased pulmonary function tests, with decreased respiratory flows

and respiratory compliance, and altered tidal breathing patterns. (198-200) These changes lead to increased risk in childhood of wheezing, hospitalization for respiratory infections, and asthma.(201-203) Studies of the effects of nicotine on lung development have been performed in mice, rats, sheep and monkeys with strikingly similar results between animals and humans.(204) In humans, the clearest, most consistently measured effect of maternal smoking during pregnancy on offspring respiratory health is decreased forced expiratory flow.(195-198) In both monkeys and mice, exposure to prenatal nicotine alone, at levels similar to that of smokers, causes similar decreases in forced expiratory flow.(205-207) A primary mediator of this effect appears to be the $\alpha 7$ nAChR, as the effect of nicotine was lost in $\alpha 7$ nAChR knockout mice.(205)

Studies on non-human primates point to the potential mechanisms of nicotine's actions on lung development. Treatment of pregnant rhesus monkeys with nicotine causes marked increases of levels of $\alpha 7$ nAChR in fibroblasts surrounding airways and blood vessels in the fetal monkey lung, and increases in collagen in a similar distribution.(208-210) Similar effects are seen in mice.(205) The increased collagen and decreased elastin caused by prenatal nicotine exposure likely underlies the decreases in lung compliance seen in the offspring of smokers. Prenatal nicotine exposure leads to thickening of walls surrounding airways and pulmonary vessels in animal models,(209, 210) a finding that has also been reported in the human offspring of smokers,(211, 212) along with similar increases in connective tissue and $\alpha 7$ expression.(212) In addition, consistent with the long term effects on offspring pulmonary function and increased risk of asthma associated with maternal smoking during pregnancy in humans, smoking during pregnancy causes long-lasting changes in DNA methylation in offspring(213) that are observed in fetal lung,(214) cord blood,(214) and which continue to be present in the blood of school-age children.(215) In rodent models, prenatal nicotine exposure causes similar DNA methylation changes, including changes in Runx1 methylation, which has been associated with increased risk of asthma,(216-219) Research by Rehan and colleagues supports that DNA methylation changes caused by in utero nicotine exposure may persist for multiple generations.(217, 218) Rodent models also suggest that prenatal tobacco exposure can cause decreased histone deacetylase activity in offspring lung, accompanied by changes in expression of the glucocorticoid receptor splice variant 1.7.(220) While the immediate human clinical impact of these findings are unclear, they suggest that epigenomic modifications in important inflammatory and pulmonary maturation pathways (i.e., glucocorticoid receptors), may result from *in utero* nicotine exposure. Whether this ultimately translates into increased risk of asthma and pulmonary atopic disease among offspring remains unknown.

3. Tobacco use and nicotine exposure during adolescence

3.1 Tobacco use during adolescence

Tobacco use among adolescents in the United States is changing rapidly. While the prevalence of cigarette smoking has steadily declined over the past decade(18, 221-223), the use of alternative tobacco products, including electronic cigarettes, has increased.(224) Conventional cigarettes were the most commonly used tobacco products by U.S. youth in 2013 (225), and many youth who used electronic cigarettes—more than a quarter million—

had never smoked combustible cigarettes (226). A subsequent survey in 2014 and 2015 found that past-month e-cigarette use has surpassed conventional cigarette use among middle and high school students.(227, 228) Several longitudinal studies have found that electronic cigarette use at baseline is associated with increased risk of future use of combustible tobacco products.(9, 10, 229, 230)

