Review Article

E-cigarettes: A novel therapy or a looming catastrophe

Shahzad Hussain, Zainab Shahid[1], Mahtab B. Foroozesh, Umar F. Sofi

Department of Pulmonary/ Critical Care and Sleep Medicine, Virginia Tech Carilion School of Medicine, Roanoke, VA, [1]Department of Internal Medicine, Rowan University SOM, Stratford, NJ, USA

Address for correspondence:
Dr. Shahzad Hussain, Department of Pulmonary/ Critical Care and Sleep Medicine, Virginia Tech Carilion School of Medicine, 1906 Belleview Avenue, Roanoke, VA 24014, USA.
E-mail: shussain1@carilionclinic.org

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Abstract:

Electronic cigarettes (e-cigarettes) were originally developed in 2003 as healthier alternatives to conventional tobacco cigarettes. Their popularity has since significantly increased and both users and nonusers are exposed to their aerosol and product constituents. Although some evidence suggests that e-cigarette use may facilitate smoking cessation, definitive data are lacking and e-cigarettes are not approved by the Food and Drug Administration as a cessation aid. While e-cigarette aerosol contains fewer toxins than conventional cigarette smoke, studies evaluating whether e-cigarettes are less harmful are inconclusive. The health impact of e-cigarettes for both users and nonusers cannot be determined with currently available data, and there are both environmental concerns and issues regarding nonuser exposure. Most of the currently available data related to the health effects of e-cigarettes do not evaluate their effects on the general population and evidence regarding the systemic health effects of e-cigarettes is limited. In addition, there has been a recent rise in vaping-related lung injuries. Therefore, the detrimental effects of e-cigarette use should be further investigated, and every effort should be made to increase public awareness of the harmful effects of e-cigarettes.

Keywords:

Conventional cigarette, electronic cigarette, EVALI, vaping

Electronic cigarettes (e-cigarettes), also known as electronic vaping devices, were originally developed in 2003 and were promoted as healthier alternatives to conventional tobacco cigarettes. Their popularity has since increased significantly; 3.2% of the U.S. adults reported e-cigarette use in 2018 and the prevalence of e-cigarette use in the U.S. high school students increased from 11.7% in 2017 to 20.8% in 2018.[1,2] An e-cigarette was originally designed to resemble conventional cigarettes but has since evolved to contain three main parts: a battery, an atomizer composed of a wick and metal coil, and a liquid stored inside the atomizer. On inhalation, the electrical current from the battery heats up the metal coil inside the atomizer and vaporizes an e-liquid. This is followed by rapid cooling, which forms an aerosol that is inhaled by the user in a process referred to as "vaping." The liquid used in these devices consists of a combination of four main ingredients, including propylene glycol (PG), vegetable glycerin (GLY), flavorings, and sometimes nicotine.[3,4]

There are currently four generations of e-cigarettes on the market.[5] First-generation devices resemble conventional cigarettes and consist of a lithium battery and a cartomizer. Second-generation devices are larger, have more powerful rechargeable batteries, and a tank that can be filled with e-liquid. Third-generation devices, also called "mods," consist of a lithium battery with an integrated circuit that allows the user to manipulate the flow, thickness, and volume of vapor produced. Fourth-generation devices, or "mod pods," are the most powerful e-cigarettes on the market and are highly customizable,

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Table 1: The health effects of e-cigarette

Body system	Health effects
CNS	Dizziness
	Neuroplastic changes in brain
	Nicotine interferes with brainstem autonomic nuclei development
	Alters the neocortex, hippocampus, cerebellum
	Affect Limbic system
Eye	Irritation
	Redness
	Dryness
Cardiovascular	Increased oxidative stress and endothelial dysfunction
	Atherosclerosis
	Cardiac arrhythmias
	Myocardial Infarction
	Sudden death
Respiratory	Mouth and Throat Irritation
	Cough
	Chemical Pneumonitis
	Acute eosinophilic Pneumonia
	Acute/Subacute Hypersensitivity Pneumonitis
	Lipoid Pneumonia
	Acute lung Injury
	Acute Respiratory Distress Syndrome
	Exacerbate asthma symptoms
GI	Nausea
	Vomiting
Reproductive	Decrease in semen volume
	Increase semen leukocytes
	Increase level of immotile sperm
Hematological	Increased platelet aggregation

allowing for high coil temperatures [Figure 1]. The most popular fourth-generation device is the JUUL, a flash-drive-shaped device which entered the market in 2015 and contains as much nicotine as 20 cigarettes in a single pod.[6] JUULs contain nicotine salts rather than alkalinized nicotine, allowing for particularly high levels of nicotine to be inhaled with less irritation than that caused by free-base nicotine and previous e-cigarettes.[7] Some e-cigarette labels do not disclose that they contain nicotine, and some e-cigarettes marked as being nicotine free have been found to contain nicotine.[8]

