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Clearing the Haze: What Do We Still Need to Learn about Electronic Nicotine Delivery Systems?

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ABSTRACT

Electronic nicotine delivery systems (ENDS; i.e., electronic cigarettes, e-cigarettes, vaping devices, vape pens) were introduced to the U.S. market in 2007 as a potential harm reduction alternative for people who smoked combustible cigarettes. Since that time, ENDS popularity grew very quickly, particularly among individuals who smoke cigarettes. However, young people and never smokers also started using ENDS, cohorts for whom these products were not intended. There are now a broad range of devices and e-liquid constituents. ENDS devices vary considerably in their design and generation of potentially toxic chemicals, with higher power devices likely much more hazardous than lower power devices. This landscape may further change after September 9, 2020, when all ENDS manufacturers are required to submit a premarket tobacco product application to the FDA to obtain authorization for marketing. Research has not kept pace with this rapidly changing technology and important questions remain regarding the relative benefits versus risks of ENDS. In light of these challenges, we propose key ENDS research priorities to address these gaps.

Introduction

Electronic nicotine delivery systems (ENDS), also referred to as electronic cigarettes, e-cigarettes, vaping devices, or vape pens, are battery-operated devices that heat and aerosolize a liquid solution that may contain nicotine. ENDS were introduced to the United States in 2007 as a potential harm reduction option for individuals who smoke cigarettes (1). Indeed, some evidence supports ENDS for smoking cessation and tobacco-related harm reduction (2). Since their introduction, however, controversies over the public health impact of ENDS have shifted the focus to ENDS away from combustible cigarettes, the most harmful tobacco products. These controversies included the uptake of ENDS among youth and a recently discovered epidemic of e-cigarette, or vaping, product use–associated lung injury (EVALI).

Between 2011 and 2014, ENDS use increased by 900% among U.S. middle and high school students (3) and ENDS have been the most commonly used tobacco product among U.S. youth since 2014 (4). Several factors contributed to ENDS use among young people. ENDS were easy for youth to obtain (1). ENDS are available in many flavors that appeal to youth (e.g., candy); most youths report flavor as a key reason for trying these products (4). The ENDS industry aggressively marketed products to youth using attractive lifestyle claims and media outlets that youth frequent (4). New technology in 2015, specifically pod mod e-cigarettes that resemble USB flash drives, also made it easier to use and conceal use from others (1).

Besides nicotine, vaping is a drug delivery system for other substances including THC (5). THC vaping, however, was recently linked to an outbreak of e-cigarette, or vaping, product use–associated lung injury (EVALI) in the United States (1), which, as of February 18, 2020, resulted in 2,739 hospitalized cases and 68 deaths. The preponderance of evidence indicates that EVALI is linked to THC vaping. It is still unclear whether any cases were caused by use of only nicotine e-liquids. Nevertheless, EVALI raised public concerns about vaping. A survey of patients in the United States during the EVALI outbreak found that most patients did not perceive ENDS to be safe; roughly 55% believed that ENDS were less safe than cigarettes (6). Likewise, a recent U.K. report of adult smokers suggests that U.S. EVALI cases impacted smokers' perceptions of ENDS' safety (7). The proportion who reported that ENDS use was safer than smoking declined from 45% in 2014 to 34% in 2019. There are important differences between the devices and solvents used to vape nicotine versus THC (8). THC and nicotine vaping need to be clearly distinguished with respect to adverse health effects.

Despite these controversies, ENDS may still play a role in reducing the substantial morbidity and mortality attributed to combustible cigarette smoking. There is evidence that ENDS alone or in combination with nicotine replacement therapy may promote smoking cessation or reductions in smoking (9–11). Complete switching to ENDS from smoking is also associated with significant reductions in exposure to carcinogens and toxicants. Yet, important research gaps remain regarding the long-term health effects of chronic ENDS

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use, the potential long-term harm reduction benefit of switching to ENDS from smoking, whether ENDS will increase or decrease future smokers and smoking-related deaths, and if there are differences in ENDS use that that may exacerbate smoking-related health disparities. In this commentary, we outline a research agenda to address these gaps.

