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REVIEW

E-cigarettes in patients with COPD: current perspectives

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Abstract: Conventional cigarette smoking is known to result in significant COPD morbidity and mortality. Strategies to reduce and/or stop smoking in this highly vulnerable patient group are key public health priorities to reduce COPD morbidity and mortality. Unfortunately, smoking cessation efforts in patients with COPD are poor and there is a compelling need for more efficient approaches to cessation for patients with COPD. Electronic cigarettes (ECs) are devices that use batteries to vaporize nicotine. They may facilitate quit attempts and cessation in many smokers. Although they are not risk free, ECs are much less harmful than tobacco smoking. Hence, the use of ECs in vulnerable groups and in patients with challenges to abstain or multiple relapses to this habit may be promising. To date, little is known about health consequences of EC use among COPD smokers and whether their regular use has any effects on subjective and objective COPD outcomes. In the current review, we discuss the current perspectives and literature on the role of ECs in abstaining from conventional smoking and the effects of ECs on the respiratory tract in patients with COPD.

Keywords: smoking cessation, electronic cigarette, COPD, tobacco harm reduction

Introduction

COPD is a progressive and debilitating disease that is estimated to become the third leading cause of death in 2030.[1] COPD is a condition that may result in respiratory symptoms, progressive decline in lung function, respiratory failure, cor pulmonale, and death due to the underlying relentless inflammatory response in the airways.[2–4]

The COPD inflammatory response is often associated with smoking and only marginally responds to anti-inflammatory medications, including topical corticosteroids.[5,6] In addition, current and ex-smokers with COPD have an augmented risk for lung cancer,[7] cardiovascular diseases,[8,9] and diabetes.[10]

The only evidence-based strategy known to improve the COPD prognosis is smoking cessation.[11] For example, abstaining from smoking not only improves overall health status but also attenuates the rate of annual pulmonary function decline and respiratory symptoms of cough and sputum.[12–14] Importantly, the discontinuation of smoking decreases the risk of developing lung cancer, cardiovascular disease, and other tobacco-related illnesses.[15]

Therefore, encouraging smoking patients with COPD to relinquish their habit as early as possible is pivotal. Unfortunately, once established, smoking is a tough addiction to break, even for those with a strong desire to quit. This is not surprising given that nicotine dependence shows many features of a chronic disease, with the majority of smokers typically experiencing multiple periods of remission and relapse. Approximately 80% of smokers who attempt to quit independently have been shown

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to relapse within the first month of abstinence, and only about 5% achieve long-term abstinence.[16]

Recognizing the relapsing nature of the condition emphasizes the importance of ongoing care, and numerous treatment alternatives are now available to aid with the repeated attempts to quit and to decrease episodes of relapse. Currently approved smoking cessation medications (such as nicotine replacement therapy, the antidepressant, bupropion, and the partial agonist of the α4β2 nicotinic acetylcholine receptor, varenicline) in combination with counseling have been shown to double or triple quit rates under ideal circumstances of stringent settings of clinical trials.[17,18] Nonetheless, relapse is common in the course of a smoking cessation program.[19] Relapse rates are very high in patients with COPD compared to smokers in the general population,[20] and failed smoking cessation and relapses are more commonly noted in patients with COPD undergoing smoking cessation programs with or without psychological interventions alone or in combination with other pharmacological interventions.[21] This has been attributed to their higher pack-year history, enhanced degree of nicotine dependence and risk for depressive symptoms, and poor motivation to quit.[22,23] Hence, better quit rates are warranted in a population that usually responds poorly to smoking cessation attempts, and there is a compelling need for more efficient approaches to cessation for patients with COPD. Electronic cigarettes (ECs) are devices that vaporize nicotine, which may aid smokers in quitting or attenuating their tobacco habits.[24–26]

In this review, we present an overview on the potential role of ECs in smoking cessation and harm reduction, with an emphasis on COPD.

Electronic cigarettes

ECs are electronic devices with three main parts: a battery, an atomizer composed of a wick and metal coil, and a liquid (e-liquid) stored inside the atomizer. ECs were invented and patented in 2007 by Hon,[27] a pharmacist from China who was seeking to develop an alternative-to-smoking method of nicotine intake. The patent describes a battery-operated device intending to provide a much less harmful means for and method of smoking by replacing burning tobacco and paper with a heated, moist, flavored aerosol.