There is an ongoing debate about whether e-cigarettes are a solution to the tobacco epidemic or a new public health hazard. Some evidence suggests that e-cigarettes may facilitate smoking cessation, but definitive data is lacking. Those in favor argue that e-cigarettes help smokers quit conventional cigarettes, play an important role in tobacco harm reduction, and contribute to a reduction of exposure to environmental tobacco smoke.[9-11] Those against e-cigarette use argue that they prolong or have no effect on smoking cessation, have an adverse effect on systemic health, and encourage dual use of both electronic and conventional cigarettes, thus effectively supplementing their habit.[12,13] Although e-cigarettes contain fewer toxins compared to conventional cigarettes, they contain certain carcinogens that exist in conventional cigarettes, such as formaldehyde and acetaldehyde, and certain heavy metals that are not in conventional cigarettes, such as chrome and nickel. In addition, studies have shown that e-cigarettes serve as a gateway to conventional cigarette smoking among adolescents.[14] Although they are commonly used to inhale nicotine, they can also be used to deliver substances such as tetrahydrocannabinol (THC), cannabidiol (CBD), and butane hash oils.[15] In this article, we discuss the effectiveness of e-cigarette use for smoking cessation, the multiple systemic effects of e-cigarette use [Table 1], and the risks of exposure for nonusers.

Effects on Smoking Cessation

Current data on whether e-cigarette use assists in smoking cessation are limited and conflicting. The prevalence of tobacco smoking in the US has declined to 14.0% but still exceeds 25% among high-risk subgroups.[16,17] Many cigarette smokers report attraction to e-cigarettes due to reduced cost, perceived reduced toxicity, and more freedom of use. Although users recognize that e-cigarettes are not safe, they believe e-cigarettes are safer and less addictive than cigarettes.[18] E-cigarettes are not approved by the Food and Drug Administration (FDA), but a large number of conventional cigarette smokers try to quit using e-cigarettes rather than FDA-approved cessation aids.[19]

E-cigarette promotion is justified by the claim that they assist conventional tobacco smokers in cessation. However, current data on the efficacy of e-cigarettes as a smoking-cessation aid are limited. Several observational studies and randomized controlled trials (RCTs) have been conducted to address this question and the results are conflicting. Participants had generally low sustained cessation rates, but evidence from some observational studies suggested that e-cigarettes can assist in smoking cessation attempts.[20-25] One study found a significantly higher quit rate when e-cigarettes are combined with counseling by a health professional and other smoking-cessation aid.[26] Other studies have shown a short-term reduction in tobacco smoking while using e-cigarettes and in some, smokers have reported fewer withdrawal symptoms when using e-cigarettes.[20,27-29]

In one study by Polosa *et al*., 40 regular tobacco smokers with no intention of quitting used e-cigarettes of the same brand for 6 months and their daily cigarette consumption decreased by 50% in 32.5% of participants and 80% in 12.5% of participants.[21] In another study with 1374 participants, Biener and Hargraves concluded that