Current Combustible Cigarette Smoking in the United States

Through advances in tobacco control and prevention, cigarette smoking prevalence in the United States has declined dramatically from approximately 42% 50 years ago to 14% today (1). Consequently, mortality rates from smoking-related diseases including lung cancer and heart disease have declined (1). Nevertheless, cigarette smoking remains the leading preventable cause of death in the United States, contributing to 480,000 deaths annually, and smoking rates remain disproportionately high and relatively unchanged among vulnerable populations of smokers (1). Smoking rates are higher among individuals of lower socioeconomic status, who are members of marginalized populations, and who experience serious psychiatric distress (1). Smoking prevalence is also higher among individuals with some medical conditions such as chronic obstructive pulmonary disease (COPD) and HIV and remains common among individuals with other conditions (e.g., cancer, cardiovascular disease) despite the substantial harm of continued smoking (1).

An interesting question is whether the widespread availability of ENDS will reduce future smokers and smoking-related morbidity and mortality. Smoking prevalence has been declining every year since ENDS were introduced and has reached an all-time low, including among youth (12). Thus, it is possible that ENDS may keep young people, who would otherwise try smoking, away from cigarettes, resulting in fewer cigarette smokers in the future. Alternatively, ENDS may introduce new public health concerns; young people who would have never smoked cigarettes may initiate ENDS use and/or ENDS use may increase risk of becoming a smoker. There is some evidence that ENDS use among young people predicts future cigarette smoking initiation (13, 14). Conversely, the findings from simulation studies suggest that replacing all or most cigarette smoking in the United States with ENDS could yield substantial public health gains even under more pessimistic assumptions related to ENDS health effects, youth initiation, and long-term use among adult smokers who might have otherwise quit nicotine/tobacco use (15).

ENDS Use and Health Outcomes

Research on ENDS use and health is complicated by several factors. ENDS devices vary considerably in their design and generation of potentially toxic chemicals. They are on a continuum from likely more hazardous, high-power devices such as mods to likely less hazardous, low-power devices like pods. It is difficult to generalize about the effects of ENDS on health outcomes without documenting what devices are being used. New products are also frequently introduced. Epidemiologic data suggest that there may be potential associations between ENDS and adverse health outcomes (16), but causation cannot be concluded from cross-sectional studies. To establish causality, temporal data are necessary regarding the onset of cigarette smoking, vaping, and health outcomes. Such high-quality, longitudinal studies to establish causation between ENDS use and health are lacking at this time. The next best evidence comes from animal and human laboratory studies in which ENDS are administered under controlled conditions. It can be difficult, however, to extrapolate some of these findings. Moreover, human laboratory studies are typically limited to current and former smokers, potentially due to ethical concerns about giving ENDS to never smokers (17), which limits our understanding of ENDS health effects.

The most studied health outcomes of ENDS exposure include respiratory and cardiovascular diseases and cancer. In 2018, the National Academy of Sciences issued a report on the health effects of ENDS (2). On the basis of the available evidence at the time, the report established that there is: (i) conclusive evidence that ENDS contain and emit many potentially toxic substances, but substantial evidence that this toxin exposure is significantly lower compared with combustible cigarettes; (ii) substantial evidence that heart rate increases shortly following nicotine intake with ENDS and that ENDS aerosols/aerosol components can induce acute endothelial dysfunction, promote oxidative stress, and are capable of causing DNA damage and mutagenesis, but insufficient evidence to draw conclusions about long-term health effects of ENDS use.

Since this report, there are new data on ENDS use and clinical and subclinical disease markers. Recent surveillance surveys of adults demonstrated significant relations between ENDS use and chronic respiratory disease. In one study, ENDS use was significantly associated with COPD and asthma, independent of smoking, demographic, and physical covariates (18). The risk for asthma was similar for smoking, ENDS, and dual use, but dual use was associated with the greatest risk for COPD. This study is the first to show an independent association between ENDS use and COPD; prior studies have demonstrated links with asthma. A second study found that current ENDS users who were ex-smokers or never smokers had significantly lower associations with self-reported COPD diagnosis compared with current smokers (19).

