

Electronic cigarettes in smoking cessation

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ABSTRACT

Background: Tobacco use is the most prevalent preventable cause of death in the United States, accounting for approximately 20% of all deaths each year. Despite available treatment options, many smokers still experience multiple failed quit attempts indicating a need for development of novel therapies. When the electronic cigarette (e-cigarette) was introduced to the United States' market in 2007, patients began to discuss its possible use as the newest form of nicotine replacement therapy (NRT).

Methods: A PubMed search was performed for the following terms: "Electronic cigarettes, e-cigarettes, and smoking cessation". A manual search of references from articles found was performed to identify additional relevant articles.

Results: Most evidence surrounding use of e-cigarettes for smoking cessation is found in self-reports and user surveys. One study looking at short-term effects of e-cigarettes on desire to smoke found a decreased desire in subjects inhaling from both nicotine-containing and placebo e-cigarettes. Three studies from Italy looked at natural reduction of cigarette use when subjects were allowed to freely use e-cigarettes. All three studies showed a natural reduction indicating potential efficacy for e-cigarette use in smoking cessation. A recently published randomized controlled trial was unable to prove superiority of e-cigarettes over transdermal nicotine patches for smoking cessation.

Conclusions: A few studies have explored the possibility of replacing tobacco cigarettes with e-cigarettes to facilitate a natural reduction in use and have shown minimal positive results in a population not intending to quit. A recent randomized controlled trial comparing e-cigarettes with nicotine patches for smoking cessation was unable to prove superiority. Until these products are regulated and efficacy can be shown with well-designed studies, e-cigarettes are not a viable treatment for use in smoking cessation or as nicotine replacement therapy.

KEYWORDS

e-cigarettes, nicotine replacement, smoking cessation

INTRODUCTION

Tobacco use in the United States has trended down over the past decade, but it is still the most prevalent preventable cause of death in the country accounting for approximately 20% of all deaths each year.¹ Cigarette smoking has been linked to the development of many medical conditions such as lung and throat cancers, chronic obstructive pulmonary disease, cardiovascular disease, and glaucoma. These conditions resulted in an estimated \$193 billion healthcare cost per year in the United States between 2000 and 2004.² Even in patients with a long history of smoking cigarettes, the benefits of quitting include a well-documented reduction in morbidity and mortality.^{3,4,5,6} There are several treatments available to aid in smoking cessation including nicotine replacement therapy, bupropion sustained-release (Zyban®), and varenicline (Chantix®), all of which are recognized as first-line therapies by current guidelines

(in addition to counseling).⁷ Nicotine replacement therapy (NRT) is available in many forms (gum, lozenges, transdermal patches, nasal spray, and inhalers) allowing for individualization of treatment. Despite the wide array of treatment options, many smokers still experience multiple failed quit attempts indicating a need for development of new treatments. When the e-cigarette was introduced to the United States' market in 2007, patients began to discuss its possible use as the newest form of NRT.

HISTORY OF ELECTRONIC CIGARETTES

The first "smokeless non-tobacco cigarette" was patented in 1965 by Herbert A. Gilbert of Beaver Falls, Pennsylvania, but never reached the consumer market.⁸ Nearly forty years later, the modern e-cigarette was invented in China by pharmacist Hon Lik.⁹ The modern e-cigarette device mimics the shape of a regular cigarette and is available in re-chargeable and disposable forms.

The devices utilize a battery and atomizer to heat and vaporize a nicotine solution for inhalation. The solution consists of pure nicotine dissolved in a liquid, often propylene glycol or vegetable glycerin.¹⁰ The contents of this simple solution represent only a fraction of the chemicals found in tobacco smoke and have led some to speculate that e-cigarettes may be a safer alternative to tobacco cigarettes.¹¹ Unlike most approved cessation treatments, e-cigarettes tap into the psychological component of cigarette addiction by simulating the tactile sensation of handling and inhaling a cigarette. Nicotine inhalers (Nicotrol®) also mimic the handling of a cigarette, but e-cigarettes are more reminiscent of actual cigarette use because of the vapor that they emit. E-cigarettes may also be more appealing than currently available quit aids due to the variety of styles and flavors available as well as successful marketing strategies.

When e-cigarettes first appeared on the market, they were sold by small companies with no ties to big tobacco companies. Today however, many large tobacco companies including Lorillard, Philip Morris, Altria, Imperial Tobacco, and British American Tobacco have either already marketed an e-cigarette or have announced future plans to.¹² This presents a potential conflict of interest if e-cigarettes were to obtain approval as medication delivery devices.

