HHS Public Access

Author manuscript

J Addict Med. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

J Addict Med. 2020 December ; 14(6): 443–445. doi:10.1097/ADM.0000000000000627.

Historical Perspective of Proactive and Reactive Regulations of e-Cigarettes to Combat Nicotine Addiction.

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Abstract

Cigarettes and electronic cigarettes (e-cigarettes) are major sources of exposure to nicotine, an addictive chemical. Although these products are being regulated by the Food and Drug Administration (FDA) under the Tobacco Control Act, specifications about the nicotine content in these products have not been established yet. In e-cigarettes, nicotine concentration ranges from 0 to >50mg/mL, and the recent e-cigarette devices provide control to change nicotine flux for higher nicotine delivery. Due to the lack of robust regulations in manufacturing, distribution and marketing, e-cigarettes have already infiltrated the market with youth appealing flavors and devices. As a result, the country is facing a youth epidemic of e-cigarettes. The unregulated nicotine levels in both cigarettes and e-cigarettes can lead to repeated and overexposure of nicotine to youth which can lead to the addiction and detrimental effects on their cognitive functions. Over the past decade, the corrective measures being taken by the FDA for cigarette and e-cigarette regulations also should focus on nicotine exposure levels. Before it is too late to prevent youth from lifetime addiction to nicotine, it is important to address the issues of nicotine concentration, nicotine flux and the e-cigarette device regulations while offering adults with smoking disorder less harmful alternatives to cigarettes.

Keywords

nicotine; electronic cigarette; addiction; nicotine flux

There are 480,000 deaths per year in the United States (US) alone due to use of tobacco products and more than 34 million Americans still smoke cigarettes[1]. Additionally, cigarettes have become the leading cause of lung cancer in the US[2]. Taking into consideration this severity of addiction, the Tobacco Control Act (TCA) was signed on June 22, 2009 to protect the public and create a healthier life for Americans[3]. The TCA gives the FDA authority to regulate manufacturing, distribution and marketing of tobacco products. Since then, the FDA has taken many regulatory steps such as mandatory warnings on tobacco products, specifications about the warning labels and a ban on certain kid-appealing cigarette flavors.

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In addition to cigarettes, the country is also facing a youth epidemic of electronic cigarette (e-cigarettes) use since 2018. These e-cigarettes were introduced to the US market around 2007. In 2009, the FDA prohibited import of these products under Food, Drug and Cosmetic Act (FDCA) by classifying e-cigarettes as drug delivery devices. The FDA contended that these products appeared to be drug-device combination products intended to prevent or alleviate nicotine withdrawal symptoms. Consequently, e-cigarette companies challenged the FDA's decision in court. In Dec 2010, the court ruled that the FDA cannot regulate e-cigarettes as drug devices but only as tobacco products and cannot prevent import or sale of these products. After six years, in May 2016, the FDA issued the final deeming regulations, effective from Aug 8, 2016, to regulate all tobacco products which also include electronic nicotine delivery systems (ENDS) such as e-cigarettes. During the six years of an unregulated market of e-cigarettes, a variety of flavors and e-cigarette devices were introduced in to the market. As per the 2014 data, there were 7764 e-liquid flavors available in the market[4]. After the onset of regulations in Aug 2016, the FDA started taking regulatory steps such as a minimum age requirement (18), warning label requirements, mandatory submissions of premarket tobacco product applications, conducting inspections and issuing warning letters to retailers and e-liquid manufacturers for non-compliance. Nevertheless, the pace at which the regulations were being set was lagging behind the increase in popularity of e-cigarettes in the US. As a result, since Dec 2018, the country is facing a youth epidemic of e-cigarettes[5] and there are multiple cases of lung illnesses related to vaping due to adulterated market of e-liquids[6].

When the FDA's decision to include e-cigarettes as drug delivery devices was challenged in 2010, e-cigarette manufacturers confirmed that their products were targeted at people who smoked for enjoyment and not as a smoking cessation tool. However, e-cigarettes were publicized as safer alternatives to smoking cigarettes[7]. This description is applicable to Modified Risk Tobacco Products (MRTP) and such products must be approved by the FDA before marketing. As of now, none of the e-cigarettes have been approved by the FDA as MRTP. Nevertheless, JUUL Labs Inc. conducted presentations in high schools where their products were touted as safer alternatives to nicotine addiction due to cigarettes. As a non-compliance issue, the FDA sent a warning letter (2019) to JUUL Labs for marketing JUUL products as MRTP without FDA's approval[7].

