CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will advise patients who smoke not to use e-cigarettes as a form of nicotine replacement therapy

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E-cigarettes: Safe to recommend to patients?

ABSTRACT

Electronic cigarettes (e-cigarettes)—devices that generate a nicotine vapor that can be inhaled by the user in a fashion that mimics the experience of smoking—are increasing in popularity, and many people seem to view them as reasonable alternatives to nicotine replacement therapy to help them refrain from smoking. Physicians should not encourage such a view. E-cigarettes are unregulated nicotine delivery systems that have never been subjected to any kind of testing of safety or of efficacy as nicotine replacement therapy. Moreover, for young people who have never smoked, these devices could potentially serve as a gateway drug.

KEY POINTS

Although the vapor from e-cigarettes does not contain any tobacco combustion products, which are believed to be responsible for most of the adverse health effects of smoking, it does contain nicotine, which is addictive and poses health risks by itself.

E-cigarette vapor also contains propylene glycol, which has not been adequately studied with regard to its safety when inhaled deeply and repeatedly. Also present are a variety of additives and contaminants.

E-cigarette manufacturers make no therapeutic claims about their products, and therefore the US Food and Drug Administration does not regulate them as it does nicotine replacement therapy.

doi:10.3949/ccjm.82a.14054

Most people assume that electronic cigarettes (e-cigarettes) are safer than conventional tobacco products. Nevertheless, we should not encourage addicted smokers to try "vaping" as an alternative to nicotine replacement therapy,and we should discourage never-smokers from taking up vaping as vigorously as we try to discourage them from taking up smoking.

This article examines the prevailing assumptions and the evidence regarding the safety of e-cigarettes and traditional nicotine replacement therapy.

SMOKING IS DECLINING BUT FAR FROM GONE

While smoking rates have been declining over the past 50 years, the burden of disease attributable to tobacco use remains high. In the United States, it is estimated that nearly 6 million of those currently under the age of 18 will die of tobacco-related illnesses.[1] In the 50 years since the US surgeon general first reported on the health concerns related to tobacco, smoking has claimed the lives of nearly 21 million Americans[1] and continues to kill more than 400,000 every year.[2]

Even though the risks of smoking are well known, smoking remains one of the most difficult habits to quit. Indeed, about half of all smokers attempt to quit each year, but very few succeed.[3]

NICOTINE REPLACEMENT: GUM, PATCHES…E-CIGARETTES?

Nicotine replacement therapy was born out of the thought that, though nicotine is responsible for tobacco's addictive quality, most tobac-

co-related disease is attributable to the 7,000 other substances found in tobacco smoke.[4] Nicotine polacrilex gum was approved by the US Food and Drug Administration (FDA) in 1984, and nicotine transdermal film was approved in 1991.[5]

Nicotine replacement therapy, in the form of patches and gum, has been shown to improve the odds of successfully quitting smoking by a factor of nearly 1.5 to 2.[6] Nicotine patches and gum were initially prescription medications but became available over the counter in 1996.[7] They quickly became first-line agents for smoking cessation, and their over-the-counter availability softened any potential concerns about the possible deleterious health consequences of nicotine itself.

E-cigarettes—devices that generate a nicotine vapor that can be inhaled in a fashion that mimics the experience of smoking—were introduced in China in 2004.[8] By 2012, sales of these devices in the United States had reached $500 million and in 2013 were expected to top $1 billion.[9,10]

E-cigarette manufacturers make no therapeutic claims about their products, thus allowing them to escape regulation by the FDA as nicotine replacement therapy. A recent FDA proposal, however, is likely to change their "protected" status.[11] Despite the lack of regulation up to this point, patients generally assume that e-cigarettes are just another form of nicotine replacement therapy, even though they contain substances other than nicotine.

Smoking continues to kill more than 400,000 Americans every year

WHAT'S IN E-CIGARETTES?

