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ETTER, Jean-François

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Gateway effects and electronic cigarettes

Jean-François Etter

Institute of Global Health, Faculty of Medicine, University of Geneva, Switzerland

ABSTRACT

Background E-cigarettes are alleged to be a gateway to cigarette smoking in non-smokers. This study examines whether the gateway theory has value, whether the criteria to establish causality have been met and what type of evidence is required to test this theory. **Analysis** Experiments are impractical, and we may not be able to test properly the gateway effects via observational studies that simply adjust for confounders. Multivariate models cannot eliminate all the variance in propensity to smoke captured by the variable 'vaping' because of the proximity of these two behaviours. It may be difficult to prove that vaping precedes smoking when product use co-occurs and when, in fact, smoking usually precedes vaping. The gateway theory is not compatible with either (1) the decrease in smoking prevalence observed in adolescents in countries where vaping increased or (2) an increase in smoking among teenagers after age restrictions were imposed on e-cigarette purchases. A spurious gateway effect can be produced artificially by mathematical models in which a propensity to use substances is correlated with opportunities to use substances. Finally, neither nicotine medications nor smokeless tobacco produce gateway effects. Available data are compatible with a common liability model in which people who are liable to use nicotine are more likely to use both e-cigarettes and cigarettes. **Conclusions** Despite its weaknesses and scant empirical support, the gateway theory of smoking initiation has had enormous political influence. Policies based on this theory will not have the intended effects if the association between vaping and smoking is explained by common liabilities.

Keywords E-cigarette, electronic cigarette, gateway effect, gateway theory, nicotine, smoking, tobacco use disorder.

Correspondence to: Jean-François Etter, Institute of Global Health, University of Geneva, 9 chemin des Mines, Campus Biotech, CH-1202 Geneva, Switzerland.
E-mail: jean-francois.etter@unige.ch
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INTRODUCTION

The gateway theory was formulated originally in the 1970s as a mix of academic, media, political and popular explanations of the frequently observed sequence in licit and illicit drug use [1–3]. Initially descriptive only, the theory soon became predictive and causal. In particular, it was used to support the idea that marijuana use caused heroin use [4]. This theory has three main components: first, the temporal sequence of substance use (adolescents first use marijuana and then progress to using heroin); secondly, the increased risk of subsequent use of hard drugs in marijuana users compared to non-users; and thirdly, the dose–response relationship between the frequency or intensity of marijuana use and the subsequent risk of starting heroin [4]. The causal relationship was explained either because the pharmacological effects of cannabis increased the propensity to use hard drugs: marijuana supposedly primed the brain for heroin use; because marijuana and hard drugs were sold on the same black markets and used in the same peer networks, increasing the opportunities for marijuana users to try hard drugs [5]; because of behavioural and psychological mechanisms: using marijuana supposedly reduced the perceived health and legal risks of using hard drugs; or because the effects of marijuana raised the users' interest in experiencing stronger forms of intoxication [6]. The gateway theory has always been controversial because of the difficulty of excluding alternative explanations, in particular the likelihood that use of all drugs is caused by some shared characteristics of users, especially a propensity to use drugs.

Today, the gateway theory is applied to e-cigarettes and other nicotine vaporizers, as it is alleged that vaping may cause subsequent smoking in young non-smokers. This theory is used to justify restrictive regulations of e-cigarettes and vaporizers. For example, the European Tobacco Products Directive states that 'Electronic cigarettes can develop into a gateway to nicotine addiction and ultimately traditional tobacco consumption [...]. For this reason, it is appropriate to adopt a restrictive approach' [7].

This study examines whether the gateway theory has value in the case of vaping and smoking, whether the criteria to establish causality are met and what type of evidence would be required to test this theory.

