Electronic nicotine delivery systems: a research agenda

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Abstract

Electronic nicotine delivery systems (ENDS, also called electronic cigarettes or e-cigarettes) are marketed to deliver nicotine and sometimes other substances by inhalation. Some tobacco smokers report that they used ENDS as a smoking cessation aid. Whether sold as tobacco products or drug delivery devices, these products need to be regulated, and thus far, across countries and states, there has been a wide range of regulatory responses ranging from no regulation to complete bans. The empirical basis for these regulatory decisions is uncertain, and more research on ENDS must be conducted in order to ensure that the decisions of regulators, health care providers and consumers are based on science. However, there is a dearth of scientific research on these products, including safety, abuse liability and efficacy for smoking cessation. The authors, who cover a broad range of scientific expertise, from basic science to public health, suggest research priorities for non-clinical, clinical and public health studies. They conclude that the first priority is to characterize the safety profile of these products, including in [...]
Electronic nicotine delivery systems: a research agenda

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Electronic nicotine delivery systems (ENDS, also called electronic cigarettes or e-cigarettes) are marketed to deliver nicotine and sometimes other substances by inhalation. Some tobacco smokers report that they used ENDS as a smoking cessation aid. Whether sold as tobacco products or drug delivery devices, these products need to be regulated, and thus far, across countries and states, there has been a wide range of regulatory responses ranging from no regulation to complete bans. The empirical basis for these regulatory decisions is uncertain, and more research on ENDS must be conducted in order to ensure that the decisions of regulators, health care providers and consumers are based on science. However, there is a dearth of scientific research on these products, including safety, abuse liability and efficacy for smoking cessation. The authors, who cover a broad range of scientific expertise, from basic science to public health, suggest research priorities for non-clinical, clinical and public health studies. They conclude that the first priority is to characterize the safety profile of these products, including in long-term users. If these products are demonstrated to be safe, their efficacy as smoking cessation aids should then be tested in appropriately designed trials. Until these studies are conducted, continued marketing constitutes an uncontrolled experiment and the primary outcome measure, poorly assessed, is user health. Potentially, this research effort, contributing to the safety and efficacy of new smoking cessation devices and to the withdrawal of dangerous products, could save many lives.

INTRODUCTION

New products, electronic nicotine delivery systems (ENDS) also known as electronic cigarettes (or e-cigarettes), have recently become popular in spite of a dearth of research on their safety and efficacy.1–3 ENDS look like cigarettes, but do not burn tobacco. Instead they produce a vapour from a battery-powered heater and cartridges.4 5 Depending on the brand, cartridges usually contain nicotine, humectants to produce the vapour (eg, propylene glycol or glycerol) and flavours (eg, tobacco, mint, fruit, chocolate). Some brands contain other medications (eg, rimonabant, amino-tadalafil).6 In addition to the delivery of nicotine, the visual, sensory and behavioural aspects of these devices are similar to tobacco cigarettes and may explain why they decrease craving and tobacco withdrawal symptoms,7–9 are perceived by users as effective for smoking cessation,10 or are used as substitutes for cigarettes.10 11 However, there is little objective information concerning the safety, abuse potential and efficacy of these products.12 Other concerns have been expressed, including that some flavours may appeal to children, that ENDS may become a gateway to smoking or to nicotine addiction, that they undermine smoke-free laws, delay a smoker’s decision to quit or might be used in conjunction with drug misuse.2 3 13 14 As with any other drug delivery vehicle, these products need to be regulated.13 15 Thus far, there has been a wide range of regulatory responses ranging from no regulation to complete bans. WHO’s Study Group on Tobacco Product Regulation advised a precautionary approach to ENDS,16 and with few exceptions (eg, a recent court decision barred the US Food and Drug Administration (FDA) from regulating ENDS as drugs),17 most national regulatory agencies have also adopted a similar stance.18 The empirical basis for these regulatory decisions is uncertain, and more research on ENDS must be conducted in order to ensure that the decisions of regulators, healthcare providers and consumers are based on science.

The aim of this paper is to identify priorities for non-clinical, clinical and public health research on ENDS (box 1). We cover a broad range of scientific expertise, from basic science to public health.

