Annals of Pharmacotherapy
2014, Vol. 48(11) 1502–1506

DOI: 10.1177/1060028014547076
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Efficacy of Electronic Cigarettes for Smoking Cessation

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Abstract

Objective: To review data demonstrating effective smoking cessation with electronic cigarettes (e-cigarettes). **Data Sources:** A literature search of MEDLINE/PubMed (1946-March 2014) was performed using the search terms *e-cigarettes, electronic cigarettes*, and *smoking cessation.* Additional references were identified from a review of literature citations. **Study Selection and Data Extraction:** All English-language clinical studies assessing efficacy of e-cigarettes compared with baseline, placebo, or other pharmacological methods to aid in withdrawal symptoms, smoking reduction, or cessation were evaluated. **Data Synthesis:** A total of 6 clinical studies were included in the review. In small studies, e-cigarettes significantly decreased desire to smoke, number of cigarettes smoked per day, and exhaled carbon monoxide levels. Symptoms of nicotine withdrawal and adverse effects were variable. The most common adverse effects were nausea, headache, cough, and mouth/throat irritation. Compared with nicotine patches, e-cigarettes were associated with fewer adverse effects and higher adherence. Most studies showed a significant decrease in cigarette use acutely; however, long-term cessation was not sustained at 6 months. **Conclusions:** There is limited evidence for the effectiveness of e-cigarettes in smoking cessation; however, there may be a place in therapy to help modify smoking habits or reduce the number of cigarettes smoked. Studies available provided different administration patterns such as use while smoking, instead of smoking, or as needed. Short-term studies reviewed were small and did not necessarily evaluate cessation with a focus on parameters associated with cessation withdrawal symptoms. Though long-term safety is unknown, concerns regarding increased poisoning exposures among adults in comparison with cigarettes are alarming.

Keywords

smoking cessation, ambulatory care, evidence-based practice, community practice, drug information, FDA issues

Request

Is there evidence that electronic cigarettes (e-cigarettes) are effective for smoking cessation?

Response

Background

In the United States, 42.1 million adults (18.1%) are current cigarette smokers.[1] Smoking accounts for 480 000 deaths per year from cardiovascular disease, respiratory disease, various cancers, and other ailments. Approximately 42 000 deaths per year are attributed to second-hand smoke exposure. For each tobacco-related death, there are 30 more individuals suffering from a tobacco-related illness. The cost on society in the United States is staggering: an estimated $133 billion in direct medical care and $156 billion in lost productivity, equaling an annual loss of $289 billion.[2]

Treatment of tobacco dependence includes patient counseling and/or medications, and health care professionals should implement the 5As when addressing tobacco use: ask, advise, assess, assist, and arrange. Patient counseling incorporates motivational interviewing, managing withdrawal symptoms, and behavioral modifications to change activities associated with smoking.[3] There are 7 first-line products approved by the Food and Drug Administration (FDA) that are available as smoking cessation aides, including nicotine replacement therapies (NRTs), bupropion SR, and varenicline.[3] First-line products have safety and efficacy data to support use and can approximately double a patient's quit rate.[3] Though counseling and medications are each individually effective, combined they significantly increase chances of quitting.

Electronic cigarettes, or e-cigarettes, are battery-powered electronic nicotine delivery devices allowing nicotine

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vapors to be inhaled. They are available in many flavors, including fruit, mint, or chocolate. e-Cigarettes reinforce smoking behaviors while providing nicotine vapor, and it is claimed that they are safer alternatives to cigarettes without burning tobacco and the combustible products causing tobacco-related illness.[4] e-Cigarettes vary in nicotine content and delivery, equaling 0 to 35 μg per puff—up to 20% of that delivered from nicotine cigarettes. Grana et al[5] estimated that approximately 30 puffs from an e-cigarette, with 30 μg per puff, would equal 1 mg of nicotine delivered from a tobacco cigarette. The actual amount of nicotine delivered depends on the device used and is not solely dependent on the nicotine content within the e-cigarette cartridge.

Because safety and potential toxicity concerns have come to the forefront, the Centers for Disease Control (CDC) evaluated calls to poison centers from September 2010 to February 2014.[6] Of total exposures to e-cigarettes (device or liquid cartridge) and cigarettes reported, e-cigarette exposures rose from 0.3% to 41.7%. Reports for cigarette poisonings occurred mostly in children 0 to 5 years old (94.9%), in contrast to e-cigarette poisoning, which occurred in 51.1% of this age range and in 42% of those >20 years old. Patients were more likely to report an adverse event with e-cigarettes versus cigarettes (57.8% vs 36%; $P < 0.001$).[6] The rapid increase in e-cigarette poison exposures reported is a public health concern worthy of note among children and particularly adults.

