EDITORIAL

Randomized Trials of e-Cigarettes for Smoking Cessation

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Few topics in public health and medicine are as contentious as electronic cigarettes (e-cigarettes), a diverse and rapidly evolving array of products that appeared on the consumer market a decade ago. e-Cigarettes are battery-powered devices that heat a solution, typically containing nicotine and other chemicals including flavorings, to produce an aerosol that users inhale or "vape."[1] e-Cigarettes do not burn tobacco to generate smoke, and it is the many chemicals in tobacco smoke—not the nicotine—that are responsible for the global burden of tobacco-related disease that accounts for an estimated 6 million deaths worldwide and nearly half a million deaths in the US each year.[1-3]

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The potential for smokers to reduce their health risks by switching from cigarettes to e-cigarettes has intrigued medical and public health communities. When used temporarily, e-cigarettes could be cessation aids, whereas when used long-term, these products could be harm-reduction tools. Either way, individual smokers could benefit because use of e-cigarettes is likely to have a substantially lower health risk than continuing to smoke cigarettes.[1]

However, the effects of e-cigarettes in the entire population must also be considered. This includes risks to nonsmokers—primarily youths—who would never have used cigarettes but experiment with e-cigarettes, with some becoming addicted to nicotine and transitioning to smoking. Even if e-cigarettes are only used for a relatively short period of time, they are not harmless. In the end, e-cigarettes may benefit some individuals (ie, adult smokers) and harm others (ie, young nonsmokers). Research to clarify the balance of these benefits and harms is ongoing and is needed to craft appropriate policies. In the meantime, most simulation models estimate that e-cigarettes provide a net benefit to public health.[4]

The case for the potential benefit of e-cigarettes largely rests on whether these products help smokers stop using combustible tobacco products. The answer to this question requires evidence from population studies and from large high-quality randomized clinical trials. However, few trials have been reported, despite e-cigarettes having been available for more than a decade. In the US, investigators' ability to conduct these trials has been slowed by Food and Drug Administration (FDA) regulatory requirements.

Recent large randomized trials in England and New Zealand have begun to fill the evidence gap.[5,6] In the trial from England, which included 886 participants who smoked cigarettes, use of e-cigarettes increased the rate of sustained cigarette abstinence at 1 year compared with nicotine replacement therapy (NRT), with quit rates of 18.0% vs 9.9%, respectively.[5] In the trial from New Zealand, which included 1124 cigarette smokers, adding an e-cigarette to NRT increased sustained cessation rates at 6 months compared with NRT alone, with cessation rates of 7% vs 2%, respectively.[6] Yet, questions remain about how e-cigarettes compare with behavioral support alone or with other FDA-approved pharmacotherapies.

The trial reported by Eisenberg et al[7] in this issue of *JAMA* is the first large North American randomized clinical trial to address this evidence gap. This multisite open-label trial tested the efficacy of e-cigarettes for smoking cessation among Canadian adults seeking to quit smoking. The investigators compared a second-generation e-cigarette containing 15 mg/mL of nicotine vs 2 alternatives, an identical e-cigarette without nicotine and a no e-cigarette condition. All participants received smoking cessation counseling, and e-cigarettes were provided for 12 weeks. Smoking cessation outcomes were measured at 12 weeks and at 6 and 12 months. The study was powered to test the comparison of the nicotine-containing e-cigarette vs the no e-cigarette condition. The nonnicotine e-cigarette group was apparently included to generate hypotheses about the mechanisms by which e-cigarettes promote cessation. e-Cigarettes without nicotine may provide substitution for behavioral and social aspects of smoking even though they will not treat nicotine withdrawal symptoms.

Despite careful planning, this trial experienced an unexpected complication during recruitment. The e-cigarette device became unavailable, and this necessitated a premature end to study enrollment, after only 376 (77%) of the planned sample of 486 participants were randomized. This smaller sample left the trial underpowered to test its primary end point, smoking abstinence at 12 months. With approval by the data and safety monitoring board, the investigators redefined the primary end point to be self-reported abstinence from smoking for the past 7 days, with biochemical confirmation (using exhaled carbon monoxide) at 12 weeks, the end of active treatment and a point when abstinence rates in the e-cigarette group would be expected to be highest. The study detected a statistically significant difference for the revised primary outcome. The abstinence rate in the nicotine-containing e-cigarette group was significantly higher than that in the counseling-only group (21.9% vs 9.1%; risk difference, 12.8 [95% CI, 4.0 to 21.6]; rate ratio, 2.4). The 12-week abstinence rate in the nicotine-free e-cigarette plus counseling group was 17.3%, and was not significantly different than that in the counseling-only group (risk difference, 8.2 [95% CI, −0.1 to

16.6]).The abstinence rate in the nicotine e-cigarette group declined after treatment ended and although still higher, was not significantly different from the counseling group at 6 months (17.2% vs 9.9% risk difference, 7.3%; 95% CI, −1.2 to 15.7). Results at 1 year were not reported.