PRECONDITIONS REQUIRED FOR RESEARCH ON ENDS

Several issues should be considered first: product purpose, standardisation and regulation. With regard to purpose, many users report using ENDS to reduce or stop smoking, to substitute for cigarettes in smoke-free environments, to inhale various medications, to save money, because these products are perceived to be safer than tobacco, or to experiment with a new product.1 11 18 Because ENDS are frequently described as smoking cessation aids,1 13 we have examined them mainly with this purpose in mind.

Another important concern is standardisation and good manufacturing practice. There are many manufacturers of the devices and their contents, largely based in China, and many different models, with limited quality controls in place. At the least, production must ensure that cartridges are filled true to label and that dose delivery is consistent. Without standardisation, the results from any particular study may not be generalisable because of uncontrolled variability in vapour content within or across studies.

Additionally, research is also impeded by a lack of regulation. To be approved as a medicine or medical device, specific requirements for manufacturing processes, design of the device, safety and efficacy must be met. However, to the best of our knowledge, no ENDS brand has yet been approved in any country as a medicine. Nevertheless, some regulation of safety standards is needed, possibly by licensing of the manufacturers in the country of manufacture, as FDA does for many pharmaceuticals exported from China to the US. Currently, there is no regulated requirement to manufacture at an approved site and to test every batch. In the absence of licensed manufacture and regulations, manufacturers may change product designs and contents at will, so that any research only applies to the specific ENDS model and batch tested with no certainty that the findings will apply to future models or batches.19 20 Furthermore, this technology evolves rapidly and research reports may become obsolete by the time they are published.
Box 1 List of suggested studies

Non-clinical studies
- Composition of refill liquids.
- Composition of vapour.
- Product quality, description of the diversity of products and product change over time.

Animal studies
- Pharmacodynamics (PD), pharmacokinetics (PK), toxicokinetics.
- Toxicology, carcinogenicity.
- Effects of long-term exposure.

Clinical studies
- Deposition of droplets, exposure to nicotine, propylene glycol, flavours, etc.
- PD, PK, toxicity, carcinogenicity, infectivity.
- Addictive potential, abuse liability, risks of nicotine refill bottles.
- Puff topography, dosage, duration, reasons for use, brand switching.
- Optimal dosage, dosing regimen, effect of user experience with the device.
- Effect on tobacco withdrawal symptoms, adverse effects.
- Efficacy for smoking behaviour (cessation and reduction), comparison with nicotine replacement therapy (NRT).
- Efficacy for administering other medications.

Public health studies
- Prevalence of use in population subgroups.
- Utilisation patterns (long-term use), preferred brands, satisfaction of users.
- Use to administer illicit drugs or medications.
- Surveillance, pharmacovigilance, sales data.
- Effects of exhaled (‘secondhand’) vapour. Fewer fires and burns due to less smoking?
- Effect of good manufacturing practice on the quality of products.
- Economic studies, cost effectiveness, impact on healthcare costs.
- Impact on prevalences of quit attempts, quit rates and smoking in the population.
- Policy analysis, efficacy and impact of regulations, public opinion surveys.

NON-CLINICAL STUDIES
The main objective of non-clinical studies is to determine the potential safety of ENDS in the short and long term by detecting potential target organs for toxicity, identifying safe dosage schemes and identifying parameters for clinical safety monitoring.

At the time of this writing, eight non-clinical studies had evaluated ENDS.5 6 14 20–24 A study carried out by the FDA on two brands of ENDS found that they contained carcinogens, namely tobacco specific nitrosamines (TSNA), albeit at lower levels than in tobacco cigarettes and in similar levels to those found in nicotine medications.25 26; that similarly labelled cartridges emitted markedly different amounts of nicotine with each puff (27–43 μg nicotine/100 ml puff); and that nicotine was detected in cartridges labelled as containing no nicotine.12 Moreover, one cartridge contained 1% diethylene glycol, a toxicant implicated in mass poisonings.27 28

The second non-clinical investigation, conducted by a private company funded by an ENDS manufacturer, showed that