3.2 Brain development in adolescence

Concerns about nicotine toxicity do not end after birth or infancy. Brain development continues well into the third decade of life, and the adolescent and young adult brains differ from those of the fully mature adult, both physiologically and neurochemically. For example, adolescent synapses are more numerous and more “plastic,” or moldable by experience.(231-233) Hence, adolescents have superior learning and memory skills compared to adults, with synaptic formation and learning highly strengthened by stimulation from environmental experience.(234) This feature of adolescent brain development can have detrimental consequences when inappropriate stimulation is evoked by exposure to neuroactive chemicals. For example, addictive stimuli or drugs can activate and strengthen reward circuits to create an addicted state.(235) Adolescents and young adults are thus more vulnerable to addiction than adults.(223) In support of this, epidemiologic studies document that individuals who begin smoking as teens are more likely to become life-long smokers than those who start smoking in their 20’s or later.(236-238) Furthermore, adolescents experience symptoms of dependence at lower levels of nicotine exposure than adults.(239-241) Consequently, it is harder to reverse addiction originating in this stage compared with later in life.(242) Animal studies confirm the heightened response of adolescents to nicotine exposure.(243) Adolescent rodents self-administer nicotine more than adults and adolescent exposure leads to increased self-administration of nicotine (244) and other drugs in adulthood.(245)

The special vulnerability of the adolescent brain extends to areas involved in higher cognitive function, such as the prefrontal cortex where circuit formation continues into the 20s. During this extended maturational period, substantial neural remodeling occurs in a variety of pathways, including those governed by dopamine or acetylcholine. Dopamine is critical to reward function, and acetylcholine plays a central role in cognitive maturation, including executive function mediated by the prefrontal cortex.(246)

Functional magnetic resonance imaging (fMRI) has been used in numerous studies of adult smokers to examine the neural circuitry involved in nicotine craving and addiction,(247-255) but in fewer studies of adolescent smokers.(256-261) Peters et al. examined neural responses to anticipation of financial reward in adolescent smokers (age 14 years)(262) and found that they had smaller neural responses in the ventral striatum and midbrain compared to matched non-smoking controls. Moreover, the reduced response showed a clear-cut relationship with the frequency of smoking. These findings suggest that adolescent smokers display a hypo-responsivity to the anticipation of non-drug reward (i.e., financial reward) relative to non-smokers, and this hypo-responsivity becomes more severe with increased smoking. There is also evidence that adolescents who smoke 5 cigarettes per day display attenuated responses to other non-drug rewards, including pleasurable food images, relative to non-smokers, in

areas including the insula and inferior frontal region.(256) The implication of both these studies is that the use of extremely rewarding drugs, such as nicotine, may decrease the perception of the pleasure obtained from non-drug rewards. Furthermore, the fact that this was demonstrated in young- and light-smoking teens indicates that such changes in the brain occur in early phases of smoking.

3.3 Cognitive outcomes

Nicotine withdrawal produces transient cognitive impairment and negative affective states, while smoking relapse alleviates these symptoms (reviewed by Hall et al., 2015).(263) In addition, adult smokers show more rapid cognitive decline with age than nonsmokers, (264-268) although it is unclear whether the underlying mechanisms involve nicotine, products of combustion, or both.(15) The few studies that have been done in adolescents and young adults also suggest that cigarette smoking has adverse effects on cognition.(269-271) For example, one study found that current smokers aged 17-21 who smoked throughout their adolescence performed significantly worse than their nonsmoking counterparts on a variety of neurocognitive tasks, even after adjustment for educational attainment and family income. (271) In a separate study of adolescent daily smokers and nonsmokers who were similar in age, sex, and education, smokers showed impairments in accuracy of working memory performance, irrespective of recency of smoking.(269) Earlier age at onset of smoking was associated with more severe performance decrements, and smokers experienced depressed mood and further disruption of working memory and verbal memory during abstinence. Furthermore, male smokers initiated smoking at an earlier age than females and were more impaired during tests of selective and divided attention than female smokers and nonsmokers. Abstinent adolescent smokers have also been found to exhibit reductions in the efficiency of their working memory neurocircuitry.(270) In a study of adolescent smokers and non-smokers who were similar with respect to age, education, IQ, parental education, and symptoms of inattention, prenatal and adolescent exposure to tobacco smoke were both associated with increased fractional anisotropy in anterior cortical white matter.(258) Disruption of auditory corticofugal fibers may interfere with the ability of these fibers to modulate ascending auditory signals, leading to greater noise and reduced efficiency of neurocircuitry that supports auditory processing. In a study of young adult non-abstinent smokers and non-smokers age 18-29 years who were matched for age, education, income, and sex, smokers showed significant cognitive impairments in sustained attention, spatial working memory, and executive planning.(272) In a study of young adults age 18-35 years, the authors found prefrontal attentional network activity was reduced in smokers compared with non-smokers using fMRI, and the degree of diminished attentional network activity was correlated with the number of years participants had smoked.(273) Finally, cognitive deficits have also been associated with childhood and adolescent exposure to secondhand cigarette smoke.(274, 275)

