



Cross-fading: The importance of tissue injury research on dual misuse of alcohol and JUUL

As witnessed in late 2019, a multifactorial public health crisis occurred involving the use of e-cigarettes (e-cig). Otherwise healthy youth and young adults were hospitalized with life-threatening and life-altering acute pulmonary maladies. The use of e-cig, commonly known as vaping, was the common factor between the victims. This crisis underscored the many factors that complicate biomedical research involving the use of electronic nicotine delivery systems (ENDS): type of vaping device (pod-like system or refillable liquid chamber), source (retail or black market) of vaping fluid or pod, fluid type (nicotine, flavored nicotine, THC, CBD), and vitally, the degree to which users are ‘cross-fading’ with alcohol.

Cross-fading is a term popularly used to describe polysubstance (mis)use. The term is used by youth and young adults to describe binge drinking and vaping, although the term's origins arise from using alcohol and marijuana products concurrently (Patrick & Lee, 2018). Simultaneous and repeated use of multiple substances, such as alcohol and nicotine, results in greater hypersensitivity and craving to polysubstance cues than to the individual cues (Clayton, Bailey, & Liu, 2019). Polysubstance use has been the focus of several recent population survey studies. For instance, epidemiological studies demonstrate an increased association between e-cig use and higher-risk alcohol use among cohorts in Australia (Chan et al., 2019), Korea (Oh et al., 2019), Sweden (Lindstrom & Rosvall, 2018), England (Jackson, Beard, Michie, West, & Brown, 2020), and the United States (Conway et al., 2017; Hershberger, Karyadi, VanderVeen, & Cyders, 2016; Lanza & Teeter, 2018; Nicksic & Barnes, 2019; Roberts et al., 2018). More important are the recent findings that early use of e-cigs in young people of high school age is associated with greater rates of concurrent vaping and alcohol use by early adulthood (McCabe, West, & McCabe, 2018; Zuckermann et al., 2019), with approximately one-third of polysubstance-using college students reporting alcohol and vaping (Wong, Lin, Piper, Siddiqui, & Buu, 2019).

The generic definition of vaping includes a large range of vapable substances: nicotine, THC, cannabidiol (CBD), cannabigerol (CBG), and alcohol, among others. JUUL is overwhelmingly the most popular e-cig system. When sold legally, JUUL delivers nicotine via a closed system or pod, which is not a refillable liquid chamber like some of the older e-cig devices. Conversely, retail and black market pod-like imitations exist and can contain any number of substances, as listed above. These pods, anecdotally, are potentially refillable. The combination of refillable and black market devices and products introduces an additional confounder

to the study of tissue injury potentially caused by the coincident use of alcohol and vaping.

Over the last decade, the wide variety of vaping products on the market has made research studies difficult from a reductionist cause-and-effect approach with regard to public health relevancy. All of this is changing, however, with the recent dominance of one product – JUUL, which holds approximately 80% of the e-cigarette market share (Fadus, Smith, & Squeglia, 2019). Its seemingly hyperbolic growth in the last three years is driven by its proprietary nicotine salts that more closely mimic inhaled free-acid nicotine contained in tobacco cigarette smoke than all other competitors (JUUL; Lawler, 2015). JUUL pods contain either 3% or 5% nicotine, representing up to 4 times the nicotine concentration of cigarettes. JUUL pods were available in several flavors until late 2019, but the manufacturer has ceased production of all but tobacco and mint flavors as of this time. Current federal legislation is proposed that would prevent marketing pod-based vaping flavors.

Even with its current market dominance, JUUL has not been well studied as of this writing. There are no published studies on polysubstance use of JUUL and alcohol. Furthermore, nothing exists in the literature regarding tissue injury in response to alcohol and JUUL. Because the biomedical literature is replete in establishing the association between cigarette smoking and alcohol misuse, there are numerous examples of the many types of resultant tissue injury from dual use. Certainly, a strong argument can be made by behavioral and population studies that alcohol use in the context of JUUL may be no different than that of other nicotine replacement devices (Jackson et al., 2020; Thrul, Gubner, Tice, Lisha, & Ling, 2019), but future studies are required to elucidate acute vs. chronic exposure-related tissue injuries that may result from JUUL and alcohol co-exposure. In addition, identified differences in vaping and alcohol use with regard to biological sex (Conway et al., 2017; Morean et al., 2018) need to be specifically examined with regard to JUUL. Furthermore, current limitations in the use of JUUL in bio-behavioral studies will need to be addressed.

This editorial represents a call for: 1) increased research on dual use tissue injury from alcohol and vaping, in general, 2) the importance of studying JUUL rather than other ENDS products in tissue injury, and 3) investigation of age- and sex-related differences in dual use injury resulting from JUUL and alcohol. The Population Assessment of Tobacco and Health (PATH) study administered by the NIH and FDA may be a highly effective tool to help researchers understand the current scope of tobacco and nicotine product usage (pathstudy.nih.gov).

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