Nicotine and the Developing Human

Introduction

The rapid elimination of cigarettes and other combusted tobacco products in the U.S. would prevent tens of millions of tobacco-related deaths in the coming decades.[1] Strategies proposed to reduce the size of the tobacco epidemic include aggressively strengthening established comprehensive tobacco control programs, including advertising restrictions, mass media campaigns, health warnings, smoke-free policies, restricting youth access, and price increases.[1, 2] Ending death and disease caused by smoking would require implementing additional approaches.[1] The Surgeon General outlined in the 50th Anniversary Report the most plausible strategies for the U.S. in the coming decade, which included reducing the nicotine content of cigarettes to non-addictive levels, restricting sales at the state or municipal level of some or all combusted products, and reducing product toxicity and appeal through regulatory standards.[1] Some tobacco control advocates, stakeholders, and tobacco companies argue that the introduction of less harmful nicotine delivery devices, such as electronic cigarettes and other electronic nicotine delivery systems (ENDS), will greatly accelerate progress toward ending combustible cigarette use,[1] and that the public health community should enable and encourage substitution of the these products through low or no taxes to widen the price differential in favor of less harmful products,[3] tolerating public use,[4] and health authority endorsement.[4]

Electronic cigarettes and other ENDS are battery-operated devices that heat a liquid (usually glycerin or propylene glycol) to create an aerosol. The liquid usually contains nicotine, as well as flavors, additives, and varying amounts of contaminants.[5] In the U.S., the Food and Drug Administration (FDA) regulates cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco.[6] Electronic cigarettes are currently unregulated. Although the FDA issued a proposed deeming rule to regulate electronic cigarettes in April 2014, developing and implementing final federal regulations can take years.[7]

Electronic cigarettes are currently widely available, often less expensive than combusted cigarettes, sold legally to minors in many states,[8] and often contain fruit and candy flavorings such as “Snappin’ Apple,” “Cherry Crush,” and “Chocolate Treat.”[9, 10] Nicotine concentrations typically range from 6 to 24 mg/mL, but products purporting to contain up to 100 mg/mL can be purchased wholesale on the Internet.[11, 12] Warning labels and childproof packaging are often absent, even in products intended for consumer use. Six companies invested $60 million in electronic cigarette marketing in 2013 (twice that invested in 2012),[10] using many approaches formerly employed to market cigarettes but now banned, including TV advertisements, celebrity endorsement, sponsorship of sports events and music festivals, and cartoon advertisements.[9, 10, 13, 14] These marketing strategies are known to result in youth smoking initiation, and some, such as TV advertisements, have been banned for cigarettes for decades.[15] Also concerning are claims that electronic cigarettes and nicotine are safe and even beneficial, which now appear frequently in the media and on company websites.[16, 17, 18, 19, 20, 21] Not surprisingly, youth experimentation and recent use has increased dramatically in recent years.[22, 23] Wells Fargo analysts recently predicted that, based on past sales, the consumption of electronic cigarettes “could surpass consumption of conventional cigarettes within the next decade.”[24] Other marketing strategies that could appeal to youth are placement of products in easily accessible locations in stores,[10] and social networking and other technical capabilities not related to use of the product.[25, 26, 27]

Numerous issues related to the public health consequences of widespread availability and unrestricted marketing of electronic cigarettes have been debated, including effects on youth smoking initiation, quitting, dual use among established smokers, and relapse among former smokers.[28, 29] However, careful consideration of the potential

adverse health effects from nicotine itself is often absent from these debates. Because the health effects of combusted products are so devastating and medicinal nicotine products approved for smoking cessation pose far fewer health risks than smoking, the effects of nicotine itself are often regarded as being of minor importance. Further exploration of the potential unintended consequences of facilitating a transition from combusted to non-combusted products is warranted, and special consideration of the effects of nicotine exposure among vulnerable populations—including pregnant women and fetuses, children, and adolescents—is urgently needed. This paper synthesizes relevant literature regarding biological properties of nicotine and its effects during development, and presents potential measures for consideration to protect the health of these vulnerable populations.

