

## Is There A Role for Electronic Cigarettes in Tobacco Cessation?

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Since their introduction in the United States and Europe in 2006–2007, electronic cigarettes (e-cigarettes) have become popular nicotine-delivery devices. Estimates vary, but our analysis of the Behavioral Risk Factor Surveillance System (BRFSS;  $n=466\ 842$ ) indicated that in 2016, 4.5% of US adults (aged  $\geq 18$  years) were current e-cigarette users, corresponding to 10.8 million adults.<sup>1</sup> Of these, 1.4% (1.9 million adults) were sole e-cigarette users; among current users, 33.5% used e-cigarettes daily and nearly half the users were current combustible cigarette smokers.<sup>1</sup> The high prevalence of e-cigarette use may be attributed to many factors, including the perception that e-cigarettes are safer than combustible cigarettes and that the use of e-cigarettes can help smokers quit combustible cigarettes. Indeed, e-cigarettes have been promoted as reduced-harm products, and it has been argued that their continued availability may lessen the burden of disease and disability associated with smoking combustible cigarettes.<sup>2</sup>

The easy accessibility of e-cigarettes and the perception that they are reduced-harm products has led to the recruitment of a new group of nicotine-addicted youth, otherwise at low risk for tobacco use, who are ultimately more likely to transition from e-cigarettes to combustible cigarettes.<sup>3</sup> Moreover, many former smokers (7.6%) who had quit tobacco report using e-cigarettes, and the prevalence of daily sole e-cigarette use is highest among former cigarette smokers.<sup>1</sup> It

seems likely that the availability of e-cigarettes is leading to net increases in the numbers of both nicotine-dependent users and combustible cigarette smokers. Even with the unlikely and unsubstantiated assumption that e-cigarettes are 95% safer than conventional smoking, simulation models of population-level health benefits in the United States suggest a net population-level harm (1.5 million years of life lost).<sup>4</sup> This is consistent with the results of several studies showing that e-cigarette use is associated with marked changes in vascular, respiratory, and immune functions.<sup>5</sup> Our analysis of the BRFSS data showed that dual use of e-cigarettes and combustible cigarettes is associated with higher odds of cardiovascular disease.<sup>6</sup> While reverse causality cannot be ruled out, there is sufficient evidence to raise concern regarding the adverse health outcomes of e-cigarette use.

An additional justification for advocating continued availability of e-cigarettes is the claim that e-cigarettes assist chronic smokers in quitting combustible cigarettes and potentially other tobacco products. Several randomized and observational studies have been conducted to address this issue; however, no clear consensus has emerged. The results of early trials comparing e-cigarettes with nicotine replacement therapy (NRT) were inconclusive because of small sample size, low acceptability of first-generation e-cigarettes, and issues related to specific study designs. Nonetheless, a recent report from the National Academies of Science, Engineering, and Medicine concluded that there is limited evidence to support the notion that e-cigarettes help people stop smoking because the current evidence was insufficient to assess the effectiveness of e-cigarettes as a smoking-cessation aid.<sup>7</sup>

Whether e-cigarettes facilitate quitting has also been examined in several observational studies. A 2014 Eurobarometer survey of 28 European countries found that e-cigarette use was associated with inhibiting rather than assisting with smoking cessation.<sup>8</sup> Similarly, in a study of 1357 hospitalized adult cigarette smokers who planned to stop smoking and received counseling in the hospital, the use of e-cigarettes was associated with less tobacco abstinence at 6-month follow-up than attempted abstinence without the use of e-cigarettes.<sup>9</sup> Likewise, in a population-based prospective cohort study of 1284 US adult smokers, the use of e-cigarettes did not help adult smokers quit at rates higher than smokers who did not use