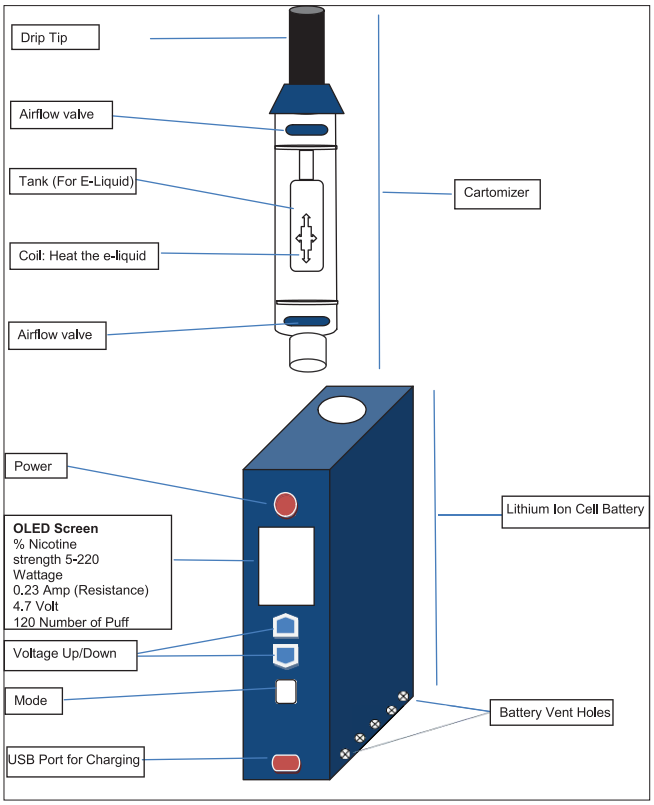

Figure 1: Representative diagram of a 4th generation e-cigarette. A new faster chip set and low ohm heating element allows for customization of voltage, airflow and temperature of inhaled vapor to enhance taste and personalize the experience. Pulse mode allows for delivery of increased amounts of atomized vapor. Safety features to prevent overheating and short circuit are also build in this model

e-cigarette use on a daily basis for 1 month was effective for smoking cessation.[23] A study of 1263 young adults aged 19–23 surveyed over 4 years found that the use of e-cigarettes was associated with reduced smoking in highly nicotine-dependent smokers.[30] An analysis of the Population Assessment of Tobacco and Health data of 5832 participants found that those who used e-cigarettes to quit conventional cigarettes had an increased probability of persistent cigarette abstinence.[31] In a RCT, Bullen *et al*. found that nicotine-containing e-cigarettes reduced the desire of smoking and withdrawal symptoms in conventional cigarette users while causing less oral and throat irritation than nicotine inhalers.[29] Another RCT by Bullet *e al*., the ASCEND trial, enrolled 657 people, of whom 289 received e-cigarettes, 295 received nicotine patches, and 73 received placebo e-cigarettes. At a 6-month follow-up, 7.3% in the e-cigarette group and 5.8% in the nicotine patch group were found to be successful in cessation.[32]

Although these RCTs showed promising findings, evidence from the RCTs was limited by study design, study size, and the duration of follow-up. It is not possible to control an e-cigarette trial, as there are many factors independent of the device.[33] For example, uptake depends on personal references, support provided from peers, cost, risk perceptions, regulatory issues, accessibility, and other uncontrollable factors. The process of finding a suitable e-cigarette and e-liquid is not linear and not easily randomizable. There is an unlimited range of choices and most users experiment with different e-cigarette models, e-liquid strengths, and flavors before finding the right one. The typical binary choice of a RCT is also not suited to this type of decision-making. In addition, these findings must be considered in the context of FDA-approved medications for smoking cessation which have well-known safety profiles. Treatment with nicotine replacement therapy (NRT) and bupropion achieves an approximately 25% abstinence rate at 6 months and 20% at 1 year, with slightly higher abstinence rates for combination therapy when compared to monotherapy.[34,35] Varenicline has been shown to outperform bupropion, all forms of NRT, and placebo, with a 26% abstinence rate at 24 weeks of follow-up in participants without psychiatric diagnoses.[36] When compared to the 7.3% cessation success rate at 6-month follow-up in the ASCEND trial, NRT seems superior to e-cigarettes in promoting complete abstinence from nicotine.