Research limitations should be noted. Because of the cross-sectional nature of both studies, a causal link between COPD and ENDS use cannot be established. ENDS use may have contributed to symptom development, maintenance, or progression, but it is also possible that individuals with respiratory disease may have started vaping to alleviate symptoms. Both studies measured respiratory health by self-report and lacked detailed measures of smoking and vaping history including duration and quantity. Longitudinal studies with

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more comprehensive assessments of behavior and respiratory health are crucial for determining if ENDS use is related to the onset or progression of respiratory disease and whether there is a health benefit of switching to ENDS for individuals with respiratory disease.

ENDS for Smoking Cessation/Harm Reduction among Smokers

Some smokers report using ENDS for cessation (20) and this strategy may be effective. A survey of current and former cigarette smokers found that 46.8% of respondents had tried ENDS (21). The prevalence of established use was low at 3.8%, but greater for former smokers than current smokers. Large U.S. population surveys have found significant cross-sectional associations between daily ENDS use and smoking cessation (22, 23) and significant prospective associations between daily ENDS use and future odds of smoking cessation (24). These relations, however, were only observed for daily ENDS users not infrequent ENDS users. None of these surveys assessed participants' reasons for ENDS use, so it is not clear whether the association between daily ENDS use and smoking cessation is due to differences in the reason for ENDS use among more frequent versus less frequent users. Future studies should assess reasons for ENDS use to better characterize these associations.

Controlled studies of ENDS for smoking cessation are limited but provide some support for this approach. A randomized, controlled trial in the United Kingdom provided smokers with either nicotine replacement therapy (NRT), for up to 3 months, or an e-cigarette starter pack with a recommendation to purchase further e-liquids of their choice (9). At one year, the e-cigarette group was significantly more likely to be abstinent than the NRT group (i.e., 18% vs. 9.9%). Importantly, participants in the e-cigarette group were more likely to report using their assigned product at follow-up compared with the NRT group (80% vs. 9%). Another trial in New Zealand evaluated nicotine patches in combination with e-cigarettes for smoking cessation (11). Participants ($n = 1{,}124$) received: (i) nicotine patch only; (ii) nicotine patch + nicotine e-cigarette; or (iii) nicotine patch + nicotine-free e-cigarette for 14 weeks. The combined nicotine patch + nicotine e-cigarette group had higher smoking quit rates at 6 months than the nicotine patch + nicotine-free e-cigarette group (i.e., 7% vs. 4%). A web-based trial in the United States tested the effectiveness of different smoking cessation interventions for employees including free pharmacotherapy, free e-cigarettes, and financial incentives for abstinence (25). All of the interventions resulted in low rates of smoking abstinence and offering free pharmacotherapy or e-cigarettes did not increase abstinence. Roughly 1% of participants allocated to free nicotine e-cigarettes were abstinent at 6 months. It is worth noting that all of these studies tested older ENDS devices. Newer devices are available that better deliver nicotine and warrant investigation for smoking cessation.

Other studies have examined ENDS for smoking reduction. Current smokers participating in a lung cancer screening program received counseling to support smoking behavior change and were randomized to 1 of 3 groups: (i) nicotine e-cigarette; (ii) nicotine-free e-cigarette; or (iii) counseling only (26). After 6 months, 20% of participants stopped smoking and the nicotine e-cigarette group smoked fewer cigarettes than any other group. In another study, current smokers not ready to quit were randomized to either a 4.5% nicotine concentration disposal e-cigarette or a placebo one for 3 weeks to test the effect on smoking reduction (27). Both groups reduced smoking over time, but the e-cigarette group achieved a greater reduction in smoking than the placebo group.