ANALYSIS

Definitions and measures of behaviours

In order to test the theory, it is essential to define and measure vaping and smoking correctly. 'Ever use' of either an e-cigarette or a tobacco cigarette is certainly not an adequate measure in this context. It is hardly plausible that a single puff or a few puffs on an e-cigarette can cause subsequent regular smoking. Past 30-day use is often used as a measure of current use [8], but it is not a satisfactory measure because in adolescents past 30-day use is a heterogeneous category that includes both experimentation (single use), occasional use and regular use [9,10]. Experimentation with tobacco is certainly not what is meant by the gateway theory. Rather, the theory is relevant only in so far as it describes mechanisms that cause the onset of regular smoking, as only regular smoking represents a public health problem. When it is used as an indicator of regular use, past 30-day use inflates artificially the prevalence of regular vaping or smoking. Conversely, because past 30-day use includes one-time experimentation of e-cigarettes, any observed association between past 30-day vaping and subsequent smoking understates the true effect of regular vaping on smoking.

Self-reports of smoking are notoriously unreliable in adolescents [11], and this may also apply to self-reports of vaping. Inaccurate reports of behaviour will produce invalid studies, as even small rates of misclassification may impede adjustment for confounders [12,13].

Establishing causality

The gateway theory is a theory of causality, and causality can be examined using the framework proposed by Hill in 1965 [14]. He described nine aspects or 'viewpoints' that we should consider before deciding whether an association is causal [14]:

1. Strength of the association
2. Consistency (across trials, investigators, individuals, research methods, replications)
3. Specificity (can other things cause it?)
4. Temporal precedence (do we know if cause precedes effect?)
5. Dose responsivity
6. Plausibility (biological and psychological)
7. Coherence (consistent with other lines of evidence)
8. Experiment
9. Analogy (do similar agents act similarly?)

None of these aspects or viewpoints may be sufficient to claim causation, but they can help us decide whether there is any other way of explaining the data than cause and effect.

Strength of the association

The association should have a minimal strength to establish that the link is causal. Given the imprecision of measurements, the inevitable confounding effects in observational studies and the infrequency of regular vaping in non-smokers [15], a small relative risk may not be detectable. Besides, given the very low prevalence of vaping in non-smokers [16], we should perhaps start by building a consensus on the level of population risk above which action is required. This level should represent a public health problem of sufficient importance to warrant the effort and money invested in research and interventions, and the adverse consequences of restrictive regulations aimed at preventing gateway effects.

Specificity (can other things cause it?)

For the gateway theory to be accepted, studies should prove that vaping is a specific cause of smoking and should exclude other causes, e.g. the propensity to use nicotine, the presence of smokers among family and friends, genetic factors, personality traits (e.g. novelty-seeking, risk-taking) or psychiatric problems [17–19]. Proving the specificity of this causal link is made difficult by the proximity of the two behaviours: use of any nicotine delivery system is correlated inevitably with use of other nicotine delivery systems. Statistical adjustments for confounders do not eliminate all the variability in propensity to smoke that is captured by the variable 'e-cigarette use'. As a result, vaping is still likely to predict smoking in the best multivariate models, even though this association may reflect common liability rather than causality [12,13]. Residual confounding may either decrease or increase apparent effects. The unavoidable presence of residual confounding is a very important point in this context.

Common liability theory should be considered as a plausible alternative to the gateway hypothesis. This theory states that a propensity to use nicotine influences both vaping and smoking and so these behaviours would be correlated [4]. Even though the common liability theory is not documented extensively in the case of vaping, it is appealing because it is supported by a large body of evidence showing that smoking is determined by social, familial, individual and genetic factors [13,17,19].

Common liability theory does not account for the ordering of behaviours (first vaping, then smoking) that is required for gateway effects to occur. To account for this phenomenon, one must hypothesize that the ordering of

product use depends upon adolescents' opportunity to use the various products [4]. Adolescents with a liability to try nicotine will initially use the product that is most easily available, most heavily advertised, about which they are most curious or for which peer pressure to use is highest. The sequence of product use will also depend upon the prevalence of use of each product in the population. Adolescents are likely to first try the product that is used most frequently around them [4]. This is a crucial point, because the sequence of behaviours is a core element of the gateway theory. The temporal sequence argument would not hold if the ordering of product use was explained solely by the ordering of opportunities to use the products, rather than by some inherent capacity of vaping to cause smoking.