The term EC includes a large variety of devices with different design and functional and performance characteristics. Although there is still no consensus on terminology, currently marketed ECs are mainly of three types:[28] first-, second-, and third-generation devices. First-generation (cig-alike) devices have comparable size, shape, and appearance to conventional tobacco cigarettes. They consist of a small lithium battery and a cartomizer; with the battery either disposed (discarded after being discharged) or recharged. The cartomizer is a specific type of atomizer, consisting of a sponge-like polyfil (polyester fiber) material, which is soaked with the e-liquid. There is no tank where the liquid is stored. Usually, cartomizers are prefilled with liquid, although empty cartomizers are also available which can be refilled with the smokers' choice of e-liquid. Second-generation devices consist of a larger rechargeable lithium battery (eGo-type batteries) and cylindrical shape resembling a large pen. The atomizer is refillable and has a tank design, with a storage space for the e-liquid and a transparent window so that the user may visualize the e-liquid level. Initially, the whole atomizer had to be discarded after several milliliters of e-liquid consumption; however, in the recent past, they have been available with removable heads so that the resistance and wick parts may be changed and the body retained. Third-generation devices, called "mods" or "advanced personal vaporizers," consist of a large-capacity lithium battery with an integrated circuit that permits the user to regulate the energy delivered to the atomizer. They usually have either a cylindrical or a box-like shape and can be amalgamated with either second-generation atomizers or re-buildable atomizers, where users can prepare a custom setup of resistance and wick. Most of these atomizers have a tank-type design.

Irrespective of the classification, all ECs works on the same operating principle; upon inhalation, the electrical current from the battery heats up an element (most commonly, a metal coil inside the atomizer) that vaporizes a solution (e-liquid; largely consisting of propylene glycol [PG], distilled water, glycerol, and flavorings with or without nicotine) producing a visible aerosol. The user inhales the aerosol generated by vaporizing the e-liquid in a process commonly referred to as "vaping." ECs do not contain tobacco, create smoke, or rely on combustion to operate. Rapid innovation is characteristic of these products; cig-alike devices with low aerosol volume production[29] and low nicotine delivery potential[30,31] have evolved to newer devices that produce more sensory satisfaction[32] and more nicotine delivery and absorption,[31] very close to the delivery rate and level of tobacco cigarettes.[33]

ECs and tobacco harm reduction (THR)

THR is the strategy of decreasing the net damage to health associated with the use of combustible tobacco products by considering their substitution with alternative low-risk sources of nicotine in smokers who are unable or reluctant to stop smoking. It is based on the well-known notion that

smokers die from inhaling thousands of toxic substances and carcinogens present in cigarette smoke and not from nicotine.[34,35] Although nicotine in itself may not be absolutely harmless, it is not considered a carcinogen by the International Agency for Research on Cancer[36] and is relatively safe for human consumption.[37] A recent US Surgeon General's report examined the harm caused by nicotine and concluded that it does not contribute to respiratory diseases.[15]

The toxicology for EC vapor is by far less problematic than that for tobacco smoke[31] due to the simple composition of EC aerosols[38–40] contrasting to the thousands of constituents found in cigarette smoke.[41] EC use is regarded as having lower levels of risks than smoking, having been reported by the Royal College of Physicians[42] and Public Health England[43] to be 95% less injurious than conventional cigarettes.[44] More recently, an important confirmation of the reduced harm from ECs is the dramatic reduction in exposure to carcinogens and toxins (biomarkers) measured in EC users compared to tobacco smokers. Shahab et al[45] found that long-term EC users (>6 months) had substantially reduced levels of selected tobacco-related carcinogens and toxins in the saliva and urine compared to continuing smokers. Other studies have found similar results.[46–48] However, there is concern that long-term exposure to their residual toxicological load might nevertheless carry some health risk.