The association between adolescent cigarette smoking and long-lasting deficits in cognition is especially troubling because several mental health disorders that include changes in cognition are also associated with higher rates of tobacco use.(276-283) For example, an elevated prevalence of cigarette smoking has been noted among individuals with schizophrenia, ADHD, depression, anxiety disorders, bipolar disorder, and others.(284, 285)

There is evidence to support a bidirectional relationship—attributes that predispose individuals to these conditions could also predispose them to tobacco use and nicotine use—and addiction could result in or exacerbate symptoms accompanying these disorders.(263, 286) Similar phenomena could occur in individuals with subclinical affective or cognitive disorders.(263)

Existing human studies of cognitive outcomes are mainly cross-sectional in nature, making it difficult to determine whether tobacco use results from premorbid cognitive problems or causes these problems. However, studies of laboratory rodents provide strong evidence that isolated nicotine exposure during adolescence produces long-lasting deficits in learning and cognitive processes.(182, 287-290) For example, adolescent nicotine exposure was associated with adult deficits in contextual fear conditioning, but not cued fear conditioning, in both rats and mice,(288) suggesting altered function in brain regions involved in contextual processing, such as the hippocampus. In support of altered hippocampal function, adolescent nicotine exposure was associated with reduced hippocampal CA1 dendritic length and apical dendritic branch complexity. (291) The effects on learning were not seen in adults similarly exposed to nicotine.(182) In addition, adult rats exposed to nicotine during adolescence had deficits in attention and displayed increased impulsivity.(292) These cognitive deficits may be related to long-lasting changes in cellular processes involved in synaptic plasticity, as adolescent nicotine exposure altered adult medial prefrontal cortical long-term potentiation of synaptic activity.(289)

Animal studies also provide evidence for long-lasting changes in mental health-related behaviors after adolescent nicotine exposure.(293-295) For example, adolescent nicotine exposure increased anxiety in adult rats,(296) decreased the sensitivity to natural rewards, and fostered depression-like behaviors.(295) Further, changes in anxiety related to adolescent nicotine exposure were associated with increased corticotropin-releasing factor, a neuropeptide involved in stress response initiation, in the hypothalamus and frontal cortex and increased neuropeptide Y, a neuropeptide that may play a protective role in responses to stress, in the hypothalamus and hippocampus.(297) Together, these findings raise serious concerns about the long-term impact of adolescent nicotine exposure on mental health through adverse effects on cognition, anxiety, impulsivity, depression, and drug reward and reinforcement.

3.4 Trajectory of tobacco and other substances use

There is evidence that nicotine exposure in adolescence affects the use of other substances. In the U.S. population, the use of tobacco often precedes the use of other drugs including marijuana, which in turn generally precedes the use of cocaine and other illicit substances for those who go on to use other drugs.(298-300) Although this pattern may reflect that tobacco is legal and easier to access than illicit substances, evidence from translational research in rodents supports a causal mechanism for the observed sequence of progression from tobacco to other drugs. Nicotine pretreatment in mice and rats enhances the subsequent response to cocaine, but the effect is unidirectional, as the reverse order (cocaine followed by nicotine) does not result in enhancement of the response to nicotine.(301-303) At the molecular level, nicotine exerts a priming effect by enhancing the ability of cocaine to

induce *FosB*, a key mediator of addiction.(304, 305) It does so by inhibiting histone deacetylation. The consequent enhancement of gene expression leads to an increase in the response to cocaine in reward-based areas. These results provide a biological basis and a molecular mechanism for nicotine as a gateway drug.