Moreover, the puff strength had to be increased and the aerosol density decreased as the puff number increased, while smoking characteristics, such as vacuum and density, varied considerably within and between ENDS brands.5 The potentially adverse effects on lungs if strong suction is required to smoke ENDS needs to be documented in the long term.5

The fifth study found hazardous aldehydes in a Japanese brand of ENDS (formaldehyde: 8.3 mg/m³, acetaldehyde: 11 mg/m³ and acrolein: 9.3 mg/m³) in concentrations respectively 1.2, 1.5 and 30 times less than from the tobacco cigarette brands also tested.23 However, these concentrations largely exceed international maximum exposure limits for formaldehyde (2.5 mg/m³) and acrolein (0.8 mg/m³).29 30 Glycerol is used to improve mist generation, but if heated to 280°C can produce acrolein, a potentially critical toxicant in ENDS vapour, and other ENDS brands should be tested for it.

The sixth study tested the nicotine content in 2 brands of ENDS cartridges (5.2–4.1 mg/cartridge) and in the vapour of 1 brand (1 μg per puff for puffs 1–10, then <0.5 μg per puff for puffs 11–50).14 This level was far below the levels found by FDA scientists,12 and suggests malfunctioning of ENDS, as the authors found.

The seventh study found that ENDS advertised as containing E-Cialis did not contain tadalafile (ie, Cialis) but contained its analogue amino-tadalafil, and that ENDS advertised as containing E-Rimonabant contained rimonabant and an oxidative impurity of rimonabant.6 These products contained nicotine, even though they were advertised as containing no nicotine.6 The eighth study evaluated five brands of ENDS and found that fluid leaked out of most cartridges, that the labelling of cartridges was poor and that most packs lacked warning information about potential risks.24

Thus, although some non-clinical research has been conducted that is relevant to predicting health effects in humans, much work remains to be done. For example, tests of pharmacokinetics and toxicokinetics should be conducted in animals (including absorption, distribution, metabolism and excretion of all compounds in ENDS vapour), and their toxicity and carcinogenicity should be characterised using standard tests of cytotoxicity and mutagenicity. Studies should also be conducted to explore the likely health effects of long-term ENDS.
use. The effect of good manufacturing practice in improving quality and minimising hazardous impurities needs to be assessed, and the effect of higher-voltage modified ENDS brands on hazardous volatiles should be monitored. Finally, there is a need to describe the variety of ENDS brands, models and refill liquids ('juice'), and their evolution over time.

**CLINICAL STUDIES**

**Safety**

Health risks are clearly important to evaluate, in particular, if the chemicals or any contaminants in ENDS cartridges or the vapours were toxic, carcinogenic or infective, or if the devices were used to deliver drugs of harm or drugs with addictive potential. As yet, there is no, or only very limited and conflicting data on toxicity, carcinogenicity and infectivity. Standardised methods for evaluating the safety of such novel potential reduced exposure products for tobacco users remain elusive, but safety studies are likely to involve topics such as pharmacokinetics (PK; drug concentration time course), pharmacodynamics (PD; drug action time course), deposition of vapour droplets, toxicity and abuse liability. In addition, ENDS cartridges are sometimes refilled with nicotine-containing liquid, and bottles of this liquid may be dangerous as they contain up to 1 g of nicotine: the fatal dose of nicotine is estimated to be 50–60 mg for adults and 10 mg for children. At the least, monitoring must be initiated to evaluate the public health effects of easy access to lethal nicotine doses that are sold in a pleasantly flavoured vehicle.

**Pharmacokinetics, pharmacodynamics and effects on withdrawal**

The efficacy of ENDS as a means of aiding smoking cessation is likely to depend largely on their ability to deliver nicotine to the brain at adequate doses and speeds, and PK and PD studies are important in this regard. To date, two reports, using different brands, have addressed the PK and PD of ENDS, with respect to nicotine. In the first study, 32 ENDS-naïve participants, smokers were assigned on different days to use an ENDS with a 16 mg or a 0 mg nicotine cartridge, a nicotine inhaler, or their usual brand of cigarette. In a PK study involving a subgroup of nine participants, the 16 mg ENDS yielded a maximum nicotine concentration in blood plasma of 1.3 ng/ml, the inhaler 2.1 ng/ml and the tobacco cigarette 13.4 ng/ml. Importantly, the 16 mg ENDS, 0 mg ENDS and nicotine inhaler all significantly decreased desire to smoke. The tobacco cigarette produced the greatest decreases in desire to smoke. The 16 mg ENDS was rated as more pleasant than either the 0 mg ENDS or the inhaler.