ECs are quickly becoming the most promising THR products to date.[49] This is due to their effectiveness in decreasing conventional tobacco consumption, competitive price, and the discernment of being a much less detrimental smoking substitute, and also they permit the smoker to maintain a "smoking experience without smoking."[50–52] Currently, they are the only products in the arsenal that replicate the habits of conventional cigarette smoking along with nicotine delivery As such, they may encourage harm reduction in three ways: allowing smokers to quit, helping former smokers avoid relapse, and preventing nonsmokers from initiating smoking. Population studies[53–55] have shown that regular EC use is predominantly noted in former and current smokers (and very rare among never smokers), supporting the argument that these products are currently used for harm reduction.

ECs and abstinence from smoking

ECs are effective aids for some smokers to quit smoking including those challenging patients with several comorbidities.[56] Evidence from large observational studies suggest that ECs can assist in quit attempts and cessation.[52,57,58] One study has found significantly higher quit rates when ECs are combined with counseling by a health professional and other stop-smoking medication.[59] Interestingly, vape shops provide valuable advice and support for smokers wanting to switch and can help smokers achieve high success rates.[60,61]

However, the best evidence for the efficacy of ECs for smoking cessation is in real-world population studies. For example, in 2014, in the European Union, over 6 million smokers reported having quit smoking using an EC.[62] In the UK, 1.5 million former smokers are now vaping.[63] Smoking prevalence in countries where ECs are widely available (eg, UK and USA) is declining faster than ever.[63] It is very likely that ECs are a contributing factor to this rapid decline, although it is not possible to prove cause and effect.

Evidence from randomized clinical trials (RCTs) is less compelling.[64–66] However, RCTs are often not suited to public health research on complex consumer behaviors and are often misleading.[67] It is impossible to control an EC trial, as there are many factors independent of the device.[68] Uptake depends on personal preferences, support provided from vape shops or peers, cost, risk perceptions, regulatory issues, accessibility, and other uncontrollable factors. The process of finding a suitable EC and e-liquid by a smoker is not linear and not easily randomizable. There is an unlimited range of choices, and most users experiment with different models, e-liquid strengths, and flavors before finding the right one. The typical binary choice of an RCT is not suited to this type of decision making. It is important to note that early studies used now-obsolete first-generation ECs with low nicotine delivery and technical flaws. Nonetheless, the results were comparable with those from nicotine replacement therapy products.[69] More advanced devices, which deliver higher nicotine levels, have been shown to be more effective.[66,70]

Vaping and the respiratory tract

Among many of the constituents of e-liquid, glycerol and PG are the most abundant. The US Food and Drug Administration (FDA) and the US Environmental Protection Agency (EPA) categorize glycerol and PG as Generally Recognized as Safe (GRAS).[71] Despite their good safety profile, exposure to aerosols containing glycerol and PG may elicit transient irritant responses (ie, dry cough, throat, and other symptoms of respiratory irritation) in predisposed individuals.[64,72,73] In addition, given that the particle size in EC aerosols is well within the respiratory range,[74,75] high levels of vapor particle deposition are expected to penetrate into the lungs with every puff.[76,77] Thus, the airways are the primary target of any potential harmful effects of constituents in the aerosol emissions of ECs.

Wu et al[78] have demonstrated that cultures of human airway epithelial cells infected with human rhinovirus increased viral load and production of antiviral proteins

as well as inflammatory markers when exposed to e-liquid treatment. Although these findings may have relevance to respiratory exacerbations in COPD, studies of e-liquid exposure have been criticized because they are not representative of exposures under normal conditions of use.

Some authors have reported acute changes using sensitive respiratory functional tests;[79] however, this may simply reflect the physiological response of the respiratory tract against transient irritation from EC aerosols. Nonetheless, it cannot be excluded that more serious adverse events may occur in predisposed individuals "sensitized" to contaminants or by-products contained in EC aerosol. The issue of whether such an acute irritation may be interpreted into clinically meaningful lung disease remains unanswered, and there is indeed no evidence to suggest that such irritation may result in clinically significant adverse lung effects. For example, the clinical relevance of the small and well within test variability 16% decrease in exhaled nitric oxide levels and 11% increase in peripheral flow resistance 5 min after EC use is questionable.[79] More importantly, no significant changes could be detected by standard spirometry immediately after EC use.[79] Other researchers have confirmed the absence of airflow obstruction after EC use.[80,81] Although exhaled nitric oxide findings immediately after EC use have been conflicting,[79,80] changing over to EC use quickly and generally leads to a near normalization in noxious levels of exhaled carbon monoxide levels.[73] Overall, studies that have focused on the acute effects on lung function and airway responses with EC use have not substantiated negative respiratory health outcomes in EC users.