A multicenter randomized trial by Hajek *et al*. found that among participants with sustained abstinence at 1 year, 80% in the e-cigarette group continued to use e-cigarettes, while only 4 of 9% in the nicotine-replacement group continued using nicotine replacement.[37] These results suggest that the use of e-cigarettes primarily promotes switching from one form of nicotine delivery to another. Several studies have shown that e-cigarette use increases addiction, particularly in the young and in those who have never smoked. A 2014 Eurobarometer survey of 28 European countries found that e-cigarette use was associated with inhibiting rather than assisting with smoking cessation.[34] In a study by Vickerman *et al*., the rate of smoking cessation was found to be statistically lower in e-cigarette users compared to those who did not use e-cigarettes ($P < 0.001$).[38] In another study of 2530 students from 10 schools in Los Angeles, those who had ever used e-cigarettes at baseline were more likely to report initiation of conventional tobacco use over the next year when compared to nonusers.[14]

Similarly, in a study of 1357 hospitalized adult cigarette smokers who planned to stop smoking and received counseling in the hospital, the use of e-cigarettes was associated with less tobacco abstinence at 6-month follow-up when compared to attempted abstinence without the use of e-cigarettes.[39] In a population-based prospective cohort study of 1284 US adult smokers, the use of e-cigarettes did not help adult smokers quit at rates higher than smokers who did not use these products, suggesting that the use of e-cigarettes in real-world

situations is not effective in decreasing smoking or promoting tobacco cessation.[40] A meta-analysis by Kalkhoran and Glantz concluded that e-cigarette use for smoking cessation was paradoxically associated with even lower quitting rates than not using e-cigarettes, perhaps because e-cigarettes perpetuated nicotine addiction.[41] E-cigarettes seem to promote dual use which, in those not motivated to quit, is either maintained or leads to a return to the sole use of conventional cigarettes.[42-44] In those motivated to quit, a small percentage do achieve smoking cessation but with continued nicotine addiction.[31,43]

Addicting a New Generation E-Cigarette Use in Youth

The variety of e-cigarettes, with their multiple colors, shapes, and flavors, has appealed to the youth. Adolescents have become particularly susceptible, potentially because it makes them more socially acceptable and "in-trend" and they have lower perceived health risks. For adolescents who have never before smoked, exposure to nicotine in e-cigarettes constitutes a risk for developing nicotine dependence.[45] It is estimated that approximately 1 in 5 high school students and 1 in 20 middle school students currently use e-cigarettes, which is a 78% increase among high school students and 48% increase among middle school students from 2017 to 2018.[46,47] These findings were also corroborated by the National Youth Tobacco Survey by the Centers for Disease Control and Prevention in 2017, and represent the largest increases in the prevalence of e-cigarette use among adolescents ever recorded.[48] A study quantifying the population-level health benefits and harms of e-cigarettes in the US in 2015 estimated about eight new young smokers for every adult smoker who quit, yielding a substantial net negative effect on public health.[49]

A longitudinal study of 1152 students ages 11–18 in 2016 found that participants who ever tried e-cigarettes at baseline were 12 times more likely than never users to begin using conventional tobacco cigarettes, and 52% of these participants did become smokers.[50] Multiple other longitudinal studies, summarized in a recent meta-analysis, have found that adolescents who use e-cigarettes are at an increased risk of becoming conventional tobacco smokers. Recent data from the annual Monitoring the Future survey showed a 5.2% increase in the use of nicotine products among youth from 2017 to 2018, with 28.9% of adolescents using at least one nicotine product.[5] E-cigarette use, in particular, is enabled by the multitude of new products on the market, the most popular of which is the JUUL. The JUUL, a device that contains a higher concentration of nicotine than other e-cigarettes and produces a more rapid increase in nicotine levels, has become so popular that "to JUUL" has become a colloquial term.[51] In a recent survey, 23% of high school students were ever JUUL users and 17% were current users.[52]

E-cigarettes are heavily marketed, and the history of conventional tobacco has shown that marketing is a risk factor for smoking initiation.[53-55] E-cigarettes are advertised using the same themes and tactics as cigarettes once were, and in 2016, 8 in 10 middle-school and high-school students, totaling more than 20 million youth, said that they had seen e-cigarette advertisements. Many adolescents reported using e-cigarettes because they are curious about these new products and because they believe these products to be less harmful than conventional cigarettes.[56] About a quarter of adolescents who have tried e-cigarettes do not fit the risk-taking profile of a smoker, and yet many of them become established cigarette smokers.[57] These statistics are particularly alarming considering that, after decades of persistent public health efforts, the percentage of adolescents who had ever smoked cigarettes had finally fallen to 3.4% in 2016.[58] This increased use of e-cigarettes among the youth has been declared an epidemic by the Office of the Surgeon General and the FDA.[46] Given that we do not know the long-term health consequences, more aggressive regulation is needed to curb the rapidly expanding use of JUUL and other e-cigarette devices among youth. This might include additional attention to new devices as they enter the market, restrictions on where e-cigarettes are sold, and restricting flavors marketed to adolescents (such as candy, mint, and menthol).