Biological Properties of Nicotine

Nicotine is readily absorbed through the skin and lungs and is metabolized by the lungs, liver, and kidneys.[30] Nicotine exerts its physiologic effects by binding nicotinic acetyl choline receptors (nAChRs), which are expressed by both neuronal and non-neuronal cells throughout the body.[31] The cholinergic system in the central nervous system is associated with cognitive function, including memory, selective attention, and emotional processing.[31] Non-neuronal nAChRs are found in respiratory tract, endothelial, and immune cells, and the non-neuronal cholinergic system plays a critical role in numerous cell functions, including proliferation, differentiation, migration, and apoptosis (programmed cell death).[32, 33] Nicotine exposure during periods of developmental vulnerability can impair development of neurons and brain circuits, leading to changes in brain architecture, chemistry, and neurobehavioral function and may impair or dysregulate non-neuronal cellular function.[34]

Pregnant Women and Fetuses

An estimated 10% of pregnant women in the U.S. smoke cigarettes, exposing more than 400,000 fetuses annually to nicotine and other toxicants such as carbon monoxide.[1] Nicotine is a developmental toxicant and adversely affects pregnancy and infant outcomes.[1] Nicotine crosses the placenta and binds to nAChRs, which are widely expressed throughout the fetal nervous system.[35] NAChRs regulate fetal brain maturation, and expression of nAChRs is elevated during critical periods of development.[36] Animal models designed to simulate levels of human nicotine exposure, including non-human primate studies,[37] provide compelling evidence that exogenous nicotine has detrimental effects on neurodevelopment, resulting in cell damage, reduced cell number, impaired synaptic activity, and premature change from cell replication to differentiation and initiation of apoptosis.[38, 39, 40] Associations between maternal smokeless tobacco use and adverse outcomes provide additional evidence that the use of nicotine-containing products during pregnancy causes significant damage to fetal and neonatal well-being, even in the absence of combustion.[1] Specifically, studies of maternal smokeless tobacco use and pregnancy outcomes conducted in India, Sweden, and the U.S. have found relatively modest effects on birth weight but increased risk of preterm birth, stillbirth, and neonatal apnea comparable to the effects of cigarette smoking.[1, 41, 42, 43, 44, 45, 46] In addition, nicotine is thought to play a key role in the increased risk of sudden infant death syndrome (SIDS) in infants of mothers who smoke during pregnancy through its effects on cardiorespiratory responses.[1] An estimated 5.3%–7.7% of preterm births (a major cause of infant morbidity and mortality) and 23.2%–33.6% of SIDS deaths in the U.S. are attributed to maternal smoking.[47] Although the precise fraction of those attributable specifically to nicotine has not been precisely quantified, it is clear that prenatal nicotine exposure contributes substantially to adverse health outcomes in infants.

Fetal tobacco exposure has been associated with adverse neurocognitive outcomes, such as disruptive behavioral disorders and attention deficit hyperactivity disorder in humans.[1] Although causal mechanisms have not yet been established, these findings are supported by animal studies of nicotine.[48, 49, 50, 51, 52] Furthermore, rodent and primate studies found that the effects of maternal secondhand smoke exposure on developmental outcomes are comparable to effects seen with isolated nicotine, including effects on number of neurons, neuronal and synaptic

damage, and cognitive dysfunction.[53]

Effects of nicotine on the fetus are not limited to the nervous system. For example, exposure to prenatal tobacco smoke affects offspring lung development, including reduced respiratory compliance, forced expiratory flow, and tidal breathing ratio in infants and impaired lung function with reduced expiratory flow rates in school-aged children.[1] Primate studies[54, 55, 56, 57, 58, 59, 60, 61] indicate that nicotine plays an important role in the effects of maternal smoking on lung development; primates with in utero nicotine exposure have decreased lung size and volume, increased type I and type III collagen, decreased elastin in the lung parenchyma, increased alveolar volume, and increased airway wall area. In addition, epidemiologic and animal studies[62, 63, 64] suggest that nicotine exposure in utero can have multigenerational effects, adversely affecting lung development of both first- and second-generation offspring, likely through epigenetic mechanisms.