Nicotine, which is bad in itself

E-cigarettes contain nicotine in varying amounts (some cartridges contain none at all). Though nicotine replacement therapy is less harmful than tobacco, nicotine by itself is associated with its own health problems, notably cancer, cardiovascular disease, birth defects (possibly), and poisoning.

Carcinogenesis. Nicotine plays a direct role in carcinogenesis through a variety of mechanisms, including increasing the activity of tumor growth-promoting transcription factors, decreasing apoptosis, and increasing angiogenesis in tumors.[12] Additionally, specific types of nicotinic acetylcholine receptors—eg, alpha 7 receptors, which are stimulated by nicotine—are found in many malignant tumors and are thought to play a role in tumor progression.[12] Blockade of alpha 7 nicotinic acetylcholine receptors has been shown to decrease the growth of certain cancers.[12]

However, these findings were from in vitro studies, and the concerns they raised have not been reflected in in vivo studies. Despite having been on the market for 30 years, nicotine replacement therapy has as yet not been associated with any "real world" increase in cancer risk.

Smoking is one of the leading risk factors for cervical cancer, and nicotine itself may play a contributing role. Nicotine has been shown to increase cellular proliferation in cervical cancer.[13] Some evidence suggests that it may also play a role in the lymphogenic metastasis of cervical cancer.[13]

Cardiovascular disease. Nicotine has been linked to cardiovascular disease. It directly affects the heart's rate and rhythm via nicotinic acetylcholine receptors in the peripheral autonomic nervous system. It impairs endothelial-dependent dilation of blood vessels in response to nitric oxide, and this inhibition in the coronary arteries may contribute to smoking-related heart disease.[14,15] Nicotine has also been shown to raise serum cholesterol levels, increase clot formation, and contribute to plaque formation by increasing vascular smooth muscle.[14]

Possible teratogenic effect. There is some theoretical concern regarding exposure to nicotine in utero, as nicotinic acetylcholine receptors develop before neurons, and nicotine may therefore interfere with the natural influence of acetylcholine on the development of this system.[14]

Direct toxicity. Nicotine is toxic at high levels. The overdose potential associated with nicotine is particularly worrisome with e-cigarettes, as the nicotine solution they use is typically supplied in 5-mL, 10-mL, or 20-mL vials that range in concentration from 8.5 to 22.2 mg of nicotine per mL.[16] The fatal single dose range of nicotine has been reported at 30 to 60 mg in adults and 10 mg in children and can be achieved by oral, intravenous, or transdermal absorption,[16] so one vial, if consumed orally, could be fatal.

The number of calls to US poison control centers regarding e-cigarettes has increased, closely paralleling their rise in popularity. In 2010, there were only 30 e-cigarette related calls to poison control centers; in 2011 the number increased to 269, and in 2012 it had reached 459 and included one fatality that was deemed a suicide.[17–19] Even though such toxic nicotine overdoses are rare, physicians should exercise caution and avoid recommending e-cigarettes to individuals with mental confusion, psychotic disorders, or suicidality, who might consume an entire vial.

Possible positive effects? Smoking is one of the worst things that people can do to their body, but the picture is complicated by a few possible positive effects. In the brain, although smoking increases the risk of Alzheimer disease, it is associated with a lower risk of Parkinson disease. In the bowel, it increases the risk of Crohn disease but may decrease the risk of ulcerative colitis. Gahring and Rogers[20] pointed out that neuronal nicotinic receptors are present in nonneuronal cells throughout the body and proposed that expression of these receptors may play a role in mediating the consequences of nicotine use, both good and bad. The lesson may be that nicotine is very active in the body, its effects are complicated and still incompletely understood, and therefore we should not encourage people to inhale nicotine products ad lib.