Common liability theory can also account for the dose–response effect, if propensity to use nicotine is associated with more frequent use of nicotine among users. In this case, the frequency of vaping would be associated with a higher risk of subsequent smoking because both are controlled by propensity to use nicotine.

In short, a gateway effect is not required to explain any of the three core elements of the gateway theory: the temporal ordering of behaviours, the higher relative risk of smoking in vapers than in non-vapers and the dose–response effect. All these phenomena can be explained by a common liability model. In addition, the common liability theory provides a theoretical foundation for research and action. The gateway theory is therefore a weaker base for prevention and policy than the common liability theory. For example, the common liability theory suggests that prevention interventions should focus upon adolescents who have risk factors for any nicotine use (e.g. parents who smoke, psychiatric disorders, etc.) (Fig. 1).

Temporal precedence

Logically, the cause must precede the effect. Although the ordering of the temporal sequence of events is a necessary condition of causation, it is not a sufficient condition, because non-causal antecedence is irrelevant [20]. There may be a period during which adolescents try various nicotine and tobacco products, without a clear sequence. When product use co-occurs it is very difficult to establish which product was used first, thus the gateway theory can be extremely hard to test. Also, studies should assess smoking onset, a non-repeatable event, rather than smoking prevalence at a given time-point. This means that longitudinal studies are required to establish the temporal sequence; cross-sectional studies and retrospective assessments provide very weak evidence for a gateway hypothesis.

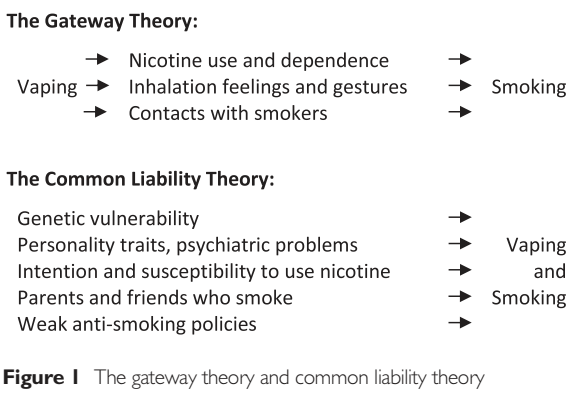

Figure 1 The gateway theory and common liability theory

Plausibility

Is the gateway theory plausible? It states that there are successive stages in adolescent involvement in substance use [2]. Each device is supposed to be used only when this stage is reached, even though the sequencing of behaviours actually goes in both directions and smoking usually precedes vaping in adolescents [21]. The observation of the more frequent reverse sequencing (first smoking, then vaping) is a convincing argument against the gateway theory.

In many social contexts tobacco cigarettes are omnipresent, barriers to trying them are extremely low and advertisements for cigarettes are ubiquitous and target adolescents [22]. There is no need for a gateway or for any other facilitator for vulnerable young people to try smoking. In fact, in many social environments access to cigarettes is easier than access to e-cigarettes. This contrasts with gateway theories for other substances, which claim that a drug that is easy to access and use (marijuana) facilitates access to a more dangerous drug that is either more difficult to access or to use, or that is more frightening (heroin). This point also decreases the plausibility of the gateway theory.

A central assumption of the gateway theory is that people who choose to vape instead of smoking will change their mind after some time and start smoking because they think smoking has some advantages over vaping that even the latest models of vaporizers cannot offer [20]. Such advantages may include more rapid nicotine delivery to the brain, and thus more pleasurable effects or faster relief of craving, the presence of other psychoactive substances in smoke [23], the richer taste and flavour or some social advantages (e.g. giving in to social pressures to smoke or to social pressures to stop vaping). However, we are not aware of any studies that have documented that such elements actually cause vapers to switch to smoking.