In general, women's awareness that smoking during pregnancy causes fetal harm is high, and cessation rates in preparation for or during pregnancy have been estimated to be as high as 40%.[65] However, a new emphasis on "harm reduction" by tobacco and electronic cigarette companies could diminish concerns about non-combusted tobacco use such as electronic cigarettes. It is currently unknown what percentage of pregnant women use electronic cigarettes, but if tobacco companies successfully convince women that these products are safe or minimally harmful, women of childbearing age who do not smoke could take up electronic cigarettes and pregnant women who smoke could switch to electronic cigarettes or use them to cut down on cigarette smoking, rather than quitting tobacco entirely. In addition, because half of pregnancies are unplanned[66] and because many women do not quit tobacco after they become pregnant,[67] the number of pregnancies affected by nicotine exposure will be highly dependent on the prevalence of smoking and electronic cigarette use among women of reproductive age. Recent national surveys indicate that female non-smokers and female smokers are more likely than their male counterparts to experiment with electronic cigarettes,[68, 69] and electronic cigarette use is increasing sharply among females, adults aged 25–44,[69] and high school students.[70, 71] If total tobacco use prevalence increases above its current level, the number of fetuses exposed to nicotine could increase. For electronic cigarettes to have a neutral or a beneficial effect on this vulnerable population, the health benefits of reduced prevalence of cigarette smoking must not be outweighed by adverse health effects from increased nicotine exposure due to higher prevalence of total tobacco use.

Because of the health risks associated with nicotine exposure during pregnancy, the FDA recommends that pregnant women should use nicotine-replacement therapy (NRT) products only with approval from their healthcare professional,[72] and the American College of Obstetricians and Gynecologists recommends consideration of NRT only if a woman fails behavioral interventions and after the woman and her provider weigh the potential harms and benefits.[73] Because electronic cigarettes are unproven as cessation aids, are unregulated, can contain nicotine in concentrations inconsistent with product labeling and additives that are potentially toxic, tolerating acceptance of electronic cigarette use among pregnant smokers as part of a broader public health strategy to reduce smoking puts this population at great risk.

Children

Electronic cigarettes pose numerous risks to children. Widespread advertising of electronic cigarettes on TV could easily normalize electronic cigarette use. Because the act of using electronic cigarettes can be indistinguishable from smoking, smoking cigarettes could be re-normalized for the first time since TV advertising was banned nearly 40 years ago. Parental electronic cigarette use could result in unintended direct health risks to offspring as well. Efforts to educate parents about the dangers to children from secondhand tobacco smoke have been largely successful and many adult smokers have smoke-free home and/or vehicle rules.[74, 75] However, if these adult smokers perceive electronic cigarettes to be safe and begin using them in their homes or vehicles, their children could experience increased exposure to nicotine, as well as to propylene glycol, glycerin, and other toxicants, through inhaled aerosols and surface deposits.[76] Studies of thirdhand tobacco smoke have demonstrated that smoke components, including

nicotine, are deposited and re-emitted from indoor surfaces over time even after tobacco sources have been extinguished, and can result in substantial nicotine exposure levels.[77, 78] Recent studies have demonstrated that nicotine from electronic cigarettes also deposits on indoor surfaces[79] and is absorbed by non-users.[80, 81] Thus, indoor surfaces in environments where electronic cigarette use occurs could create a reservoir of nicotine that could be ingested, absorbed transdermally, or inhaled by children (especially young children) long after electronic cigarette use.