THE EVIDENCE

Few studies assessing the safety and efficacy of e-cigarettes have been performed. Consequently, most current knowledge about e-cigarette use in smoking cessation is extrapolated from self-reports and surveys of users. A mixed-design study randomized 86 subjects to use an 18mg nicotine e-cigarette, a 0mg nicotine e-cigarette, or just to hold an e-cigarette for 5 minutes.¹³ Subjects completed scales to assess desire to smoke and withdrawal symptoms at 0 minutes, 5 minutes, and 20 minutes after using or holding the e-cigarette. Results showed that desire to smoke decreased over time in both the 18mg and 0mg e-cigarette groups as compared to the group that only held the e-cigarette. Three observational studies from Italy considered the use of e-cigarettes in smokers without intent to quit. These three studies had a major investigator in common and similar study designs. The studies allowed subjects to utilize Categoria® brand e-cigarettes as desired up to the manufacturer recommended maximum and observed for a natural reduction in tobacco cigarette use.^{10,14,15} Of note, one of the studies included only subjects with chronic schizophrenia while the other two studies excluded patients with chronic psychiatric illness or chronic use of

psychotropic medications. These three studies are detailed below.

Considering the results of the three studies detailed above, the efficacy of use of e-cigarettes to cause a natural reduction in the use of tobacco cigarettes is still not clear. In the study of smokers with schizophrenia, only 14% (2 subjects) were able to reach sustained abstinence at 52 weeks.¹⁴ In the three-armed, randomized controlled trial, again only 14% of subjects in the nicotine cartridge groups were able to reach sustained abstinence at the end of the study period.¹⁰ Similarly, in the third study, only 12.5% of subjects were able to reach sustained abstinence at the end of the study period.¹⁵ Two of these studies utilized a small sample size and observational design, limiting the ability to draw valid conclusions.^{10,14} All three of the studies relied on self-reports and carbon dioxide exhalation for determining abstinence introducing a possible confounder. Due to the fact that these three studies were conducted with subjects who did not desire to quit smoking, results cannot be extrapolated to smoking cessation.

More recently, a randomized controlled trial directly pitting e-cigarettes against nicotine transdermal patches for smoking cessation has been published.¹⁶ The study, from New Zealand, randomized 657 subjects with interest in quitting smoking to receive nicotine e-cigarettes, nicotine patches, or placebo e-cigarettes. Subjects randomized to receive patches received a supply of 21mg/24hr patches with instructions to use from 1 week prior to quit date until 12 weeks after. Participants randomized to receive e-cigarettes (either nicotine or placebo) received a device and supply of cartridges (nicotine contents were blinded) and were instructed to use the device as desired from 1 week prior to their quit date until 12 weeks after. Participants were also provided access to Quitline, a telephone-based counseling service, and were allowed to utilize it as desired. However, results revealed that less than half of the study participants in each group chose to utilize the service. The primary outcome was continuous abstinence at 6 months, confirmed using self-reports and exhaled carbon monoxide concentrations. While primary outcome results were in favor of e-cigarettes for smoking cessation over nicotine patches (7.3% nicotine e-cigarettes; 5.8% nicotine patches; 4.1% placebo e-cigarettes), there was an insufficient margin to prove superiority. Investigators did find a significant advantage for nicotine e-cigarettes in median time to relapse (35 days nicotine e-cigarettes; 14 days nicotine patches; 12 days placebo e-cigarettes) and adherence to study treatment (at 1 month: 78%, 46%,

and 82%, respectively). While the adherence results present a compelling argument for the relative tolerability of e-cigarettes in a real-world setting, they leave the question of how efficacy of e-cigarettes would compare to nicotine patches with similar adherence rates and with proper counseling support.

Although e-cigarettes are thought to be a safer alternative to cigarettes, toxins have been identified in the cartridges of many brands.^{11,17} One study compared the contents of cartridges in twelve different e-cigarette brands with the contents of prescription nicotine inhalers. Small amounts of toxic carbonyls were found in both the e-cigarettes and the inhalers.¹¹ Other toxic substances, such as nitrosamines and volatile organic compounds were found in the e-cigarettes in small amounts, but not in the nicotine inhalers. The investigators of this study speculated that some of the toxic substances are by-products of heating glycerin and may possibly only be present in the vapor. Regardless of the source, results indicate that toxins are still being inhaled by the user which may lead to detrimental health effects. The Food and Drug Administration (FDA) also tested contents of e-cigarettes for toxins in 2009 and found trace amounts of diethylene glycol, a toxic component of brake fluid.¹⁷

In addition to testing for toxins, a few small studies have tested e-cigarettes for nicotine content.^{17,18} These studies have shown that most e-cigarette cartridges do not contain the amount of nicotine indicated on the label; many contain more or less. Because e-cigarettes are not regulated by any governing body, the contents are not guaranteed to match those detailed on the label. Contents may even vary between different lots of the same brand. This presents a considerable issue if considering use of e-cigarettes as a smoking cessation aid.