Another possible reason why vapers might switch to smoking could be that e-cigarettes create an addiction to nicotine that vaping can no longer satisfy, thereby pushing addicted vapers to switch to smoking to obtain a satisfactory nicotine supply. However, the addictive potential of most current models of e-cigarettes is closer to that of

nicotine gum (which is not very addictive) than to the addictiveness of tobacco cigarettes [24,25]. Logically, instead of switching to smoking, unsatisfied vapers could switch to the latest models of e-cigarettes and heated tobacco products that deliver substantial amounts of nicotine and offer a range of pleasant flavours [26].

The gateway theory would be more plausible if there were testimonials from smokers who claimed that vaping caused them to start smoking [20]. The absence of such testimonials in the literature weakens this theory. Testimonials and other qualitative research in people who first vaped and then switched to smoking would help researchers to clarify motivations for switching, identify mediators and moderators of these effects and identify vulnerable subgroups. We are not aware of any such qualitative studies.

In fact, it is more plausible that vaping uptake is largely explained because smoking causes people who are already dependent upon nicotine to look for less dangerous, more socially acceptable and cheaper ways to obtain nicotine [27]. This reverse causation decreases the plausibility of the gateway theory. It is also possible that negative gateway effects occur; for example, if bad vaping experiences discouraged youths from smoking, or if vaping made smoking appear to be a behaviour specific to people with whom youths do not identify (e.g. older, addicted, malodorous, not tech-savvy people).

The gateway theory would be more plausible if data showed that, among non-smokers, vapers who use nicotine-containing liquids take up smoking more often than vapers who use nicotine-free liquids, and that daily vapers take up smoking more often than occasional vapers. We do not know of any such evidence.

Finally, a spurious gateway effect can be produced if a propensity to use drugs is correlated with opportunities to use them [13]. Simulation models demonstrate that the three core elements of the gateway theory (temporal sequence, increased risk and dose–response) can be produced artificially in a situation where any causal gateway effect is excluded by design [13]. This is a strong argument against accepting the gateway theory.

Coherence (consistent with other lines of evidence)

The gateway theory should not conflict with what is already known about smoking uptake in adolescents. For example, the current decrease in smoking prevalence among adolescents in countries where the prevalence of vaping is high (e.g. United Kingdom, United States) suggests that vaping is not causing many adolescents to start smoking cigarettes [28,29]. In the United States between 2013 and 2015, smoking rates in adolescents declined faster than ever [28] and this coincided with an increase in experimentation with e-cigarettes among adolescents during the same period [9]. Incidentally, an increase in the prevalence of vaping in young non-smokers would be beneficial if it meant that youngsters who are predisposed to smoke chose to vape instead.

The gateway theory would also be strengthened if there was evidence that vaping causes nicotine addiction in non-smokers, but we are not aware of any studies to test this hypothesis.

Experiment

Experimental studies are the best way to establish a causal link between an intervention and an outcome because they minimize alternative explanations, particularly confounding factors. In the words of Hill: 'Here, the strongest support for the causation hypothesis may be revealed' [14]. Experiments of the gateway effects are impossible for obvious ethical reasons, but trials that test the efficacy of vaping cessation interventions on smoking uptake in non-smokers may be feasible. It may also be possible to design social experiments, randomly allocating schools or communities to test whether interventions aimed at delaying the age at vaping initiation reduce smoking. However, because the effect of such interventions is expected to be quite small if the common liability theory is correct, then very large numbers of participants would be needed to produce reliable results. Given that regular vaping in never-smokers is rare [15], it will be difficult to enrol sufficient numbers of participants in such trials. This suggests that we may never be able to test the gateway theory in randomized intervention trials in humans.

Natural experiments can also be useful to assess gateway effects. For instance, the use of combustible cigarettes increased in adolescents after the implementation of age restrictions for the purchase of e-cigarettes [30–32]. These results suggest that there is a causal link between reduced e-cigarettes accessibility and increased demand for combustible cigarettes among minors [31]. In teenagers, there may be an unmet demand for cigarette substitution products that e-cigarettes may fill [32]. This possibility is, of course, contrary to the gateway theory. More generally, new regulations represent natural experiments that can be used to test the gateway theory empirically at the population level.