Several limitations, acknowledged by the authors, complicate interpretation of these results. One is the differential follow-up rate at 12 weeks. The rate in the counseling-only group was substantially lower than in the nicotine e-cigarette group. Because the primary analysis counted participants lost to follow-up as smokers, the differential follow-up could inflate effect sizes. When the authors conducted a sensitivity analysis with multiple imputation to handle missing data, the difference between abstinence rates in the nicotine-containing e-cigarette group and the counseling-only group narrowed and was no longer statistically significant. The broader problem is that the trial had insufficient statistical power to test hypotheses because recruitment ended prematurely.

The rapid product evolution of e-cigarettes also complicates the generalizability of trial results of this and other studies. The trial by Eisenberg et al[7] used a second-generation e-cigarette, typical of devices used when the trial began. By 2017, these products had been eclipsed by newer devices, exemplified by JUUL, with prepackaged liquid "pods" and a formulation that allows delivery of a higher nicotine dose.[8] These products now have the largest US market share.[8] With higher nicotine delivery, these products will likely be more effective for smoking cessation than earlier e-cigarettes. However, recent systematic searches revealed no randomized trials testing the effectiveness of newer devices for smoking cessation.[9] Of course, higher nicotine delivery also has a downside—a greater likelihood for the devices to produce nicotine dependence when used by nonsmoking youths, for whom the devices clearly have strong appeal.[10]

Overall, the trial by Eisenberg et al[7] contributes new data to the current limited understanding of the effectiveness and adverse events associated with e-cigarettes for smoking cessation. While this study does not provide a definitive answer due to acknowledged limitations, the data will be useful for future meta-analyses. Two new systematic reviews of e-cigarettes not including this trial were recently published,[9,11] one of which is an update of the 2016 Cochrane review.[9] Although done independently, the 2 meta-analyses produced nearly identical effect estimates for smoking cessation when nicotine e-cigarettes were compared with nonnicotine e-cigarettes (risk ratio, 1.71), nicotine replacement products (risk ratio, 1.69), and counseling only or no treatment (risk ratio, 2.05 and 2.50, respectively).[9,11] The Cochrane review concluded that "moderate certainty evidence" supports the effectiveness of nicotine-containing e-cigarettes to aid cessation when compared with nonnicotine e-cigarettes and NRT.[9] The evidence comparing e-cigarettes vs usual care or no treatment was weaker but judged to suggest a benefit.[9] The other systematic review had more tentative conclusions, but indicated that results suggested a potential benefit.[11]

The Cochrane meta-analysis also reviewed the clinical trial data about e-cigarette safety. There was essentially no evidence that e-cigarettes caused harm, although this assessment was limited by the small number of events and the relatively short duration of exposure to the devices in clinical trials.[9] The trial by Eisenberg et al[7] also found no clear evidence of harm from e-cigarette use.

In summary, the accumulating evidence from clinical trials suggests that e-cigarettes will likely turn out to be safe and effective tools to aid smoking cessation. However, as with all existing smoking cessation therapies, e-cigarettes are not the single or long-sought-after solution to help all or even most smokers to quit. More randomized trials are needed, enrolling larger samples and testing the devices with higher nicotine delivery that now dominate the market.[8] Trials should compare e-cigarette devices vs other FDA-approved cessation aids but also test whether e-cigarettes might be most effective when used in combination with other FDA-approved cessation aids. Future trials might also consider alternative designs. Most current trials consider a short course of treatment (usually 3 months) sufficient to change a long-standing addictive behavior permanently.

Tobacco dependence is now understood to be a chronic disorder that may require long-term treatment. Following a harm-reduction approach, testing the effectiveness and, especially, the safety of e-cigarettes with longer durations of use and among individuals who are less interested in complete abstinence from nicotine should be a priority. High-quality data from rigorously conducted trials are needed to know whether or how much e-cigarettes might help the 34 million US residents who still smoke cigarettes, many of them in vulnerable and disadvantaged groups,[12] to avoid a bleak future of disease, disability, and death related to tobacco smoking.

ARTICLE INFORMATION

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