Nicotine levels in infants and children exposed to electronic cigarette aerosol and surface deposits have not yet been studied and the health effects of nicotine in this age group are uncertain. However, studies of tobacco exposure from secondhand smoke in children raise serious concerns.[82] Past experience with environmental toxicants such as lead, mercury, and organophosphates has taught the public health community that exposure during vulnerable periods of brain development can have serious, long-term health consequences. Some substances, such as lead, cause irreversible damage at exposure levels much lower than initially realized, resulting in adverse outcomes such as decreased IQ and academic achievement and behavioral problems.[83, 84] Similarly, cognitive test scores in children aged 6–16 years who were exposed to secondhand tobacco smoke were inversely associated with serum cotinine levels, and the largest decrements were seen at low cotinine levels; findings were unchanged after restriction to children aged 6–11 years.[82] A subsequent systematic review[85] of studies of secondhand smoke and cognitive outcomes in children and adolescents found that 12 of 15 studies showed significant inverse associations; outcomes included poor academic achievement and neurocognitive performance, as well as neurodevelopmental delay. Animal research supports hypothesis that nicotine exposure after the prenatal period has persistent damaging effects on the brain, including cognitive deficits.[53, 86, 87] These data justify an extremely cautious approach toward children's exposure to developmental toxicants such as nicotine. Clean air laws and smoke-free rules have been a critical component of reducing children's exposure to tobacco smoke. Continued efforts to minimize children's exposure to nicotine are needed to help protect children's health and development.

Finally, in large enough doses, nicotine is toxic, and can cause nausea, vomiting, diarrhea, salivation, bradycardia, and even seizures and respiratory depression.[1] Some electronic cigarette cartridges contain enough nicotine to be fatal if ingested by a child.[88] Calls to poison control centers for electronic cigarette exposures are increasing dramatically and now make up more than 40% of all tobacco-related calls, and electronic cigarette exposure calls are more likely to include reports of an adverse health effect than cigarette exposure calls, including vomiting, nausea, and eye irritation.[89]

Adolescents

Electronic cigarette use increased sharply among youths between 2011 and 2013.[22, 23] According to a recent national survey, more than a quarter of a million youths who had never smoked cigarettes had used electronic cigarettes and nearly half expressed intention to use conventional cigarettes in the future, compared with 22% of those who had never used electronic cigarettes.[69, 90] The effects of current aggressive marketing tactics for electronic cigarettes on future youth initiation are unknown, but decades of experience with cigarette marketing would suggest increased use in youths is likely.

Trends in electronic cigarette use among youths are particularly worrisome because human brain development, including areas involved in higher cognitive function such as the prefrontal cortex, continues throughout adolescence and into the 20s.[91, 92, 93] During this extended period of maturation, substantial neural remodeling occurs and includes synaptic pruning and changes in dopaminergic input.[94, 95] The cholinergic system, which matures in adolescence, plays a central role in cognitive maturation, including executive function mediated by the prefrontal cortex.[91] Smoking cigarettes during adolescence has been associated with lasting cognitive and behavioral impairments, including effects on working memory and attention and reduced prefrontal cortex activation,[96, 97] although accurate quantification of the effects in humans is difficult because of potential residual confounding.[92]

Animal studies, however, provide compelling supplemental evidence that nicotine exposure during adolescence causes both long-term structural and functional changes in the brain.[40] These effects include upregulation of nAChRs in the midbrain, cerebral cortex, and hippocampus; reduced cell number and size in the cerebral cortex, midbrain, and hippocampus[98]; and changes in prefrontal cortex neurons such as increased dendritic length and spine density.[99]