In animals, experiments on the effects of exposure to e-cigarette aerosols on subsequent compulsive nicotine self-administration could be useful [33,34] if the dosages used in animals reasonably reflect the dosages used by e-cigarette users.

Analogy (do similar agents act similarly?)

The gateway theory would be strengthened by the observation that other nicotine-delivery systems also cause

smoking. A few cases of addiction to nicotine gum in never-users of tobacco have been described [35], but we know of no example of never-users of tobacco who became addicted to nicotine medications and started smoking later to satisfy this addiction [36]. Smokeless tobacco products also deliver substantial doses of nicotine [37], are addictive [38] and some users have never smoked cigarettes before using smokeless products [39], but smokeless tobacco use does not appear to cause subsequent smoking [40,41]. Rather, smokeless tobacco use is associated with low rates of smoking and with lower overall tobacco use in populations in which their use is legal [42,43]. However, the addictiveness of a drug-delivery device depends upon the speed of nicotine delivery to the blood and brain [44], and recent models of e-cigarettes and heated tobacco deliver nicotine more quickly than most forms of smokeless tobacco, nicotine medications and most current e-cigarettes [26,45]. They could therefore be more addictive than these products.

Comprehensive models: explaining the total effects on public health

Any satisfactory model of the effects of vaping on smoking should consider transitions from smoking to vaping and not just from vaping to smoking. Exit gateways should also be considered because population surveys suggest that e-cigarettes are used almost exclusively by current and former smokers as an aid to quit smoking [16,27]. We also need to examine the effects of dual (concomitant) use of e-cigarettes and combustible cigarettes [46]. Transitions from experimentation to regular vaping are also of interest, as e-cigarettes can be protective if people who experiment with vaping later make a transition to regular vaping rather than to regular smoking [46].

Even if new nicotine delivery devices caused some young non-users to start smoking, the total effect on the population overall would still be positive if large numbers of current smokers switched to newer, less dangerous devices (e-cigarettes or heated tobacco products) [46] or if dual users smoked for fewer years or smoked fewer cigarettes per day or both. Given the preliminary evidence from randomized trials [47,48] and population studies [49], and given the analogy with nicotine medications [50], it is a reasonable hypothesis that e-cigarettes help some smokers to quit [15,51]. In countries where smoking-related mortality is high, levels of gateway effects from vaping to smoking would need to be extremely high to offset the positive effects of vaping on smoking cessation [46].

DISCUSSION

In summary, most of the evidence that should be considered before deciding whether an association is causal have either not been met or are not documented in the case of the claim that e-cigarettes can be a cause of cigarette smoking (Table 1).

The gateway hypothesis cannot currently be either accepted or confidently refuted because the evidence for it is scarce and inconclusive. The common liability theory cannot be accepted confidently either, because it has not been tested extensively in the case of vaping and smoking. A gateway effect may exist because vaping familiarizes vapers with the gestures and feelings of inhalation and with the use of nicotine, even though many adolescent vapers report using non-nicotine refill liquids [52,53]. It is unlikely, although not impossible, that vaping non-nicotine liquids can lead to subsequent smoking in some people. Vaping may also increase the risk of smoking for some adolescents and decrease it for others, so that the net effect on population cigarette smoking is trivial. Even if there was a gateway effect, it may explain only a small part of smoking, compared to common vulnerabilities.

Even if gateway effects may not currently be very substantial or even detectable, this could change in future if vaping became more prevalent or future e-cigarette models became much more addictive than current models. This could increase opportunities for adolescents to try e-cigarettes before they try combustible cigarettes and may increase the risk of becoming addicted.