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these products,<sup>10</sup> suggesting that the use of e-cigarettes in real-world situations is not effective in decreasing smoking or promoting tobacco cessation. Indeed, it has been suggested that using e-cigarettes may make it more difficult to quit smoking combustible cigarettes.<sup>11</sup> This suggestion was based on a systematic analysis of 38 studies reporting e-cigarette use and smoking cessation in real-world and clinical settings, in which the authors found that the odds of quitting cigarettes were 28% lower for those who used e-cigarettes compared with those who did not use e-cigarettes.<sup>11</sup> In contrast, other studies have suggested e-cigarettes may be beneficial in assisting quitting. A study of a cohort of young adults (n=1263, aged 19–23) surveyed over 4 years found that the use of e-cigarettes was associated with reduced smoking in highly nicotine-dependent, young adult cigarette smokers.<sup>12</sup> Our analysis of the PATH (Population Assessment of Tobacco and Health) data set (n=5832)<sup>13</sup> indicated that those who used e-cigarettes to quit combustible cigarettes had an increased probability of persistent cigarette abstinence and that daily e-cigarette users were more likely to quit smoking or reduce their use of combustible cigarettes compared with nonusers. However, this proportion of individuals was relatively small, and less frequent e-cigarette use was not associated with combustible cigarette cessation.

Given the differences in study designs and analytical approaches, it is difficult to reconcile the results of different studies or to identify the reasons underlying disparate results. Because some studies lack appropriate comparator groups or target different populations with varying use patterns and self-selection of different devices, it seems unlikely that universally applicable conclusions could be drawn from this work. To address such uncertainty and to provide more robust evidence, Hajek et al<sup>14</sup> conducted a randomized clinical trial with 886 participants. In that trial, participants were randomly assigned to an NRT of their choice, including product combinations, or an e-cigarette starter pack. All participants received at least 4 sessions of behavioral support. The study found that the 1-year abstinence rate was higher (18%) in the e-cigarette group than in the NRT (patches and/or nicotine gum) group (9.9%). Moreover, the e-cigarette group reported a greater decline in the incidence of cough and phlegm production and found that e-cigarettes were more effective in alleviating tobacco-withdrawal symptoms. The participants also rated e-cigarettes as more helpful in refraining from smoking than NRT. Taken together, these results suggest that, at least in this study, e-cigarettes were more effective for smoking cessation than NRT. However, several issues need additional consideration when interpreting these findings. First, the 9.9% quit rate for a nicotine patch plus multisession behavioral support is low compared with similar NRT studies and suggests that the presence of extratreatment factors adversely influenced NRT outcomes. Second, even if one assumes some superiority of e-

cigarettes over NRT, risk–benefit considerations arise. For example, does the modest potential superiority of e-cigarettes as smoking cessation aids outweigh their known and emerging health risks, including dual use; the potential for cardiovascular, pulmonary, and other long-term impacts; and the high addiction potential of e-cigarettes relative to NRT products? Third, most individuals do not currently receive the behavioral support provided in this study, so one must consider what might be a realistic estimate of the population impact of this approach, should the use of e-cigarettes as cessation devices increase. Previous observational work has indicated that those most likely to switch to e-cigarettes and quit other tobacco products are those who use e-cigarettes most aggressively.<sup>13</sup> The 18% smoking abstinence rate noted earlier is routinely achieved using other, more effective cessation modalities that carry far lower health-risk concerns. For instance, the 1-year abstinence rate with NRT and bupropion was reported to be 20%, and the 24-week abstinence rate with varenicline was reported to be 26%.<sup>15</sup> Consequently, little empirical evidence advocates the use of e-cigarettes over currently available, US Food and Drug Administration (FDA)–approved NRT, along with bupropion and varenicline options.

Currently available NRT products also seem superior to e-cigarettes in promoting complete abstinence from nicotine. In the study by Hajek et al,<sup>14</sup> 80% of the participants in the e-cigarette group continued to use e-cigarettes at 1-year follow-up, whereas only 9% of those in the NRT group were still using nicotine. These results suggest that the use of e-cigarettes primarily promotes switching from one form of nicotine delivery to another while only minimally supporting complete recovery from nicotine addiction. That e-cigarette users' transition to long-term use is consistent with the highly addictive nature of nicotine. Those who use e-cigarettes display strong nicotine dependence.<sup>16</sup> In a recent study of daily smokers and dual users who did not intend to quit, nearly 44% were smoking combustible cigarettes and nearly 49% continued dual use after 1 year of follow-up, whereas only 2% of smokers and 8% of dual users achieved abstinence.<sup>17</sup> Therefore, in real-world scenarios, where many users are not highly motivated or ready to quit, most current e-cigarette devices seem to fuel nicotine addiction and thus inhibit complete switching from combustible to noncombustible tobacco products or achieving nicotine abstinence. In consideration of the potential residual harm imposed by e-cigarettes, their inability to promote complete nicotine abstinence, and their modest efficacy compared with other currently available pharmacologic options, little evidence appears to support their role in tobacco or nicotine cessation.