Another study of 11 smokers showed that ENDS decreased craving for tobacco after overnight smoking abstinence. Thus, there is some agreement between studies: the devices tested delivered far less nicotine than a tobacco cigarette, produced moderate suppression of craving and withdrawal, and were acceptable to users. The lower plasma nicotine after puffing from ENDS compared with smoking may be due to lower concentrations of nicotine in its vapour compared with tobacco smoke, and to lower absorption from the respiratory mucosa compared with alveoli. However, nicotine’s PK/PD in ENDS users is almost certainly related to additional factors including puff number, volume and duration, nicotine dose, pH, vapourisation temperature and the user’s experience with the device. These factors await parametric manipulation.

The extant PK/PD data regarding ENDS are generally confined to nicotine, although one study found that ENDS do not increase expired air CO, suggesting the carboxyhaemoglobin (COHb) concentration is unaffected. Other chemicals present in ENDS cartridges include medications, propylene glycol, flavours, additives and impurities. Propylene glycol is a solvent widely used in oral, intravenous and topical pharmaceutical products. The FDA has classified propylene glycol as an additive that is ‘generally recognised as safe’ for use in food. It is also commonly used in artificial smoke generators (eg, fire training exercises, theatre productions), and as an excipient in nasal sprays and nebulised solutions. It has low toxicity and lack of carcinogenic effects, but when delivered intravenously in high doses may produce fatal lactic acidosis. This observation suggests that PK/PD studies of ENDS should also include other potentially active chemicals to which users are exposed. Recent ENDS designs position the nicotine closer to the heating element. It is possible that different designs have improved nicotine delivery since the studies cited above were conducted. Similarly, better sealing of the nicotine cartridge may prevent nicotine degradation and leakage.

The extent to which ENDS vapour is inhaled into the lung, and where the particles are absorbed, is also uncertain. Absorption may be a function of droplet size, as particles must be small enough to penetrate sufficiently for pulmonary absorption. This issue, relevant to product safety, nicotine dosing and abuse liability, requires study.

**Abuse liability**

The abuse liability of therapeutic nicotine products has long been a topic of concern and empirical investigation, and such studies should also be conducted for ENDS. Predicting abuse liability accurately is important: drugs/devices with high abuse liability represent a potential threat to public health and should be controlled with appropriate regulatory action (eg, restricting minor’s access; requiring a prescription). Factors that contribute to abuse liability include reinforcing efficacy (will people work to obtain desired effects?), pharmacokinetics (how fast does the drug get to the brain?), dependence potential (does termination produce withdrawal, can use become compulsive?), adverse effects (does it make users sick?), and perhaps sensory characteristics. ENDS vapour contains nicotine, and nicotine may be present in users’ blood. The vapour may be delivered in a sweetened and flavoured vehicle (eg, fruit, mint and chocolate). There is, therefore, a need for clinical studies that use established methods to examine ENDS abuse liability as a function of device, medication, dose and flavour, in a variety of populations, including nicotine-naïve individuals, compared to relevant controls (eg, tobacco cigarettes and nicotine medications).

**Efficacy**

Pending product standardisation and demonstration of safety, clinical studies of tobacco dependence treatment efficacy are...
needed. These studies may include inter-
medate outcomes such as reduction in
cigarette intake, decreased tobacco with-
drawal symptoms, improved respiratory
symptoms and adverse effects.37 38 Labor-
atory work should examine which
conditions lead to maximal effect (eg, are
some doses more effective than others, is
a particular instruction set or behavioural
support required, how many cartridges
should be used in a day?). Such prelimi-
nary studies are extremely valuable for
establishing dosing regimens and
predicting efficacy in subsequent treat-
ment studies, while also addressing the
product’s safety profile. To date, three
laboratory studies have found that ENDS
decrease craving.7 8 9 Future studies might
include parametric examination of the
influence of cartridge dose, puff topog-
raphy, and user experience on withdrawal
symptoms and on smoking behaviour.
Laboratory-based research should compare
the influence of ENDS and approved
nicotine medications.7