Effects on the Body

Respiratory system

E-cigarettes are commonly used to inhale nicotine but can also be used for substances such as THC, CBD, and butane hash oils.[15] Particle sizes in e-cigarette aerosols are within the respiratory range, and high levels of vapor particle deposition occur with each puff.[59] This can result in acute pulmonary illnesses such as chemical pneumonitis, acute eosinophilic pneumonia, acute and subacute hypersensitivity pneumonitis, lipoid pneumonia, acute lung injury, and acute respiratory distress syndrome.[60,61] PG and GLY are highly hygroscopic molecules and dehydrate airways, causing irritation, and disruption of mucociliary clearance mechanisms. They also induce hyperosmotic stress, since they do not cross biological membranes, and may induce expression and secretion of pro-inflammatory cytokines in the lung. These molecules can also induce microvascular leakage and airway constriction by stimulating specific airway smooth muscle cell receptors.[62] Combined, these effects can disturb mucus/surfactant rheology properties, increase surface tension, and leads to small-airway collapse.[63]

A recent study concluded that acute vaping of PG/GLY aerosols with and without nicotine and in large amounts induces a sustained decrease in $Tcpo_2$ and airway epithelial injury in young occasional tobacco smokers. The latter effect seems driven primarily by PG/GLY rather than by nicotine.[64] Further studies are needed to confirm these observations in dedicated e-cigarette users to shed light on the precise pathogenetic mechanisms involved, and to identify the potential long-term consequences of e-cigarette use. Lim and Kim reported that the inhalation of nicotine solution in e-cigarettes is likely to exacerbate asthmatic symptoms by elevating the infiltration of inflammatory cells such as eosinophils into airways. This can enhance allergic airway inflammation and airway hyperresponsiveness, likely driven by the increase in production of interleukin-4 (IL-4), IL-5, IL-13, and immunoglobulin E.[65] Pulmonary diseases that have been linked to e-cigarette use have been limited to case reports, and there has been a recent surge in vaping related lung injury (EVALI). As of February 18, 2020, a total of 2,807 hospitalized EVALI cases or deaths have been reported to the CDC from all 50 states, the District of Columbia, and two U. S. territories (Puerto Rico and the U.S. Virgin Islands). Most of these patients had a history of using e-cigarettes containing THC or only nicotine.[66] The severity of the illness and the recent increase in the incidence of this clinical syndrome indicates that these cases represent a worrisome emerging clinical syndrome related to vaping, and additional studies are needed to characterize the pathophysiology of EVALI.

Cardiovascular system

Two-thirds of deaths associated with tobacco smoking are from heart disease (48%) and noncancerous lung diseases (17%). Conventional tobacco smoking contributes to cardiovascular disease by promoting inflammatory and oxidative pathways, promoting thrombogenesis and atherosclerosis, as well as through sympathomimetic pathways, resulting in autonomic and hemodynamic changes. Although smokers who switch from conventional to e-cigarettes reduce their exposure to 70 known carcinogens, e-cigarettes deliver ultrafine particles and nicotine deep into the lungs where they are absorbed into the bloodstream and damage the heart, blood vessels, and lungs, even at low doses.[67] Several small trials have addressed the effects of e-cigarette on cardiovascular health.

In a single-blind crossover study, Carnevale *et al*. evaluated oxidative stress and endothelial dysfunction in smokers and nonsmokers after exposure of both groups to both conventional cigarettes and e-cigarettes. It was found that exposure to either one significantly increased oxidative markers, but the increase was notably less pronounced in the e-cigarette group.[65] A case-control study which evaluated low-density lipoprotein (LDL) oxidizability, high-density lipoprotein antioxidant/anti-inflammatory capacity, and paraoxonase 1 activity in e-cigarette users and nonusers found that LDL oxidizability was significantly increased in e-cigarette users compared to nonusers, indicating an increased risk of oxidative damage and predisposition to atherosclerosis and cardiovascular risk.[68] Another study, which evaluated *in vitro* platelet function, found that platelet aggregation was enhanced and adhesion receptors were upregulated with both e-cigarette and conventional cigarette-smoke extracts, regardless of nicotine levels or duration of exposure.[69] These studies have shown that e-cigarettes do increase oxidative stress, inflammation, and platelet aggregation, thereby predisposing users to atherosclerosis.