Additives

E-cigarettes typically contain propylene glycol, flavorings, and glycerine. One study that analyzed the additive contents of e-cigarettes found that propylene glycol accounted for 66% of the fluid, glycerine 24%, and flavorings less than 0.1%.[21] Propylene glycol is the substance typically used in theater fog machines and is used to generate the vapor in e-cigarettes. Other substances such as tobacco-specific nitrosamines and diethylene glycol have also been found in e-cigarettes in small amounts.[22]

Propylene glycol, 'generally recognized as safe'

Propylene glycol has been used in theater fog machines for years—think *Phantom of the Opera*. It is also widely used as a solvent in many consumer products and pharmaceuticals. The FDA classified it as "generally recognized as safe" on the basis of one study conducted in rats and monkeys over 60 years ago.[23] As other authors have noted, however, a major manufacturer of propylene glycol recommends that exposure to propylene glycol mist be avoided.[24,25] Potential concern over propylene glycol mist was heightened when it was discovered that of all industries, the entertainment business ranked first in terms of work-related asthma symptoms and had the fifth-highest rate of wheezing.[26,27]

Consuming one vial of e-cigarette fluid could be fatal

Studies conducted over the last several decades have raised numerous health concerns about the safety of propylene glycol (**Table 1**).[26,28–36] The studies of propylene glycol fog are particularly important, as they most closely resemble the route of exposure in e-cigarette users.

Wieslander et al[28] exposed 27 volunteers to propylene glycol mist for 1 minute in an aircraft simulator under training conditions. Exposures were high, ranging from 176 to 851 mg/m^3 (mean = 309 mg/m^3). Four volunteers who developed a cough exhibited evidence of airway obstruction as indicated by a 5% de-

TABLE 1

Health risks associated with propylene glycol

Mists or fogs

Throat irritation[28]

Ocular irritation[28]

Cough and mild airway obstruction[28]

Throat and vocal cord inflammation[29]

Headache, dizziness, and drowsiness[26]

Topical exposure

Dermatitis[30]

Allergic skin sensitization[31]

Oral mucosal irritation (from propylene glycol-containing toothpaste)[32]

Coma (in a premature infant exposed to propylene glycol-containing antiseptic dressing)[33]

Oral or intravenous exposure

Systemic skin reactions[34]

Renal injury[35]

Coma and acidosis[36]

crease in forced expiratory volume in 1 second (FEV_1), while the rest did not exhibit any change in FEV_1.

Moline et al[29] conducted a non-peer-reviewed study for the Actors Equity Association and the League of American Theaters and Producers of 439 actors exposed to theater fog. They found statistically significant evidence of throat and vocal cord inflammation with prolonged peak exposure to glycols and recommended that actors not be exposed to glycol concentrations exceeding 40 mg/m^3.

Varughese et al[26] conducted a study in 101 volunteers at 19 sites. The mean concentration of glycol-based fog was much lower than that in the studies by Wieslander et al[28] and Moline et al,[29] at 0.49 mg/m^3 (the maximum was 3.22 mg/m^3). The investigators concluded that glycol-based fog was associated with deleterious respiratory effects and that employees' exposure should be limited.

The health issues related to propylene glycol are unique to e-cigarettes compared with nicotine replacement therapy. Unfortunately, the most applicable data available are from studies of persons exposed to theater fog, which involved periodic exposure and likely do not emulate the deep inhalation, multiple times daily, of propylene glycol by e-cigarette smokers. A 2014 review of the chemistry of contaminants in e-cigarettes[37] concluded that estimated levels of propylene glycol exposure in e-cigarette users come close to the threshold limit value set by the American Conference of Governmental Industrial Hygienists, and should merit concern.

Nicotine replacement therapy and e-cigarettes both maintain addiction to nicotine

These studies and real-life experience in the theater, while limited in scope, should give physicians pause and should cause increased awareness of the possibility of e-cigarette-induced pulmonary and upper airway complications. If such complications should occur, discontinuation of vaping should be advised.

