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Randomized controlled trials using electronic nicotine delivery systems as smoking cessation aids require an accurate, empirically-based understanding of the nicotine delivery profile of the products under study

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Introduction

Randomized controlled trials (RCTs) are a mainstay for determining intervention efficacy and safety and have been used for decades to investigate the role of nicotine replacement in smoking cessation (1). Notably, cessation outcomes generally improve in a nicotine dose-related manner (2), highlighting the importance of drug delivery in intervention efficacy. Since 2013, a variety of reports describe RCTs that explore the efficacy and safety of electronic nicotine delivery systems (ENDS) for smoking cessation or reduction (3–11). One serious limitation shared by all of these RCTs is that the nicotine delivery profile of the ENDS product used was either uncertain (3,5–8,10,11) or minimal (4,9). Perhaps not surprisingly, then, cessation outcomes in many of these ENDS RCTs were modest (4–10). Results from rigorous laboratory research make clear that ENDS are a heterogeneous product class (12,13), and that ENDS nicotine emissions (i.e., yield) and user plasma nicotine concentration (i.e., delivery of nicotine to blood) are influenced by the interaction of device, liquid, and user behavior (14–19). To increase the likelihood of larger effect sizes, investigators planning ENDS RCTs likely would benefit from considering these factors.

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ENDS device, liquid, and user behavior are critical for understanding ends nicotine yield and delivery

ENDS nicotine yield and delivery are a function of device power (14,15,17,18,20–22) and device construction (23,24) as well as liquid nicotine concentration (14– 16,25,26) and propylene glycol/vegetable glycerin ratio (14,20,26–28). Moreover, because of differences in device characteristics, visual appearance (e.g., “tank” or “mod”) or device “type” (e.g., 1st, 2nd, or 3rd generation) is not necessarily predictive of nicotine delivery (29,30). Therefore, choosing a device for an RCT based on its appearance or type is an unreliable method of assuring that nicotine will be delivered. Notably, several ENDS RCTs provide little information regarding the decision process used for selecting the ENDS products examined, apart from the appearance and/or popularity of the device. Also, user behavior, particularly puff duration, influences nicotine yield and delivery, with longer puffs leading to greater yield/delivery (14–16,31). Thus, even a device/liquid combination that appears to emit/deliver nicotine in controlled settings may fail to do so in an RCT if participants are not instructed regarding how to use it for maximum effectiveness.

One tool that is available to researchers planning an ENDS RCT is a mathematical model that predicts the nicotine emissions of any ENDS device/liquid combination based upon several factors including puff duration, liquid nicotine concentration and device power (15). This mathematical model explains 72% of the variability in ENDS’ rate of nicotine emissions (15) and so may be particularly useful in helping investigators select candidate ENDS devices and liquids for their RCT. For example, if investigators are interested in testing ENDSs that mimic the delivery profile of a combustible cigarette, the mathematical model will reveal which device/liquid combinations achieve cigarette-like nicotine yield in a given number of puffs of various puff durations (16). The nicotine delivery profile of those candidate products can then be determined using clinical laboratory methods.

There is a long tradition of using clinical laboratory methods to explore the nicotine delivery profile and other effects of tobacco products under controlled conditions (32–39). With some adaptation, these methods have revealed the considerable heterogeneity in ENDS nicotine delivery, with some products delivering little to no nicotine (40,41), others delivering some nicotine but dramatically underperforming a tobacco cigarette (31,42–47) and others meeting or exceeding the nicotine delivery of a tobacco cigarette after 10 puffs (18,29). Advantages of clinical laboratory methods are that they allow investigators to learn, in a single study, about how effectively various ENDS device/liquid combinations deliver nicotine to users’ blood under controlled and *ad libitum* puffing conditions; about how user behavior (i.e., puff duration) with those ENDS device/liquid combinations influences nicotine delivery; and about the acceptability of those ENDS device/liquid combinations as well as their ability to suppress tobacco/abstinence effects in smokers (17,48). Perhaps most important, relative to RCTs that often last multiple years and use between-group designs that often involve large samples [e.g., >500 people (7,10,11)] clinical laboratory studies can be rapid (i.e., 4–6 months) and use sensitive within-group designs involving 10–30 participants (16,17,42,45,48,49). Therefore, clinical laboratory studies can be a critical precursor for ensuring that an ENDS RCT involves products with known nicotine delivery profile(s) and

can also help to inform RCT participants how their behavior will influence that profile (e.g., longer puffs increase nicotine delivery).

Ethical cessation-focused ENDS RCTs require knowing nicotine delivery profile

Many investigators likely would agree that an RCT involving a novel method of delivering a proven, systemically-active, life-saving medication should not go forward if the bioavailability of the drug administered via the new method is uncertain. In such a case, where participants have a life-threatening illness, where there is a proven treatment that requires delivery of the drug to the blood, and where the novel delivery system may not deliver the drug effectively, an RCT may risk the health of participants and also expend scarce resources unnecessarily. Determining the bioavailability of the drug using the new delivery method outside of an RCT might be a better first step. Cigarette smoking is lethal and investigators conducting RCTs testing cessation interventions must be mindful of participant health and resource conservation. Proven smoking cessation medications are available, including the drug nicotine that can be delivered efficaciously via several routes of administration. Why, then, would an investigator suggest and an ethics panel (e.g., investigational review board, or IRB) approve an RCT that involves nicotine-dependent, cigarette-smoking, treatment-seeking participants who are offered a proven medication (nicotine) using a method (ENDS) that may deliver no or very little of the drug?

A more rigorous approach would be for RCT investigators to make use of existing tools and empirically-validated, clinical laboratory methods that can be used to demonstrate ENDS nicotine delivery and also provide information regarding how participant behavior can influence nicotine delivery. IRBs can then be assured, as they should be, that the ENDS that will be used in the RCT is capable of delivering nicotine to RCT participants and that the ENDS nicotine delivery profile is at least similar to that of a nicotine replacement medication that has proven efficacy and safety.

Conclusions

ENDS have been called a “disruptive technology” (50) that some advocates believe “have the potential to end cigarette use” (51). This potential is more likely to be realized when policymakers, clinicians, and combustible cigarette smokers are guided by RCTs that investigate ENDSs that have been demonstrated to deliver nicotine effectively. If the nicotine delivery profile of ENDS products is uncertain, those products should not be included in an RCT that involves treatment-seeking cigarette smokers.

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Conflicts of Interest:

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