4. Synthesis and conclusions

Historically, many clinicians and scientists have considered exposure to nicotine alone to be low risk, especially for established smokers. However, for pregnant women and adolescents, a large body of scientific evidence challenges this concept. As detailed in this review, existing human and animal research provides sufficient evidence for researchers and public health officials to draw a number of conclusions regarding the adverse effects of nicotine on human development. These conclusions could serve as a foundation for public health policy, planning, and practice regarding electronic cigarettes and other non-combustible tobacco products.

Animal models of prenatal nicotine exposure have successfully recapitulated the neurodevelopmental and behavioral phenotypes associated with maternal cigarette smoking during pregnancy,(55-57, 64, 306) and these studies show that nicotine itself is a critical contributor to the harmful neurodevelopmental effects of tobacco smoke exposure.(307-310) Similarly, the combined results from animal and human studies of prenatal cigarette and nicotine exposure provide consistent evidence that fetal nicotine exposure adversely affects lung development *in utero*, in infancy, and in childhood.(204) It is likely that the use of nicotine-containing products by pregnant women, including electronic cigarettes, will have effects on pulmonary development that are similar to those observed in the offspring of cigarette smokers. While there is evidence of variability in nicotine delivery across devices and users,(311, 312) evidence suggests that some electronic cigarette products may deliver as much nicotine as conventional cigarettes.(313, 314) Because lung development *in utero* and in childhood contributes to life-long trajectories of lung function, the effects of prenatal exposure to nicotine could have negative effects on respiratory health in middle-aged and older adults, including increased risk of asthma and chronic obstructive pulmonary disease (COPD).(315-317) In addition, human and animal studies of prenatal tobacco and nicotine effects on cardiorespiratory function provide strong evidence that fetal nicotine exposure compromises the fetal and neonatal response to hypoxic stress, which could contribute to the pathophysiology underlying SIDS.

The integration of human and animal studies of behavioral and cognitive outcomes associated with nicotine exposure is complex, but also demonstrates areas of close alignment. Maternal cigarette smoking in humans and nicotine exposure in animals have been consistently associated with auditory processing deficits, which could affect language development and speech comprehension. Rigorous studies of prenatal tobacco exposure in humans using innovative approaches to address potential confounding from genetic and environmental factors have found associations with externalizing behavioral outcomes in offspring. Furthermore, animal studies of gestational nicotine exposure provide support for the underlying biological mechanisms that could explain deficits observed in humans,

notably nicotine's actions on nAChRs. nAChRs play unique roles in development, and exposure to nicotine, even at very low levels, disrupts those developmental processes.

Human and animal studies of adolescent exposure to cigarette smoking and nicotine also have areas of convergence. It is well established from human and animal research that adolescents are highly vulnerable to addiction to nicotine.(223) More recent animal studies demonstrate a "priming" effect of nicotine that increases vulnerability to addiction to other drugs. Studies of human adolescent smokers also find deficits in working memory, attention, and auditory processing, and adolescent nicotine exposure in rodents is associated with deficits in learning and in attention, as well as in increased impulsivity and anxiety. Prospective studies of child and adolescent drug exposure, such as the recently launched Adolescent Brain Cognitive Development Study,(318) could yield additional data from subjects exposed to non-combustible tobacco products, such as smokeless tobacco and electronic cigarettes, helping to quantify the effects of nicotine exposure on cognitive, behavioral, and mental health outcomes. Finally, nicotine withdrawal in adolescent tobacco users can cause impairments in cognition and has adverse effects on mood and attention. (269-271)