Several smoking cessation efficacy trials
are already underway, in Italy, New
Zealand and Canada.9 39 40 In their
simplest form, efficacy studies might
involve parallel-group designs in which
cigarette smokers are randomised to
receive behavioural treatment alone or
behavioural treatment in combination
with ENDS and 0 mg cartridges (placebo)
or ENDS and nicotine-containing
cartridges. Dose may depend upon
smoking history, and more than one active
dose arm may be of value. Other treat-
ment trials will compare ENDS to
approved smoking cessation products
such as nicotine replacement therapy (NRT).
In this regard, the nicotine inhaler is an
obvious choice for comparison, given the
similarity in the route of administration.
However, the inhaler is less widely used
than other cessation medications, and
therefore optimal comparison products
might be those that are most more widely
used, acceptable and of proven effective-
ness, such as nicotine patch, gum or
tablet.41

The long-term use of medicinal nicotine
as a harm-reduction strategy is increas-
ingly being recognised as a possible ther-
aputic option for smokers who are
unwilling or unable to quit.42 44 Smoking
reduction may also facilitate cessation in
these smokers.45 However, ENDS will
have a positive impact on the health of
smokers only if they help people quit
smoking, as partial reduction of cigarette
intake may not be associated with a
meaningful decrease in health risk.38

The use of ENDS to administer other
medications to the bronchi and lungs
(eg, antibiotics, asthma medications)
should also be explored.6 Finally, the
effects of the long-term inhalation of the
various ingredients in ENDS vapour
should also be evaluated (nicotine, medi-
cations, flavours, humectants, etc.). As
noted, there is some evidence that nicotine
replacement is poor or non-existent with
ENDS,7 8 but product design evolves
rapidly and future models may test
differently. As urgent as this research may
be, it must be conducted according to the
ethical principles that govern all clinical
research, in particular, ensuring that
experimental procedures maximise poten-
tial benefits and minimise possible harms.

PUBLIC HEALTH STUDIES

Usage patterns and long-term exposure

ENDS are very popular. Google searches
for ‘electronic cigarettes’ increased 5000%
over the past 2 years,9 9% of UK smokers
have ever used ENDS and 5% were using
them at the time of a recent survey.11
Another survey found that 9% of Polish
adolescent smokers used ENDS.46 However,
new data exist on the characteristics of
ENDS users, how and why they use ENDS
in relation to tobacco products, smoking
cessation medications and other drugs, and
what users’ perceptions and expectations
are.1 11 The safety, efficacy and toxicity
of ENDS will depend on how the product
is used, and the balance of risks (tobacco vs
ENDS) will only be beneficial if ENDS are
mostly used for smoking cessation or
relapse prevention, rather than
for temporary abstinence, for smoking
reduction or for dual use with tobacco
cigarettes. Despite the limitations of self-
report data, surveys provide data hitherto
unavailable and would be useful to repeat
on a regular basis to track time trends.
Studies should also ascertain whether
ENDS are used for the administration of
illicit drugs or to inhale medications
designed for oral use.5 9 Epidemiological
studies should evaluate the impact of these
products on quitting activity in the
population, as it is possible that ENDS
may elicit quit attempts in smokers who
otherwise would not have attempted to
quit. Finally, economic studies should
assess the cost effectiveness of these
devices (compared with approved smoking
cessation drugs), and their impact of ciga-
rette sales and on healthcare costs.

Surveillance

Because clinical trials that lead to regula-
tory approval of a drug or device will take
time and usually involve a very small frac-
tion of the population who will actually
use the product, or are conducted in non-
representative samples, there is a need for
post-marketing surveillance and pharma-
covigilance. The ongoing collection of
surveillance data can help establish the
safety/toxicity profile of a product and
contribute to its continued availability,
modified labelling, or subsequent recall,47
even though these efforts have been criti-
cised for their voluntary nature, incomplete
and inaccurate data, and other serious
limitations.48 However, in many countries,
ENDS are available outside of a regulatory
framework and are therefore not submitted
to surveillance. Without valid and reliable
ongoing surveillance, significant health
effects may go undetected, putting lives at
risk. To our knowledge, no serious adverse
events have been reported to any national
authority, but this is no guarantee that
they have not occurred. Another need is for
data on ENDS sales, which would enable
tracking of sales in relation to tobacco
control interventions such as tobacco price
increases, and provide ecological evidence
of the reasons for purchase.

