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COUNTERPOINT:

Does the Risk of Electronic Cigarettes Exceed Potential Benefits? No

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Although the medical community is unanimous in its wish to limit or even eliminate tobacco smoking, the role of electronic cigarettes (e-cigarettes) in this process has been controversial.¹ Will e-cigarettes be part of the solution by harm reduction, and are e-cigarettes really less harmful? Or will e-cigarettes contribute to the problem by serving as a gateway to tobacco cigarettes? As we are debating, regulations are being issued—and challenged. Unfortunately, due to a paucity of data, the calls for regulations in some cases sound alarmist.²

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Certainly contributing to the strong opposition roused by the e-cigarette is our well-founded distrust of anything associated with the \$85 billion US combusted-cigarette industry. Tobacco cigarette smoke is responsible for approximately 480,000 deaths/y in the United States. Approximately 18% of adult Americans smoke, a number which has not significantly decreased for a decade, despite antismoking campaigns, high cigarette taxes, and smoke-free policies. The position argued here is that an emotion-based, rather than evidenced-based, response to e-cigarettes may lead to a premature and scientifically unjustified rejection of a potentially beneficial means to reduce the enormous adverse health effects of tobacco cigarettes.

Consistent with the position that emotion, not reason, underlies the move to ban e-cigarettes, let us revisit 1997, when another handheld nicotine vapor delivery device was introduced.³ The nicotine inhaler was readily accepted by the medical community, but this medicinal-appearing, handheld device did not catch on with smokers and is now largely forgotten. Both e-cigarettes and nicotine inhalers deliver similar aerosolized clean nicotine vapor, but it is the “cigarette-likeness,” even the “coolness,” of the e-cigarette that captivates tobacco cigarette smokers.³ Paradoxically, its resemblance to the tobacco cigarette may be its strongest weapon to defeat combusted tobacco products.

Although called “e-cigarettes,” e-cigarettes are not cigarettes at all. They contain no tobacco, and there is no combustion. Constituents of tobacco cigarette smoke and e-cigarette vapor are markedly different. Tobacco smoke is produced by combustion of organic material, which generates the particulates and gases with the greatest toxicity. Thousands of toxicants, including carcinogens, have been identified in tobacco smoke.⁴ In contrast, e-cigarette vapor contains trace to no detectable toxicants, such as volatile organic compounds, carbonyls, tobacco-specific nitrosamines, and polycyclic aromatic hydrocarbons.⁵ The level of any of these toxicants in e-cigarettes, if detectable at all, is orders of magnitude less than that found in tobacco cigarette emissions. Even in licensed nicotine replacement therapies (NRTs) already approved by the US Food and Drug Administration (FDA), such as gum or patches, trace levels of tobacco-specific nitrosamines and metals are present.⁶ Additionally, e-cigarette emissions do not contain carbon monoxide or other toxic gases. e-Cigarette emissions include flavorings, but the principal component is the carrier compound, propylene glycol. Propylene glycol is present in several FDA-approved injectable

medications, and aerosolized propylene glycol is being evaluated for delivery of inhaled medications.⁷ In summary, although not everything is known about e-cigarette vapor, the available data support the notion that it is vastly less toxic than tobacco cigarette smoke.

Nicotine is the principal bioactive constituent in e-cigarette emissions and is recognized as the powerfully addictive component in tobacco cigarettes. Nicotine binds to central nicotinic acetylcholine receptors, releasing rewarding neurotransmitters and reinforcing further use. A strategy to help smokers quit has been NRT in the form of gum or patches, generating a significant database demonstrating the safety of nicotine in the absence of toxic particulates and gases. The available data show that NRT is safe even in individuals with cardiac disease, even following an acute coronary syndrome.⁸⁻¹⁰ In > 3,000 participants in the Lung Health Study treated with NRT (gum), the rates of cardiac hospitalizations or deaths during the 5-year follow-up were not related to NRT use, NRT dose, or to dual NRT and cigarette use. In contrast, continued smoking was highly related to fatal and nonfatal cardiac events.¹¹