Contaminants

The issue of adulterants is common to both e-cigarettes and nicotine replacement therapy. Several unlisted substances have been found in analyzed samples of e-cigarette fluid, including tobacco-specific nitrosamines (TSNAs), diethylene glycol (found in only one e-cigarette cartridge), cotinine, anabasine, myosmine, and beta-nicotyrine.[22] The tobacco-specific nitrosamines N´-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanabasine, and nitrosoanatabine have been found in five e-cigarette cartridge samples from two manufacturers in amounts similar to those found in nicotine replacement products.[22]

Goniewicz et al[38] tested the vapor generated by 12 e-cigarette brands and found trace amounts of TSNAs. NNN was present in the vapor of eight of the samples in concentrations ranging from 0.8 to 4.3 ng per 150 puffs, and NNK in the vapor of nine of the samples in concentrations ranging from 1.1 to 28.3 ng per 150 puffs. Neither NNN nor NNK was found in blank samples nor with the Nicorette inhalator tested in the same study.[38]

Because TNSAs can be formed from nicotine and its metabolites, there is also concern that cancer-causing nitrosamines may be formed from nicotine after it is absorbed into the body (ie, endogenously). While endogenous formation of NNK from nicotine has never been demonstrated, endogenous formation of NNN has been seen in some nicotine patch users.[39] The presence of these nitrosamines has raised concern that e-cigarettes and nicotine replacement therapy may have carcinogenic potential. The amounts of tobacco-specific nitrosamines found in e-cigarettes are also found in some nicotine replacement products.[40]

Investigators have examined a possible connection between e-cigarettes and potentially carcinogenic carbonyl compounds, including formaldehyde, acetaldehyde, and acrolein. Formaldehyde (a known carcinogen) and acetaldehyde (a potential carcinogen) have been detected in e-cigarette cartridges and vapor.[38,41–43] Acrolein, a mucosal irritant, has been found in e-cigarette vapor.[38,43] Goniewicz et al[38] suggested that acrolein may be formed by the heating of the glycerin contained in the e-cigarette solution.

An extensive review of the studies of possible contaminant exposures (including polycylic aromatic hydrocarbons, TSNAs, volatile organic compounds, diethylene glycol, and inorganic compounds) with e-cigarette use according to occupational hygiene standards concluded that there was no cause for concern

about increased health risk.[37] The study by Goniewicz et al also concluded that using e-cigarettes instead of traditional cigarettes may significantly reduce exposure to some tobacco-specific toxins.[38]

E-CIGARETTES VS NICOTINE REPLACEMENT

Traditional nicotine replacement therapy products are regulated by the FDA and therefore standardized in terms of their contents. E-cigarettes, on the other hand, are unregulated vehicles for supplying nicotine, and may pose other health risks. One such risk is related to exposure to propylene glycol, which has never been studied under conditions (in terms of mode of delivery, frequency of dosing, and total duration of exposure) that approximate the exposure associated with e-cigarettes. Furthermore, the high concentration of nicotine in e-cigarette fluid poses a real risk of toxicity and potentially fatal overdose.

Nicotine replacement therapy and e-cigarettes both maintain addiction to nicotine if used in a harm-reduction strategy as a maintenance medication. Whether the ongoing nicotine addiction makes it more likely that individuals would switch back and forth between nicotine replacement and tobacco-based products is not clear. Also not known is whether e-cigarettes may serve as the "gateway drug" by which teens enter into nicotine addiction, but we believe that the potential exists, as these products are potentially more appealing in terms of the lack of pungent smell, the perception of safety, and the variety of flavors of e-cigarettes.

The efficacy of nicotine replacement therapy in improving smoking cessation has been reviewed extensively elsewhere[37] and is beyond the scope of this article. E-cigarettes may be appealing to many cigarette smokers because they deliver smokeless nicotine, and they more closely emulate the actual experience of smoking compared with traditional nicotine replacement therapy. Though some evidence suggests that e-cigarettes may be modestly effective in helping tobacco smokers quit nicotine, they are not FDA-approved for smoking cessation and are not marketed for that indication.[44] Medical practitioners should see them for what they are: a new nicotine product with a novel delivery system that is not approved as treatment. Because of the inherent risks involved with e-cigarettes, medical practitioners are best advised to remain neutral on the relative value of e-cigarettes and should continue to motivate patients to discontinue nicotine use altogether.

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