The evidence presented in this review has often been overlooked in discussions about the relative harms and risks of electronic cigarettes, perhaps in part because of the paucity of studies of isolated nicotine exposure in humans. Randomized trials of nicotine exposure in humans that could determine effects of nicotine on development are unethical, so researchers rely on observational studies of human smokers. Human smokers, however, are exposed not only to nicotine, but to hundreds of other toxic components generated by combustion, such as carbon monoxide, acetaldehyde, and polycyclic aromatic hydrocarbons. In addition, there are numerous methodological challenges inherent in studies of smokers, including residual confounding from socioeconomic, environmental, genetic and other factors. Although considerable progress has been made in overcoming these limitations, controlled animal experiments remain a critically important supplement to human studies in establishing the consequences of nicotine exposure. In fact, rodent models historically have served as the "gold standard" for evaluating developmental neurotoxicants,(64, 319) and regulatory decisions on product safety are routinely made using animal data. Of particular relevance to nicotine is the example of chlorpyrifos, an acetylcholinesterase inhibitor and widely-used organophosphate insecticide that leads to inappropriate overstimulation of cholinergic receptors similar to that caused by nicotine.(57)¹

Despite the strength of data in support of adverse effects of nicotine exposure during pregnancy and adolescence, important research gaps remain that, if addressed, could better characterize these effects. An improved understanding of how the timing of nicotine exposure during pregnancy affects fetal development could lead to more effective strategies to limit nicotine's effects, such as intensified efforts to promote cessation by a specific gestational age or prior to conception. Research could also expand our understanding of the

¹In 2002, chlorpyrifos was banned from residential use by the US Environmental Protection Agency based almost entirely on neurodevelopmental deficits demonstrated in rodent studies that were explicitly modeled after those conducted for nicotine.(57, 64, 320)

relative contributions of nicotine and products of combustion to effects on brain development and cognitive outcomes in adolescence. Indeed, several recent studies indicate that other tobacco smoke components amplify the adverse effects of nicotine, and that even the low levels of nicotine exposure associated with secondhand smoke are injurious to fetal brain development and cognitive function.(79, 321, 322)

Recently, important steps were taken that will help protect vulnerable populations from exposure to nicotine. The Child Nicotine Poisoning Prevention Act, which requires child-resistant containers for liquid nicotine e-cigarette cartridges, was signed into law in February 2016.(323) In May 2016, the U.S. Food and Drug Administration finalized a rule extending its authority to all tobacco products, including electronic cigarettes. Federal law will require health warnings on electronic cigarette packages and advertisements that read “WARNING: This product contains nicotine. Nicotine is an addictive chemical.” The law prohibits the sale of electronic cigarettes to individuals under the age of 18 years, the sale of electronic cigarettes in vending machines, and the distribution of free samples.(324) In the future, additional potentially effective strategies could include strong prohibitions on electronic cigarette marketing to reduce youth uptake, health warnings specific to pregnant women and adolescents, and protection from exposure to secondhand electronic cigarette aerosol. Measures could also include consideration of the impact of pricing on youth initiation and use; product addiction potential and youth appeal, including youth-oriented flavorings; accessibility of products through placement in retail venues; and social networking potential. In addition, policies related to the age of legal sale of electronic cigarettes and other nicotine-containing products could benefit if informed by our knowledge of the developmental stages during which humans are most vulnerable to the adverse effects of nicotine. Because the brain does not reach full maturity until the mid-20s,(325) restricting sales of electronic cigarettes and all tobacco products to individuals aged at least 21 years and older could have positive health benefits for adolescents and young adults. Finally, it is important for clinicians to deliver a clear message that nicotine adversely affects health by providing unequivocal advice to pregnant women and adolescents to avoid the use of all tobacco products, as well as exposure to both secondhand smoke and secondhand aerosol. If these measures are accompanied by intensification of established comprehensive tobacco control programs as recommended by CDC,(326) they would be expected to have an even greater impact.

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Highlights

- Electronic cigarettes are often promoted as a safer alternative to combusted cigarettes.
- Human and animal research supports that nicotine contributes to the adverse effects of gestational tobacco exposure on fetal development.
- Nicotine exposure during adolescence is associated with cognitive deficits.
- Measures to protect pregnant women and adolescents from nicotine exposure are warranted.