Another significant concern regarding adolescent experimentation and use of electronic cigarettes is that it may lead to future use of combustible tobacco products, or aid in the consolidation of smoking in adolescents already experimenting with smoking. Although definitive proof of this relationship could require decade-long prospective studies, recent trends in Poland reinforce this concern. Surveys of 15–19-year-olds conducted in 2010–2011 and 2012–2013 found marked increases in electronic cigarette use, dual use of electronic cigarette and smoked tobacco, and overall smoking prevalence, suggesting that in Poland, electronic cigarettes are not displacing conventional cigarettes, but that they could be contributing to smoking initiation.[100]

The observation that adolescent smokers are more likely than adult smokers to become dependent on nicotine is well described and data support that nicotine has stronger rewarding effects in adolescents than adults.[101] The phenomenon has been replicated in animal models, and age-dependent mesolimbic dopaminergic mechanisms may be involved.[102, 103] Epidemiologic and animal data support that nicotine acts as a gateway to addiction to other substances such as cocaine, and an understanding of potential underlying molecular mechanisms is beginning to unfold.[104] Ethical issues make it unlikely that there will ever be definitive human studies that fully quantify the effects of nicotine on the developing brain. However, existing animal and human research consistently supports the conclusion that nicotine exposure during adolescence affects brain development, and the evidence is currently sufficient to warrant extreme caution regarding exposure of adolescents to exogenous nicotine. Because of the unique vulnerability of adolescents to developing nicotine addiction, strictly enforced measures to limit youth access to nicotine-containing products are an especially critical component of public health efforts to reduce and prevent tobacco use in this age group.[1]

Conclusions

If electronic cigarettes are to play a beneficial role in strategies to end the tobacco epidemic without causing unintended harm, steps to protect the health of millions of pregnant women, infants, children, and adolescents are needed. Because nicotine exposure during vulnerable periods of brain and lung development can have lasting detrimental effects, regulatory and policy measures for electronic cigarettes or nicotine-containing products are imperative. Among these are (1) strong prohibitions on marketing that result in youth uptake; (2) enforceable youth access laws identical or similar to those in effect for other tobacco products; (3) appropriate health warnings for all vulnerable populations; (4) packaging to prevent accidental poisonings; and (5) protection from exposure to secondhand electronic cigarette aerosol. Measures should also include consideration of the impact of pricing on youth initiation and use, and product addiction potential and youth appeal, including youth-oriented flavorings, accessibility of products through placement in retail venues, and social networking potential. Product regulations should address nicotine concentration and total amount of nicotine per vial, as well as quality control. The age of legal sale of electronic cigarettes and other nicotine-containing products should reflect the developmental stages during which adolescents/young adults are most vulnerable to the adverse effects of nicotine. Because the brain does not reach full maturity until the 20s,[93] restricting sales of electronic cigarettes and all tobacco products to individuals aged at least 21 years and older could provide positive health benefits to both youth and young adults. These steps should be concurrent with the intensification of established comprehensive tobacco control programs and the introduction of the novel strategies previously discussed.

In conclusion, as stated in the 2014 Surgeon General's Report, efforts to drastically reduce the number of cigarette smokers to improve health in the U.S. should be intensified. It is most likely that impact of electronic cigarettes on the population's health will be beneficial if accessibility, promotion, and use of combusted products are rapidly reduced.[1] There is no evidence that unfettered access to electronic cigarettes or other non-combusted products and aggressive

marketing that appeals to youth are necessary components of a strategy to reduce combusted product use. In the current, unregulated environment, electronic cigarette marketing practices could impede progress toward reducing combusted tobacco use if they glamorize and re-normalize cigarette smoking, lead to regular use of nicotine or use of cigarettes in youth or adult non-smokers, delay quitting or reduce quit rates among smokers, facilitate long-term dual use of combusted products and electronic cigarettes, discourage smokers from using proven cessation methods, or increase relapse in former smokers. In addition, in the absence of appropriate restrictions, millions of youth could become addicted to nicotine and many more pregnant women, children, and adolescents unnecessarily exposed. Regulatory and public health policies that maximize cessation of combusted products while protecting vulnerable populations from exposure to electronic cigarettes are urgently needed.