## Future Directions

Given the rapidly changing landscape of e-cigarettes, continued research, vigilance, and surveillance are necessary to

evaluate the health impact of these and other electronic nicotine delivery systems and to assess their efficacy in shifting users of tobacco products away from combustible products. In parallel, there is urgent need to support greater efforts to train healthcare providers to deliver interventions and to develop strong antivaping messages in prevention and cessation programs. Given that FDA-approved medications for tobacco treatment in combination with multisession counseling remain the most effective means of quitting tobacco, it seems important to redouble efforts to increase healthcare provider training and the availability of these options and to improve our understanding of factors that lead to an increase in the acceptability of FDA-approved medications. There is also urgent need for developing more effective tobacco cessation modalities.

Most studies to date have examined the effects of first-generation e-cigarettes or second-generation “mod” devices, but the effects of recently introduced e-cigarettes such as JUUL (Juul Labs) remain unknown. These new-generation e-cigarettes have achieved high popularity. In a recent survey, 23% of high school students were ever JUUL users and 17% were current users.<sup>18</sup> These statistics are startling considering that the percentage of adolescents who had smoked cigarettes in the past month had fallen to 3.4% by 2016,<sup>19</sup> in part due to decades of persistent public health efforts. This gain has been significantly eroded. A recent survey found that among college students, 36% reported ever use and 21% reported past-30-days use of JUUL.<sup>20</sup> This high prevalence and acceptance of JUUL is of particular concern because JUUL contains a higher concentration of nicotine than most other e-cigarettes, predominantly in the protonated form,<sup>21</sup> and produces a rapid increase in nicotine levels, potentially leading to greater nicotine addiction. Whether the high-efficiency nicotine delivery by JUUL also promotes exclusive use or cessation of other use of other tobacco products remains unknown but merits prompt attention. Of course, any findings must be evaluated within the context of known and emerging health concerns.

## Perspective

Proponents of e-cigarettes argue that the widespread use of e-cigarettes has the potential to diminish the disease burden associated with smoking combustible cigarettes by promoting tobacco cessation.<sup>2</sup> This message has resonated with many smokers, and most current users of e-cigarettes report that they use e-cigarettes to quit smoking. However, current evidence suggests that even under well-controlled conditions,<sup>14</sup> when offered e-cigarettes with supportive counseling, 82% of smokers continue to smoke combustible cigarettes and do not switch to e-cigarettes. Of those who do quit, 80% continue to keep using e-cigarettes, that is, they switch

between tobacco products rather than achieve nicotine abstinence.<sup>14</sup> In comparison with NRTs such as nicotine gum and patches, a single study suggests that e-cigarettes may be more effective, but their efficacy seems at best comparable to currently available pharmacological agents.<sup>15</sup> In real-world scenarios, e-cigarettes seem mostly to promote dual use,<sup>1,16</sup> which, in those not motivated to quit, is either maintained or leads to a return to sole use of combustible cigarettes.<sup>17</sup> In those motivated to quit, a small percentage do achieve smoking cessation but with continued nicotine addiction.<sup>13,16</sup> In terms of overall population health, however, the marginal efficacy of e-cigarettes in decreasing the use of combustible tobacco may be outweighed by the potential long-term harms associated with these products and the widespread increase in the use of e-cigarettes among youth and young adults. E-cigarettes have become the most popular nicotine-delivery devices among youths (aged <18 years) and increasingly among those who do not use other tobacco products.<sup>18</sup> Youths who use e-cigarettes are susceptible not only to nicotine addiction per se but also to transitioning to smoking combustible cigarettes<sup>3</sup> and using other drugs and addictive substances.<sup>22</sup> Consequently, the likelihood that the use of e-cigarettes drives a net public health gain remains uncertain. Moreover, it is unclear whether the marginal potential of e-cigarettes to reduce harm in current smokers justifies the recruitment of a whole new generation to nicotine and tobacco addiction. At the very least, the current evidence mandates that all measures be taken for effective prevention of youth addiction to nicotine and for efficacious treatment of nicotine addiction in youths and adults already affected. Finally, additional well-designed studies of the toxicity of e-cigarettes are warranted to enable accurate comparisons of the short- and long-term risks of combustible tobacco products, e-cigarettes, and other novel tobacco products.

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