Conventional cigarettes have a known association with atrial and ventricular arrhythmias and sudden cardiac death, likely by increasing sympathetic activity. A case–control study which evaluated the heart rate variability (HRV) in both e-cigarette users and nonusers to determine if e-cigarettes also produced a shift toward a hyperadrenergic state found that e-cigarette users had abnormal patterns of HRV similar to those caused by conventional cigarettes, consistent with activation of the sympathetic nervous system.[68] A follow-up crossover study found that using nicotine-containing e-cigarettes led to increased cardiac sympathetic nerve activity and changes in HRV when compared to nicotine-free e-cigarettes. The use of e-cigarettes was associated with an increased risk of myocardial infarction and sudden death in patients with and without known cardiovascular disease.

Gastrointestinal, nervous, and reproductive systems

E-cigarettes pose an increased risk of nicotine toxicity due to the availability of high nicotine concentrations in the e-cigarette cartridges. Exposure to inhaled nicotine can cause nausea, vomiting, dizziness, and neuroplastic changes in the brain. Studies have shown that nicotine interferes with brainstem autonomic nuclei development, alters the neocortex, hippocampus, and cerebellum, and influences the limbic system and maturation during adolescence. The e-cigarette vapors can also cause irritation, redness, and dryness of the eyes.[70] Lee *et al*. reported that smokers have a significant decrease in semen volumes, a significant increase in levels of immotile sperm and semen leukocytes, and lower sperm motion parameters.[71] Yu *et al*. demonstrated that smoking is strongly associated with abnormalities in histone-to-protamine transition and alteration of protamine mRNA expression in human sperm.[72] Furthermore, cigarette smoking reduces sperm plasma membrane integrity and sperm motility.[73]

Exposure Risk for Nonusers

Nicotine is readily absorbed through the skin, mucous membranes, airways, and gastrointestinal tract. Toxic reactions due to dermal nicotine exposure have been described after spills of nicotine-containing liquids or occupational contact with tobacco leaves.[70] Persistent residual nicotine on indoor surfaces can lead to thirdhand exposure through the skin, inhalation, and ingestion long after the aerosol has cleared the room.[74] Nicotine from aerosol or liquid can remain on surfaces for months and can react with ambient nitrous acid to produce tobacco-specific nitrosamines, leading to inhalation, ingestion, or dermal exposure to these carcinogens.[59] Children and adults have been poisoned by swallowing, breathing, or absorbing e-cigarette liquid through their skin or eyes.[70] Children are at an increased risk of toxicity from refill cartridges; the flavorings may increase appeal while the total nicotine content is potentially life-threatening. Nationally, approximately 50% of calls to poison control centers due to e-cigarettes are for kids aged 5 years or younger.

Conclusion

E-cigarettes are promoted as an alternative to conventional cigarette smoking, although their use is highly controversial. Manufacturers have turned their marketing efforts toward e-cigarettes by stating that e-cigarettes are less harmful than conventional cigarettes and that they are a method for smoking cessation, even though e-cigarettes are not FDA approved for smoking cessation. The novelty of the new technology and the variety of flavoring options have appealed to the younger generation and there are now higher rates of nicotine use in this population. Therefore, e-cigarette sales should be regulated in the same way as conventional cigarettes and must be prohibited from adolescents.

Although some studies have shown that e-cigarettes are useful in smoking cessation, many other studies have disproved this claim. Overall, the wide variability in the nicotine content of e-cigarettes and the lack of standardized testing methods make evaluation of the available data challenging. There is not enough data to support the safety of long-term e-cigarette use or a public health benefit. The efficacy and safety of e-cigarettes need to be evaluated in high-risk subgroups, and further research on the health consequences of long-term e-cigarette use is needed. Finally, the likelihood that nonsmokers will begin using e-cigarettes and transition to other nicotine-containing products due to addiction development should be thoroughly evaluated. In addition, considering the recent surge in EVALI, efforts should be made to increase public awareness of the harmful effects of e-cigarette use.

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Conflicts of interest

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