Neuroscience and Biobehavioral Reviews 72 (2017) 176–189

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

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

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ARTICLE INFO

Article history:
Received 28 September 2016
Received in revised form
18 November 2016
Accepted 19 November 2016
Available online 24 November 2016

Keywords:
Nicotine
Electronic nicotine delivery systems
Priority/special populations

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.

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☆ All authors participated in an expert meeting, Developmental Effects of Nicotine and Implications for Emerging Tobacco Products, sponsored by the Centers for Disease Control and Prevention and the National Cancer Institute, National Institutes of Health. They are listed alphabetically.

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http://dx.doi.org/10.1016/j.neubiorev.2016.11.013
0149-7634/Published by Elsevier Ltd.

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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 (Aguinaga Bialous and Peeters, 2012; Newswire, 2016; Kostygina et al., 2016). 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 (Grana et al., 2014; Singh et al., 2016; King et al., 2015). However, their arrival has also engendered debate in the public health community (Etter, 2013; Chapman, 2013). 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 (Grana et al., 2014; Primack et al., 2015; Leventhal et al., 2015). 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 (Wagener et al., 2012).

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 (Fagerstrom and Bridgman, 2014). 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 (Piano et al., 2010; Boffetta and Straif, 2009; U.S. Department of Health and Human Services, 2014; Boffetta et al., 2005). However, this assertion has important limitations. Electronic cigarette use is not limited to adults or to conventional cigarette smokers (Collaco et al., 2015). Use has increased dramatically in high school and middle school students since 2011, (Singh et al., 2016) and in 2014, twice as many youth used electronic cigarettes alone as in combination with cigarettes (Lee et al., 2015). 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 (Ojeda et al., 2016; Shariati Kohbanani et al., 2016; Chen et al., 2015; Serobyan et al., 2005; Somm, 2014), 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 (Sussan et al., 2015; Lerner et al., 2015; Garcia-Arcos et al., 2016; Ponzoni et al., 2015).

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 (U.S. Department of Health