Long-term safety has not been established, though a comparison of a dozen e-cigarette products has demonstrated that they are less toxic and have fewer carcinogenic compounds than a nicotine cigarette but more than that found in a nicotine inhaler.[5] Concerns have been raised about propylene glycol being used as a base, which may result in irritation to the lungs and potential effects on other organs. e-Cigarettes produce fine particulate matter through the inhaled aerosol. It is unknown if these have deleterious effects on the lungs as particulate matter found in nicotine cigarettes do.[5]

The administration of e-cigarettes as a treatment modality for smoking cessation has drawn attention, yet they are not approved by the FDA for this indication. If products were to make claims for a therapeutic purpose, it would require regulation through the FDA Center for Drug Evaluation and Research. Currently, cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco are regulated by the FDA Center for Tobacco Products.[7] In April 2014, the FDA proposed a plan to regulate e-cigarettes. Details include restricted sales to only those ≥18 years old, labeling of all ingredients within the products, warning labels for nicotine addiction, and a ban on health claims not supported by scientific data.[8]

Literature Review

A number of small trials have evaluated the efficacy of e-cigarettes in terms of parameters related to smoking cessation but not to actual cessation rates. The majority of studies occur in a short-term time frame and are not adequate to determine long-term cessation rates. Bullen et al[9] recruited 40 adults aged 18 to 70 years old, smoking ≥10 cigarettes/d for a single-blinded, randomized, cross-over trial. The primary outcome was change in desire to smoke as analyzed through an 11-point visual analogue scale administered prior to use and at intervals during 1 hour of administration (5, 10, 15, 30, and 60 minutes). Secondary outcomes included withdrawal symptoms, acceptability, and adverse effects. Participants were randomized to 16 mg of nicotine or placebo from an e-cigarette, a nicotine inhaler (Nicorette) 10-mg cartridge up to 6 cartridges per day, or their own cigarettes. At baseline, they smoked an average of 20.2 cigarettes/d. The nicotine e-cigarette group had significantly decreased desire to smoke compared with the placebo unit ($P = 0.006$) but with no difference compared with the nicotine inhaler. However, in comparison to the nicotine inhaler, patients reported less irritation of the mouth or throat with the active e-cigarette ($P = 0.016$) and found it more pleasant to use ($P < 0.001$).[9]

Another short-term study analyzed e-cigarette effects on desire to smoke, withdrawal symptoms, and cognition. A total of 86 patients were assigned 18 mg of nicotine from an e-cigarette, placebo e-cigarette, or just holding the e-cigarette.[10] Inclusion and exclusion criteria were not defined; the only participants were e-cigarette-naïve smokers. Desire to smoke and withdrawal symptoms were measured at baseline, at 5 minutes of use, and at 20 minutes after use of the e-cigarette device for 5 minutes. The 18-mg and placebo e-cigarette both significantly reduced the desire to smoke and many aspects of nicotine withdrawal after 20 minutes of use ($P < 0.05$) compared with just holding the cigarette. Symptoms such as anxiety, poor concentration, irritability, and restlessness in men were significantly lower, whereas in women, the only statistically significant finding was depression improvement. The desire to smoke was also significantly reduced in men with the 18-mg versus placebo e-cigarette ($P < 0.05$) but not in women. Working memory performance appeared significantly better in the nicotine groups compared with the placebo group ($P < 0.004$) and just-hold group ($P < 0.004$).[10] Though this study attempts to demonstrate that cognition is increased with nicotine, it could be more appropriate to attribute the results to effects caused by withdrawal that subside with more nicotine use.

A small study examined the effect of e-cigarettes on modifications in smoking habits of 14 patients with schizophrenia, who were currently smoking ≥20 cigarettes/d for at least 10 years.[11] The primary efficacy end point was sustained self-reported 50% reduction in the number of cigarettes-per-day at week 52. Free 4-week supplies of 7.4-mg nicotine cartridges were given at each visit, and participants were permitted to use them *ad libitum*, up to a maximum of 4 cartridges/d. Study participants were, on average, 45 years old and smoked 30 cigarettes/d, with a median Fägerstrom