A recent RCT of "healthy" smokers, for up to 1 year, invited to quit or reduce cigarette consumption by switching to ECs assessed changes in lung function, airway responses, and respiratory symptoms,[82,83] has shown normalization of both exhaled nitric oxide and carbon monoxide levels among those subjects who completely quit cigarette smoking by switching to ECs.[82] Reversal to within normal nonsmoking levels was already documented at 3 months and complete normalization observed at 6 and 12 months.[82] No evidence of airway obstruction was noted, irrespective of participants' smoking phenotype classification. This is not unexpected, given that study participants were "healthy" smokers without preexisting lung disease. Interestingly, early improvements in forced expiratory flow 25%–75% (a sensitive measure of more peripheral airway obstruction) could already be observed at 3 months after changing over to ECs among those who absolutely gave up conventional cigarette smoking, with continuing improvements at 6 and 12 months.[83] The progressive normalization of peripheral airway function was associated with a substantial reduction in self-reported respiratory symptoms (cough and dyspnea), particularly in individuals who completely gave up smoking.[83] However, it is not known whether harm reversal in peripheral airways can translate into efficient prevention of airway disease later in life.

Vaping and COPD

Findings from the 2014 and 2015 National Health Interview Survey (NHIS) indicate that EC use by current and former smokers with COPD is substantial.[84] After adjusting for demographic and socioeconomic factors, both current and former cigarette smokers with COPD in this large US population survey were more likely to have tried ECs compared to those without medical comorbidities. In addition, among former smokers with COPD regular EC use was nearly three times more frequent. It would seem that former smokers with COPD probably rely on ECs to prevent relapse to conventional cigarette smoking. Unfortunately, the design of this survey does not allow insights as to whether ECs could help quit or reduce harm from conventional cigarettes.

Nonetheless, a growing plethora of studies indicate that ECs may aid smokers stop or reduce their tobacco consumption, besides being well tolerated. Therefore, it is important to replicate these observations in vulnerable populations with high rates of unsuccessful smoking cessation and relapses. Given the pathogenetic role of tobacco smoking, the low adherence to COPD medications, and the poor response to smoking cessation efforts, it follows that EC-based interventions for patients with COPD who smoke are highly desirable.

Although reducing cigarette consumption by switching to EC use may yield considerable respiratory benefits in COPD, only limited work has addressed the health impact of EC use in users with preexisting COPD. A recent retrospective study has formally assessed the efficacy and safety of ECs in patients with COPD. No deterioration in respiratory physiology (post-bronchodilator forced expiratory volume in 1 s [FEV_1], forced vital capacity [FVC], and $\%FEV_1/FVC$) was observed in patients with COPD who stopped or considerably reduced their tobacco consumption by substituting to EC use.[85] The absence of significant increments in spirometric indices after quitting smoking is not uncommon in COPD smokers and irreversible airway obstruction.[86,87] Nonetheless, progressive significant decline in annual respiratory exacerbations, improved general health status (assessed using the COPD assessment tool [CAT]) and physical activity (assessed using the 6-minute walk distance test) were documented throughout the 2-year reporting period.[85] That respiratory exacerbations were

halved in patients with COPD who ceased or markedly reduced their tobacco consumption after switching to ECs was a key finding. Persistent exposure of cigarette smoke to the airways is known to promote infection susceptibility through several different mechanisms.[88,89] Thus, switching to ECs by abstaining from tobacco smoking may explain the attenuation in respiratory infections.[90] The reported improvement in health outcomes is in agreement with observations from an Internet-based survey of 1,190 regular COPD EC users.[51] Self-reported improvement in respiratory symptoms after switching was reported in 75.7% of the respondents, whereas worsening was reported in only 0.8%. Of note, it was reported that a fifth of all the participants stopped the use of their routine respiratory medications with the use of ECs.