CONSIDERATION IN MENTAL ILLNESS

Persons with mental illness have a higher risk for development of smoking habits compared to those without, with smoking rates for patients with schizophrenia estimated as high as 88%.¹⁹ The Centers for Disease Control and Prevention (CDC) have identified that 40% of men and 34% of women with mental illness are smokers.¹⁹ It has been speculated that this increased rate of smoking is due in part to a desire to self-medicate, especially in schizophrenia. Activity of nicotine at the alpha-7-nicotinic acetylcholine receptor has been shown to have a positive effect on cognition which can be very influential in treatment outcomes for patients with

Table 1. Relevant studies

Study (N)	Design	Results
Caponnetto P, Auditore R, Russo C, et al. 2013 (N=14)	Observational prospective study Clinic visits at weeks 4, 8, 12, 24, and 52	Sustained 50% reduction in cigarettes/day at week 52 observed in 7 subjects Sustained smoking abstinence at week 52 observed in 2 subjects Most frequent adverse events reported were throat irritation (14.4%), nausea (14.4%), headache (14.4%), and dry cough (28.6%)
Caponnetto P, Campagna D, Cibella F, et al. 2013 (N=300)	3 arm, double-blind, RCT: Group 1: 12 weeks of 7.2mg nicotine cartridges Group 2: 6 weeks of 7.2mg nicotine cartridges and 6 weeks of 5.4mg nicotine cartridges Group 3: 12 weeks of 0mg nicotine cartridges Clinic visits at weeks 2, 4, 6, 8, 10, 12, 24, and 52	Week 12, complete abstinence observed in 14% nicotine cartridge group vs. 4% placebo cartridge group Reduction and abstinence rates not statistically significantly different for the two nicotine groups Adverse events reported were not different from those reported at baseline
Polosa R, Morjaria JB, Caponnetto P, et al. 2013 (N=40)	Observational prospective cohort study Free use of 7.4mg nicotine cartridge e-cigarette up to manufacturer-recommended maximum for 6 months Clinic visits at weeks 4, 8, and 12 Post-intervention follow up: 18 and 24 months	Overall 80% reduction in median cigarette/day use observed by end of study (p<0.0001) Sustained 50% reduction in cigarettes/day at 24 months observed in 11 subjects (27.5%) Sustained 80% reduction in cigarettes/day at 24 months observed in 6 subjects (15%) By end of study, 5 subjects (12.5%) quit smoking Most common adverse events: mouth irritation (14.8%), throat irritation (7.4%), and dry cough (11.1%)

schizophrenia.²⁰ Consequently, quitting is thought to be more difficult for this population. A tobacco cigarette alternative with potentially less detrimental health effects could provide considerable benefit to patients with mental illness. In addition, cigarette smoke can induce the metabolism of many prescription medications used to treat mental illness via cytochrome P₄₅₀ 1A₂ enzyme pathway.²¹ Clozapine, olanzapine, and asenapine are among the medications metabolized through this pathway. It is unknown whether or not e-cigarettes have the same induction effect as tobacco smoke, but it is unlikely given that they do not contain the polycyclic aromatic hydrocarbons responsible for the interaction.²¹

CONCLUSIONS

With tobacco use the leading cause of preventable death in the United States, there is a large demand for novel smoking cessation treatments. Utilizing e-cigarettes for smoking cessation, however, presents a possible conflict of interest due to the involvement of big tobacco companies. Furthermore, there is an absence of long-term safety data for e-cigarettes. The World Health Organization openly discourages consumers from utilizing e-cigarettes until a competent national regulatory body approves of their safety, effectiveness, and quality.²² At this time, e-cigarettes are not regulated as tobacco products or medication delivery devices and thus cannot be recommended for use in smoking cessation or as nicotine replacement therapy. Future investigation should include larger, randomized controlled trials with primary outcomes of morbidity and mortality risk reduction.

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