There are also data that support the harm reduction potential of ENDS for smokers. In one trial, smokers were switched from cigarettes to 1 of 4 arms: a nonelectronic cigarette substitute (i.e., a plastic tube that resembled a cigarette), or 1 of 3 ENDS conditions (with 0, 8, or 36 mg/mL nicotine concentration) (28). Participants were encouraged to reduce their cigarette smoking by 50% for 2 weeks and to continue to try to reduce their smoking thereafter. The ENDS groups had significant reductions in diastolic blood pressure, pulse, and cigarettes per day compared with the cig-substitute group, but there were no differences on measures of lung function. These results suggest that short-term ENDS use may promote smoking reductions without introducing additional harms to health. The possibility that more meaningful changes in pulmonary function may be observed among patients with respiratory disease should be studied given that these individuals were excluded in this study. Small retrospective and prospective studies of patients with asthma and COPD who switched from smoking to e-cigarettes have shown improvements in symptoms (29–32). Larger, controlled studies, however, are necessary to validate and expand these findings.

Another study evaluated smoking and e-cigarette behavior and toxicant exposure if smokers switched to e-cigarettes (10). Adult smokers, not interested in quitting, were randomized to 1 of 4 conditions for 8 weeks: (i) *ad libitum* e-cigarette use; (ii) complete switching to e-cigarettes; (iii) complete switching to nicotine gum or lozenge (NRT); or (iv) continued smoking of usual cigarette brand. Participants were incentivized in the switching conditions. The complete switching e-cigarette group had lower rates of smoking and exposure to carbon monoxide, tobacco carcinogens, and other toxicants than the *ad libitum* e-cigarette group and similar levels to the NRT switching group. Furthermore, the e-cigarette switching group had a higher switching rate than the NRT switching group. This study highlights a significant challenge, specifically how to motivate smokers not seeking cessation support and/or interested in total abstinence from nicotine products to completely switch to ENDS. Participants were incentivized to completely switch to e-cigarettes, so it is difficult to generalize these results in real life. Research on effective strategies for promoting switching such as messaging and psychosocial support is warranted.

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Prior research has also tested the potential harm reduction benefit or effects of ENDS on cardiovascular health. For example, smokers were randomized to either 1 of 2 ENDS groups (nicotine or nicotine-free) or a control group (i.e., continued smoking) for 4 weeks (33). After one month, endothelial function significantly improved for the ENDS groups, with no significant difference between the groups. In addition, participants who smoked ≤20 pack-years demonstrated an improvement in vascular stiffness one month after ENDS use, but participants who smoked >20 pack-years did not show this benefit. Prior research showed that ENDS can acutely impair endothelial function (2), but this study demonstrated that longer term switching from cigarettes to ENDS can improve endothelial function. This difference highlights the limitation of acute ENDS studies showing adverse effects on vascular function and the need to study long-term ENDS use to draw conclusions about the relative health benefits versus harms of ENDS use.

Priority Populations for ENDS Health and Harm Reduction Research

Vulnerable populations of smokers

There are well-documented disparities in combustible cigarette use. Despite effective tobacco control initiatives, smoking rates are higher among specific population groups (1).

These populations may benefit the most from ENDS as a harm reduction option due to challenges that may impair their cessation motivation or success with current cessation interventions and high rates of smoking-related illnesses (1). Yet, there is emerging evidence that these populations may be missing out on this harm reduction opportunity. Large-scale population surveys have shown that smokers of lower socioeconomic status (SES), based on either education level or income, are less likely to switch to exclusive ENDS use compared with their higher SES counterparts (34, 35). Such variations may be due to a number of factors including differences in smokers' access to ENDS and/or their beliefs and attitudes about ENDS. Non-white, low-income smokers, and non-internet users may be more likely to perceive that e-cigarettes are more harmful than cigarette smoking and to maintain positive expectancies for combustible tobacco use (36).

More research is needed to understand if there are disparities in ENDS access, use, and perceptions. Likewise, studies should investigate user characteristics associated with successful switching to ENDS from smoking to determine whether there are important subgroup differences. Randomized, controlled trials of ENDS for switching/cessation have not typically focused on these populations. Moreover, research on the potential beneficial versus adverse health effects of ENDS use among smokers with medical comorbidities are largely limited to cross-sectional designs, small cohort studies. Effective strategies for disseminating accurate information about ENDS to the public should also be explored, bearing in mind gaps in access to resources such as the internet. Careful monitoring is warranted to ensure that ENDS do not widen smoking-related health disparities.