Test of Nicotine Dependence score of 7 (range = 5-10). At 52 weeks, 7 of 14 (50%) patients achieved the primary end point of 50% reduction in the number of cigarettes-per-day from 30 to 15 ($P = 0.018$). At 52 weeks, exhaled carbon monoxide (eCO) levels were also significantly reduced in 50% reducers and 100% quitters from 32 to 17 ($P = 0.028$). The largest reductions in number of cigarettes-per-day and eCO were observed from baseline to week 4. There was no correlation between the number of cartridges used per day (range = 0-4) and achievement of primary end point ($P = 0.28$) and no significant difference in positive and negative symptoms of schizophrenia on study completion. The most commonly reported adverse effects were nausea, throat irritation, headache, and dry cough; the majority were reported at the beginning of the study and were no longer reported at week 24.[11]

The EffiCiency and safety of an eLectronic cigAreTe (ECLAT) as tobacco cigarette substitute study randomized current smokers not intending to quit who were currently smoking ≥10 cigarettes/d for at least the past 5 years and in good general health.[12] Participants were permitted to use the product *ad libitum* (maximum of 4 cartridges/d) and were randomized to 3 groups based on nicotine e-cigarette cartridge: group A (n = 65) received 7.2-mg cartridges for 12 weeks, group B (n = 63) received 7.2-mg for 6 weeks then 5.4 mg for 6 weeks, and group C (n = 55) received placebo cartridges for 12 weeks. Participants returned every 2 weeks for 12 weeks for follow-up and supplies. Participants had 2 additional visits (week 24 and 52), although cartridges were only provided through week 12. Previous quit attempts occurred in 51% of participants; however, the method of cessation was not recorded. The self-reported ≥50% reduction in the number of cigarettes-per-day (reducers) and self-reported quitters were calculated at each visit. No significant differences were found in rates of reducers or quitters at week 52. The median number of cigarettes-per-day and eCO levels decreased from baseline in all 3 study groups at each visit, and overall number of cigarettes-per-day decreased from 21 to 13.9 ($P < 0.0001$) at week 52 with all study groups combined. Significant between-group differences in number of cigarettes-per-day were inconsistent and not observed beyond 8 weeks. A decrease in number of cigarettes-per-day was only seen until week 2; however, this was not sustained and increased steadily in all groups. No significant between-group differences in eCO levels were recorded, except for week 6 (all groups, $P = 0.01$). The number of cartridges used was not reported. A significant reduction in frequency of adverse effects was reported in all groups; however, no significant differences were found between any of the groups. eCO levels ≤7 ppm were recorded in patients who reported not even 1 puff of a tobacco cigarette, and there were measurable saliva cotinine levels at weeks 6 and 12 in both nicotine e-cigarette groups (A and B; no significant difference) but not in group C, as expected.[12]

A pilot study to the ECLAT study included 40 adults evaluated for smoking reduction and cessation over 24 weeks.[13] Participants were 18 to 60 years old and smoking ≥15 cigarettes-per-day for the past 10 years and not ready to quit. The study included 5 visits of assessment: baseline, week 4, week 8, week 12, and week 24. e-Cigarette use, quantity of cigarettes smoked, and eCO were measured at each visit. Participants were instructed to use the e-cigarette *ad libitum*, with a maximum of 4 cartridges/d (7.4 mg each). By the last visit, 13 participants (32%) decreased smoking by 50%, reducing mean cigarette consumption from 25 to 6 cigarettes/d ($P < 0.001$). At 24 weeks, 9 participants (22.5%) were completely abstinent from tobacco cigarettes, though still using the e-cigarette (mean number of cartridges/d = 2). No significant correlation was found between number of cartridges-per-day and reduction in smoking.

Another 6-month study randomized 657 patients to receive nicotine e-cigarettes (n = 289), 21-mg nicotine patches (n = 295), or placebo e-cigarettes (n = 73).[14] Participants were mostly female (62%), with a mean age of 42 years, and smoking an average of 18 cigarettes/d. More than 50% of patients had made at least 1 quit attempt in the past year, but details of the methods used were not collected. The primary outcome was continuous self-reported smoking abstinence at 6 months after the quit day. At 6 months, abstinence rates were 7.3% (nicotine e-cigarettes), 5.8% (nicotine patches), and 4.1% (placebo e-cigarettes). There was no significant difference in smoking abstinence between nicotine e-cigarettes and nicotine patches ($P = 0.46$) or between nicotine e-cigarettes and placebo e-cigarettes ($P = 0.44$), and 70% relapsed within 50 days. Median time to relapse for the nicotine e-cigarette group was significantly longer when compared with the patch group (35 vs 14 days, $P < 0.0001$) but not compared with the placebo e-cigarette group (12 days, $P = 0.09$). The decrease from baseline of number of cigarettes-per-day for nicotine e-cigarettes versus patches was 2 cigarettes/d ($P = 0.002$); data were not provided for the placebo e-cigarette comparison. There was no significant difference between the percentage of participants who reduced their cigarette use by half in the nicotine e-cigarette group versus placebo e-cigarette group (57% and 45%, respectively; $P = 0.08$), but a significant difference between nicotine e-cigarettes and nicotine patches was found (57% and 41%, respectively; $P = 0.0002$). Adherence was significantly higher for the nicotine e-cigarette group compared with the patch and placebo e-cigarette groups ($P < 0.0001$ for both comparisons). No significant differences in adverse events between any of the groups was noted. At 6 months, nicotine and placebo e-cigarette users (85% and 88%, respectively) would recommend their product compared with 50% in the patch group.[14]