The positive evidence from real-life surveys and clinical studies of patients with COPD supporting respiratory health benefits with EC use is in stark contrast with the concerns raised in preclinical models (ie, cell cultures and animal models). For instance, in the study by Garcia-Arcos et al,[91] prolonged exposure to inhaled nicotine-containing glycerol or PG in A/J mice stimulated the development of COPD-like effects, such as cytokine expression, airway hyperreactivity, and lung tissue destruction. The authors suggest that chronic exposure to nicotine from nebulized e-liquid may elicit features of COPD/emphysema. However, A/J mice are susceptible to develop features of pulmonary emphysema and COPD,[92–94] in particular, when exposed to toxic concentrations of nicotine (which are unrelated to normal human consumption). This may be explained, for example, by using the understanding that an average 60 kg person may absorb, from smoking one conventional cigarette, 1 mg of nicotine which is equivalent to 0.017 mg nicotine/kg bodyweight. Hence, if an individual smokes 25 cigarettes/day (a mean quantity consumed in the USA per day), then the total nicotine levels would be 0.425 mg (0.017×25) of nicotine/kg bodyweight. In the study using A/J mice, the rodents were exposed to 0.4 mL of e-liquid which had a concentration of 18 mg/mL which is equivalent to 7.2 mg. If we assume that the mice absorbed 10% of the exposed 7.2 mg (best case scenario), this would be 0.72 mg bodyweight which is approximately a doubling of the nicotine/kg human bodyweight. In addition, we consider the overall bodyweight of the mice, which would be about 25 g; then, the daily dose of nicotine exposure in the study would imply >80 times that of an average US smoker of 25 cigarettes/day. This would imply nothing but intoxication. Also, outcomes from earlier animal studies have reported conflicting results; especially, when mice of different strains have been used where the features of nicotine-dependent COPD changes have not been reproduced. In another study using A/J mice, continued intraperitoneal injections of nicotine at lower doses was shown to result in similar air space enlargement in the lungs.[95] This would imply that A/J mice may have an inherent predisposition to develop emphysematous changes when challenged with noxious stimuli.

It is evident that, due to serious methodological drawbacks and lack of standardization among many of these studies, clear conclusions cannot be drawn. Addressing common errors and developing robust and realistic methodological recommendations is an urgent priority to adequately assess the impact on human health with the use of ECs.

Conclusion

Although ECs are not risk free, they are much less harmful than conventional tobacco smoking.[42–44] The emerging clinical evidence suggests that ECs are unlikely to raise significant health concerns for the respiratory tract under normal condition of use, even in smokers with preexisting lung disease.[96] In particular, recent studies in COPD[85] and chronic asthma[97,98] suggest that substitution of conventional tobacco cigarettes for ECs can ameliorate subjective and objective disease-related outcomes and exacerbation rates as well as improving success in abstaining from smoking long term.

If these initial observations are confirmed in large prospective studies, the prospect for reducing the suffering of many patients with COPD may become tangible. In the interim, former smokers using and smokers intending to use ECs should receive correct information about residual risks and potential benefits of these products.[99] Physicians should consider all the options available to a smoking patient and opt for the ones that provide the greatest probability of abolishing exposure to tobacco smoking, including ECs.[56] For many smokers, the optimal outcome may be a long-term swapping to vaping, allowing for the small residual risk for a higher likelihood of success.

Of course, vaping products must comply with safety and quality standards to safeguard consumers; currently, the European Union CEN/Technical Committee 437[100] and the International Organization for Standardization (ISO) are together developing standards for thermal, electrical, and chemical safety and e-liquid standards, as well as analytical methods for aerosol emissions. Although there is the dilemma of the need for more independent studies, it is pivotal that we need more studies that provide unbiased evidence which use a rigorous, sound methodology that is rationally rooted to its subject matter and that leads to repeatable findings. Promoting access to safety and quality-approved vaping products may tender an opportunity to ameliorate or avert some of the

otherwise unavoidable burden of respiratory morbidity and mortality caused by conventional tobacco smoking.[101]

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