Never-smokers/exclusive ENDS users

Research on ENDS use among exclusive ENDS users who never smoked cigarettes is also warranted. Current ENDS use prevalence is lower among never smokers (6.5%) compared with current (49.4%) and former smokers (37). Studies with never smokers are crucial for understanding ENDS health effects independent of cigarette smoking. That is, the most rigorous test of any risks posed by different ENDS constituents is among individuals with no prior smoking exposure. Although ENDS are proposed as a reduced-harm nicotine product, they are not harm-free (2). Cigarette smoke contains roughly 7,000 toxicants, including formaldehyde, acetaldehyde, volatile organic compounds, heavy metals, toxic gases, and other carcinogenic compounds (1). ENDS can contain toxic and potentially harmful substances but at markedly lower levels and quantities than cigarettes and some ENDS products do not contain any of these compounds (2, 38). Long-term studies of exclusive ENDS users are necessary for determining the potential long-term risks of exposure to ENDS.

Conclusions

ENDS are now widely available across the United States. These products may provide a harm reduction benefit for smokers. At the same time, they are not harm-free and may pose public health risks to young people and never smokers. Chronic ENDS use is likely to have negative health consequences over the long term, which will likely be of less severity compared with cigarette smoking. Nonetheless, the extent of adverse health effects from ENDS remains to be determined and is not well understood. To address these gaps and inform the regulation of these products, we outline key priorities below.

Research Priorities

Future research should focus on the long-term health effects of chronic ENDS use. This research question is challenging to answer due to the long duration of ENDS use required to see disease incidence, past smoking history among most ENDS users, problems with varying and/or intermittent ENDS use, and diverse ENDS products and e-liquids, among other factors. Therefore, a multi-strategy translational approach is recommended. Animal models can simulate lifetime ENDS exposure in a short time period. This efficient design is ideal for testing several independent variables that may impact ENDS health effects such as the amount, type, and duration of ENDS exposure. Among humans, laboratory studies can similarly manipulate different independent variables and examine whether variables identified in animal studies yield similar health effects with shorter term ENDS use. Prospective cohort designs can then elucidate the potential longer term health

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effects of ENDS in humans. To be informative, however, this research needs to clarify the timing of ENDS use, other tobacco use (if relevant), and health outcomes, conduct a detailed assessment of the type, quantity, and frequency of ENDS/tobacco use, and utilize biomarkers of health status, not just self-report. These studies can enroll individuals from the general population with or without ENDS exposure at the time of enrollment, but it is important to study particular subgroups, especially exclusive ENDS users (i.e., never smokers), to best understand ENDS health effects independent of smoking over time. Randomized, controlled studies of ENDS use among smokers are also needed to determine what device, user, and ENDS messaging characteristics predict successful switching from smoking. Furthermore, work in this area should investigate understudied populations with disproportionally higher smoking rates compared with the general population and who may experience the greatest harm reduction benefit from these products. Finally, future research should explore how ENDS availability may reduce or increase the number of future smokers and smoking-related deaths and whether important disparities exist in this regard. Using both simulation models and prospective designs, studies should examine: (i) how many youths who initiate ENDS become regular, long-term cigarette smokers versus experimental smokers and quit in early adulthood and (ii) how many lives would be saved from switching to ENDS and whether this number varies for different populations. Finally, the FDA deadline of September 9, 2020, for ENDS manufacturers to submit a premarket tobacco product application (PMTA) to obtain approval for marketing will further change the ENDS landscape. Products that were available prior to August 2016 do not require a PMTA. Some manufacturers will not achieve the 2020 deadline. Thus, it is likely that ENDS availability will change and illicit markets will emerge, which raises new questions about how ENDS use and cigarette smoking may change, among what populations, and the potential health consequences of these changes.

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