In spite of all the corrective measures being taken, the FDA has not set a limit on the nicotine concentration in both cigarettes and e-cigarettes[8]. The total nicotine content in cigarettes ranges from 16.2 mg to 26.2 mg per gram of tobacco[9] and the nicotine delivery by smoking a cigarette is around 1–2 mg per cigarette[10]. On the other hand, nicotine concentration in e-liquids ranges from 0 to > 50mg/mL[11]. Additionally, the current 3rd and 4th generation box mod e-cigarette devices allow control over power settings which can change the nicotine flux. As defined by Shihadeh et al., nicotine flux is the nicotine emitted per puff second by a given e-cigarette design under given use conditions[12]. By changing the operating conditions of e-cigarette device such as high wattage and temperature, a large amount of e-liquid can be vaporized. Thus, even lower nicotine concentration e-liquids can deliver a high nicotine dose[12]. This concept of nicotine flux is more applicable to the 3rd or 4th generation box mod e-cigarettes. While the JUUL device, which is more like a first-generation e-cigarette, has a potential of higher nicotine delivery to a person using it. Recent

studies have shown that JUUL device causes faster and a higher plasma nicotine concentration as compared to other devices with similar nicotine concentration[13].

Similar to the European Commission, the FDA could have taken proactive measures in addressing at least nicotine concentration in regulating e-cigarettes. The Tobacco Product Directive (TPD), which started on 19th May, 2014, clearly specifies the maximum nicotine concentration (20mg/mL) allowed in e-liquids. Additionally, the TPD has well established regulations in terms of warning signs, marketing and promoting of e-cigarette products[14]. As a result, the usefulness of e-cigarettes as a smoking cessation tool is well implemented in the European Union (EU) countries such as UK[15]. In contrast, due to the lack of such directive or regulations, e-cigarettes with unregulated nicotine content and flavors were promoted and marketed in the US without restrictions, which may have contributed to a steady rise (>15%) in e-cigarette use among middle and high school students from 2011–2015. There was a small decline for approximately 1 year, but then a sharp surge post 2017 after introduction of JUUL in to the market[16].

As a regulating agency, the FDA holds an enormous responsibility to protect the public health. The recent acting FDA commissioner has admitted the delay in e-cigarette regulations[17] and yet some questions must be pondered upon while establishing robust regulations: 1) What if the nicotine concentration were limited and regulated (even a decade ago), would the FDA have curtailed the addiction to cigarettes and youth epidemic of e-cigarettes? 2) What if e-cigarettes were part of the initial Tobacco Control Act? 3) What if the e-cigarette devices were regulated under FDCA, and 4) Would the FDA have considered nicotine flux as important criteria for e-cigarette device regulations?

While it is not too late to prevent youth from lifetime addiction to nicotine, it is of utmost importance to address the concern of nicotine concentration in cigarettes and e-cigarettes.

Although the FDA has started the process to reduce nicotine levels in cigarettes[18], it has not yet specified such plan for e-cigarettes. In case of e-cigarettes, nicotine levels, nicotine form as well as nicotine flux play an important role in nicotine delivery to a person using e-cigarettes and all the three factors should be considered for regulations. Considering the popularity of the JUUL products which covers more than 70% market of e-cigarettes and the flux variabilities provided by 3rd and 4th gen e-cigarettes, it is important to put a cap on maximum nicotine concentration in all e-liquids.

Additionally, based on the recent clinical studies[19,13] plasma nicotine concentration-time profiles should be considered for regulating the concentrations of different forms of nicotine (salt vs free base). For example, PAX Labs studies claim that C_{max} of 2% nicotine benzoate is about 3 times higher than the equivalent free base nicotine but similar to that of cigarette[19]. If the e-cigarettes are truly to be used as safer alternatives (MRTPs) or quit agents for smoking, it is sensible to limit their nicotine exposure equal to or lower than that of cigarette. Therefore, it can be argued that the concentration of nicotine salt in JUUL or similar products should be limited to 2%. Subsequently, the variation between nicotine flux from different devices should be studied considering the battery power variables. The maximum limit for nicotine flux should be established by limiting the battery power outputs.

As of now, the loopholes to such regulations may include puffing behavior of a person who can perform deep and frequent inhalation to get higher nicotine exposure. However, it can be argued that addiction potential even in such cases would be substantially lower under regulated nicotine concentrations. Moreover, under a more regulated market, e-cigarettes can serve as a less harmful alternatives or cessation devices to quit cigarettes.

The response is critical to these issues of nicotine exposure yet offering adults a less harmful alternative to tobacco products. In addition to the FDA approved Nicotine Replacement Therapies (NRTs) and MRTPs such as Snus by Swedish Match USA, Inc. and IQOS by Phillip Morris International (under review), e-cigarettes can be a potential MRTP under proper regulations. Thus, it is in the interest of the public health to consider regulations of nicotine concentration, nicotine flux, nicotine form(s), e-cigarette devices and offering more alternative MRTPs to the public to fight nicotine addiction.

Acknowledgments

Conflicts of Interest and Source of Funding: The authors declare no conflicts of interest. This work was supported by the National Institute on Drug Abuse of the National Institutes of Health [P30DA033934-05S1]. The authors would also like to acknowledge the Virginia Youth Tobacco Projects Small Grants Program for research funding. All authors contributed significantly, and all authors have read and approved the final manuscript. The content is solely the responsibility of the authors and does not necessarily represent the views of the NIH or the FDA.

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