To choose between the alternative explanations of the gateway and common liability hypotheses, we should look for convergent evidence from a variety of sources and study types. Progress in understanding the association between vaping and smoking will be faster if social scientists, economists, psychologists, epidemiologists and behavioural pharmacologists collaborate. Useful studies would include:

- Experiments in animals to assess whether exposure to doses of vapour that reflect human behaviour cause compulsive nicotine self-administration.
- Behaviour genetic studies that test the relative roles of genes and environment in e-cigarette use and smoking, in particular studies of twins discordant for smoking and vaping.
- Large intervention studies that test the impact of policies and education interventions to determine whether delaying the age at first e-cigarette use reduces smoking initiation rates.
- Randomized trials in daily vapers who are non-smokers, to test whether vaping cessation interventions reduce their risk of subsequent smoking initiation.
- Studies of the effects of regulations on vaping and smoking in youths (natural experiments).
- Large longitudinal epidemiological studies that measure behaviours and confounders precisely and repeatedly and that assess their temporal relationship. These studies should control adequately for confounders and assess the onset of smoking, a non-repeatable event that is the

Table 1 Hill's 'viewpoints' or aspects to consider before deciding whether an association is causal, methods required to assess them, and examples of studies.

Hill's aspects of causality	*Methods*	*Examples of studies and comments*
1. Strength of the association	First, build a consensus on the level of population risk that requires action	Small relative risks may be neither detectable nor meaningful
2. Consistency (across trials, investigators, individuals)	Need for a robust set of diverse studies, and for replication studies	
3. Specificity (can other things cause it)	Studies of common liabilities	Many studies on the common determinants of vaping and smoking (not listed here), e.g. [54,55]
	Multivariate analyses. However, the proximity of vaping and smoking makes it impossible to eliminate confounding effects	
4. Temporal precedence (do we know if cause precedes effect?)	Longitudinal studies in non-smokers.	e.g. [54,55]
	Cross-sectional studies if they assess time to initiation of e-cigarettes and cigarettes	Assess smoking onset, a one-time, non-repeatable event
5. Dose–responsivity	Dose–response between intensity and frequency of vaping in never-smokers and risk of future smoking	e.g. [56]
6. Plausibility (biological and psychological)	Studies of the sequence of behaviours (expected or reverse sequence)	Reverse temporal sequence is more frequent, e.g. [27]
	Behaviour genetic studies of twins	
	Studies based on propensity scoring	e.g. [40]
	Testimonials of non-smokers claiming that vaping lead them to smoke	
7. Coherence (consistent with other lines of evidence)	Prevalence studies of smoking and vaping in youth	Smoking decreases when vaping increases, e.g. [28,29].
	Tests of whether vaping causes nicotine addiction in non-smokers	
8. Experiment	Randomized trials in non-smokers, to test the effects of vaping cessation on smoking initiation	Such trials will be difficult to conduct. None are published
	Experiments of community programs that delay the age at vaping initiation	
	Natural experiments, economic studies, in particular effects of age restrictions on use e-cigarettes and cigarettes	Age restrictions for e-cig sales increased smoking in minors, e.g. [30–32]
	Experiments in animals	e.g. [33,34]
9. Analogy (do similar agents act similarly?)	Analyses of gateway effects for smokeless tobacco and nicotine medications	No gateway effects for smokeless and for nicotine medications, e.g. [40,41]

focus of the gateway theory. Analyses of the frequency of smoking at one time-point or at several time-points do not address the relevant question.

- Studies based on propensity scoring that test whether vaping predicts smoking over and above a propensity score measure of liability to smoke. This approach has been used to assess whether smokeless tobacco is a gateway to smoking [40].
- In contrast, there is little need for more (highly publicized) studies of antecedence combined with increased relative risk [54,55]. While this approach reduces the possibility of reverse causation, it does not eliminate confounding, even after statistical adjustments.
- Finally, there are rapid changes in vaping prevalence, in the evolution of vaping technologies, and in commercial marketing strategies that may affect the likelihood of gateway effects in the future. It is therefore important to continue population monitoring and surveillance of changes in vaping and smoking behaviours.

Despite its theoretical limitations, the scarcity of empirical support and evidence for the opposite effects, the gateway theory has enormous political influence [1,7]. Its success is due perhaps to its simplicity. Policies based on this theory may not have the intended impact on smoking, and may even exert negative effects, if the association between vaping and smoking is explained by common liabilities. If access to safer alternatives to combustible cigarettes is excessively restricted because of this theory, then more people are going to smoke instead of using these disruptive alternative technologies.

Declaration of interests

None.

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