Other considerations

A partnership with consumers is being
seen by some as an essential part of good
research practice.49 However, researchers
should be aware that, in North America
in particular, ENDS consumer groups are
well organised and active in advocating the
right to use ENDS. These groups can
provide useful input, but avoiding bias
while collaborating with them might be
challenging. Incidentally, these consumer
groups themselves could be the object of
research (eg, to assess their impact on
legislation and public opinion).

There is potential for harm if ENDS
vapours can be inhaled by others besides
the user, in the same way as occurs with
secondhand tobacco smoke. However, if
ENDS were used as tobacco cigarette
substitutes, the risk of smoking related
fires and burns, a major public health
problem,50 would be reduced. Studies that
examine the policy models for balancing
such complex competing harms and
benefits are required.

CONCLUSIONS

Many questions about ENDS remain
unanswered. The priority is to charac-
terise the safety profile of these products,
including in long-term users. If these
products were demonstrated to be safe,
their efficacy for smoking cessation should
then be tested in appropriately designed clinical trials. A standard dosing regimen in these trials may be necessary for registration and practical purposes. A difficult question is how to implement such a research programme when these devices are developed and marketed by relatively small companies that may not have the resources and manpower necessary to comply with the regulation process, or even any interest in going through this process, especially because, in several countries, ENDS are marketed legally without going through clinical trials. Therefore, there is an urgent need to develop resources and a legal framework to explore the safety and efficacy of ENDS. Ideally, these studies would have been conducted prior to marketing of these products. Until they are conducted, continued marketing constitutes an uncontrolled experiment and the primary outcome measure, poorly assessed, is user health. Whether ENDS should be prohibited until safety and efficacy data are published is currently debated. Tobacco takes a tremendous toll and smoking cessation substantially decreases smoking related deaths. Potentially, this research effort, contributing to the safety and efficacy of new smoking cessation devices and to the withdrawal of dangerous products, could save many lives.

Competing interests CB’s salary is paid by the University of Auckland and his research is supported by grants from the New Zealand Health Research Council (HRC), the University of Auckland and the NZ Heart Foundation. He has previously undertaken tobacco control research supported by the New Zealand Ministry of Health, and by Niconovum, Sweden, prior to the purchase of this company by RJ Reynolds. He is currently an investigator on a study involving reduced nicotine cigarettes in which the products were purchased by the University of Auckland from Vector Group Ltd, US. He has previously undertaken research on ENDS funded by HealthNZ, in which the study products were supplied by Ruyan, Hong Kong; and he is the principal investigator on an HRC-funded efficacy trial of ENDS that will use products provided by a NZ-based ENDS retailer. Other than these relationships, he has no conflicts of interest to declare. TE’s salary is paid by Virginia Commonwealth University and his research is supported by grants from the US National Institutes of Health (R01CA138827 and R01CA120142). In the past he has served as a paid consultant to the National Association of Attorneys General regarding litigation against a tobacco company. He has served as an expert consultant for the World Health Organization regarding ENDS. Also, he has been retained by the US FDA as a consultant but, as of this writing, has not served in this capacity in any way and has received no payment from the FDA. Other than these relationships, he has no conflicts of interest to declare. J-Fe’s salary is paid by the University of Geneva. He has served as an unpaid expert consultant for the World Health Organization regarding ENDS, and as a paid consultant for Pfizer, a manufacturer of smoking cessation medications, in 2006–2007 (on the Swiss varenicline advisory board).

The University of Geneva received trial medications from Pfizer in 2006 for a study conducted by J-Fe. No competing interest since then. AF has no competing interests to declare. ML has researched various nicotine products including ENDS for several firms and universities, and advised several distributors, but has no financial interest in any of these.

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