Summary

There is limited evidence supporting the view that e-cigarettes are effective for smoking cessation; however, there may be a place in therapy to modify smoking habits or reduce the number of cigarettes smoked. Studies available used different administration patterns of e-cigarettes, such as use while smoking, instead of smoking, or as needed. The ability to use both cigarettes and e-cigarettes in combination during study periods is unlike trials with NRT, though the FDA has recently changed labeling to allow NRT to be used with tobacco products or in combination.[15] *Ad libitum* use of e-cigarettes poses difficulties in comparing current cessation products on the market and assessing exactly how they are used.

e-Cigarettes do not appear to improve cessation rates over current FDA-approved NRT products. Only 2 studies compared nicotine e-cigarettes with NRT (nicotine inhaler and 21-mg patch).[9,14] No cessation differences were detected between e-cigarettes and the nicotine inhaler, and both were superior to placebo in the short term.[9] Significant differences were found in time to relapse between nicotine e-cigarettes and nicotine patches, with no difference between nicotine and placebo e-cigarettes. Although statistically significant, only a 2-cigarette/d difference between nicotine e-cigarettes and nicotine patches was identified. At 6 months, there was a significant difference in the percentage of participants reducing their cigarette use between nicotine e-cigarette and nicotine patch groups; however, this was not found between nicotine e-cigarette versus placebo e-cigarette groups.[14] Therefore, it is difficult to extrapolate these results to support long-term cessation over NRT.

Patient preference leans toward the use of the e-cigarette device in several studies likely because of the repetitive reinforced hand-mouth pattern of smoking while using this product. This finding appears to extend to placebo e-cigarette devices as well. Very few between-group differences were found when comparing nicotine e-cigarettes with placebo e-cigarettes. Both significantly reduced the desire to smoke, nicotine withdrawal symptoms, and number of cigarettes-per-day. Correlation between number of cartridges-per-day and reduction or cessation rates varied between studies, and the only significant correlation was found using an overall comparison of reducers and quitters (including placebo groups). This suggests that the positive effect e-cigarettes have on reduction of smoking may not be related to nicotine delivery but rather to the ability of e-cigarettes to replace the ritual of smoking gestures.

Several limitations exist with data available. Short-term studies reviewed were small and not necessarily evaluating cessation; they focused more on parameters associated with cessation withdrawal symptoms. Though reducing withdrawal symptoms is important to the smoker quitting, FDA-approved cessation products are held to the standard of successful cessation rates in the long-term. Most studies showed a decrease in adverse effects, several of which can be attributed to cigarette use to begin with. One study demonstrated an improvement in breathing, but the number of cigarettes-per-day also decreased over time. Therefore, one cannot conclude that these findings are a result of the positive effect of nicotine e-cigarettes versus tobacco cigarettes.

Self-reported abstinence varied and was defined as "not even 1 puff" in some studies, whereas others considered ≤5 cigarettes in total as acceptable. All studies used eCO levels (measured in ppm) for verification of smoking cessation; upper acceptable limits ranged from ≤7 to ≤10 ppm. The ECLAT study also reported measurable cotinine levels in participants with eCO ≤7 ppm. Generally, cotinine levels are preferred in studies because of the long half-life of cotinine and accuracy in detecting long-term cessation, yet not differing by the type of product delivering nicotine; this is in contrast to eCO, which determines if one has smoked recently.

e-Cigarettes have become a popular alternative to smoking because of the perceived safety in comparison with the harmful combustion by-products of tobacco cigarettes. Long-term safety is unknown, and concerns with increased poisoning exposures among adults in comparison to cigarettes is alarming. Nicotine toxicity may be further perpetuated by dual use with nicotine cigarettes or NRT. Additional well-designed, long-term cessation studies are warranted, especially in comparison to current FDA-approved products. With pending regulations to the e-cigarette industry, this may prompt additional scientific studies to further support the use of health claims on products in the future.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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