Although NRT is safe, and its use increases quit rates twofold among smokers, sustained quit rates are only about 10% at 1 year.¹² Smokers report limited satisfaction from NRT, attributable to the relatively slow nicotine absorption and lower peak levels compared with pulmonary alveolar delivery with tobacco cigarette smoke. Also, NRT does not reproduce the behavioral and sensory pleasures associated with tobacco cigarette smoking. Nicotine delivery in currently available e-cigarettes has not overcome this hurdle. Due to the particle size, most nicotine absorption from e-cigarette vapor occurs in the oral mucosa, not the lungs, and the kinetics parallel those of available NRTs. Nicotine exposure from e-cigarettes, dependent on nicotine content in the e-liquid as well as the vaping practices of the user, is no greater and may be less than that from tobacco cigarette smoking.^{13,14} As an NRT, the potentially inferior pharmacokinetics of the e-cigarette compared with those of tobacco cigarettes may be partially offset by the physical similarity of the e-cigarette to the tobacco cigarette, and all the mimicked behaviors.¹⁵ Compared with NRT, e-cigarette use is associated with fewer withdrawal and craving symptoms and greater satisfaction, although nicotine levels are not different.^{3,13,14}

The greatest potential yet unproven benefit of e-cigarettes is complete smoking cessation. Only two randomized trials have examined the efficacy of e-cigarettes for smoking cessation.^{16,17} These studies, although

underpowered, demonstrated that e-cigarettes had similar efficacy as NRTs, approximately 10%, in sustained smoking cessation. Interestingly, e-cigarettes with and without nicotine had similar efficacy, supporting the notion that the tactile and behavioral benefits of e-cigarettes, independent of nicotine, are important. These data are intriguing, but insufficient, to support e-cigarettes as a smoking cessation tool.

Although complete cessation of tobacco cigarette smoking is the goal, reduced smoking has also been supported as worthwhile. Unfortunately, the health advantages of light vs heavy smoking are minimal and inferior to quitting.¹⁸⁻²⁰ The strongest argument for smoking reduction is to decrease lung cancer risk. The relationship between smoking burden and lung cancer risk is nearly linear, but the duration of smoking may be the key variable, rather than the number of cigarettes smoked daily.²¹ In summary, the argument that e-cigarettes may decrease the number of tobacco cigarettes smoked per day may be true, but is of little comfort.

These data support the concept that complete smoking cessation, “the endgame,” is the goal.²² One means to put an end to cigarette smoking would be the availability of a replacement product that mimics cigarette smoking behaviors, and which also satisfies nicotine addiction, but without the > 5,000 potentially toxic particulates and gases. The development of an e-cigarette with alveolar nicotine delivery may be such a product. Certainly, to have the medical community support such a product would require a sea change. Since smoking cessation in developed countries has stalled, proponents of the endgame to smoking have called for “something new, bold and fundamentally different” from available approaches.²² The acceptance within the medical community of a more potent e-cigarette would qualify as unexpected and bold, but in fact it may be the logical solution to stagnated efforts to end cigarette smoking once and for all.

Sincere concerns have been voiced that any potential benefit from an appealing e-cigarette, which successfully leads to smoking cessation in established smokers, will be offset by a new generation addicted to nicotine.²³ Although experimentation with e-cigarettes is increasing in young people, the majority of this experimentation is in established cigarette smokers. That is, approximately 90% of youth who reported trying e-cigarettes were already tobacco smokers.^{24,25} Only 0.6% of non-tobacco-smoking high school students reported using an e-cigarette in the last 30 days, and of course, experimentation does not equal regular use or addiction.^{24,25} Nonetheless, animal

studies have shown that the developing brain may be particularly vulnerable to nicotine effects,^{23,26} and, thus, the absolute prohibition of e-cigarette sales to youth proposed by the FDA must be vigorously enforced.

Rather than banning this potentially beneficial clean nicotine delivery device that has the potential to save approximately 500,000 lives/y in the United States alone, e-cigarettes should be required to meet product standards and safety requirements, with full disclosure of all ingredients, and subject to premarketing and postmarketing FDA testing. The appeal of e-cigarettes to tobacco cigarette smokers should be enhanced, through the development of nicotine delivery kinetics that replicate those of the addictive but lethal tobacco cigarettes. Finally, e-cigarettes should be placed at an economic advantage by heavily taxing tobacco cigarettes but not e-cigarettes. Most importantly, the deceptive, combusted-cigarette industry must not be entrusted with any aspect of e-cigarette development or marketing, without unceasing, highly critical, and comprehensive oversight.

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Rebuttal From Drs Avdalovic and Murin

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We agree with many of the points raised by Dr Middlekauff.¹ In comparison with traditional cigarettes it appears that electronic cigarettes (e-cigarettes) are less carcinogenic and their use in lieu of cigarettes would likely lead to less chronic cardiovascular and respiratory disease. In an ideal world, millions of traditional cigarette smokers