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SCHEER AND THE GATEWAY HYPOTHESIS

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Abstract

There is a large literature that purports to examine the so-called Gateway Hypothesis – that the consumption of e-cigarettes results in the consumption of combustible cigarettes. The recent SCHEER Opinion uncritically cites that literature. This paper sets out how the Gateway Hypothesis literature is methodologically flawed and biased, with evidence in favour of it being weak and reflecting the prior beliefs of those undertaking the research.

Introduction

The European Union’s Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) recently published a preliminary opinion examining various harms that may be associated with the consumption of e-cigarettes¹. In this paper I focus on the notion that the consumption of e-cigarettes may result in individuals (either never-smokers or lapsed smokers) consuming combustible cigarettes. This is known as the “Gateway Hypothesis”. I also address the issue of whether the consumption of e-cigarettes may undo the advances public health has made over the past few decades in stigmatising the consumption of combustible cigarettes – the so-called “Renormalisation Hypothesis”.

The SCHEER Opinion relies very heavily on meta-analyses that have been performed to argue that the empirical evidence supports a version of the Gateway Hypothesis. I argue, however, that those studies and, in particular, the studies that underpin them are methodologically flawed in that the hypotheses they test, and the alternate hypotheses are poorly specified. In particular, the Renormalisation Hypothesis has not been subject to scientific analysis, and indeed cannot be subject to scientific testing under experimental conditions. The notion of renormalisation is simply not a testable hypothesis and consequently it is not science.

Furthermore I demonstrate that the empirical strategy that informs the underlying studies has been deliberately chosen so as to derive an a priori result – i.e. that e-cigarette consumption leads to combustible cigarette consumption.

In short, the analysis that informs the SCHEER Opinion is methodologically flawed and biased.

1. SCHEER Preliminary Opinion on Electronic cigarettes. Available at https://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scheer_consultation_10_en

The SCHEER Opinion

At pages 62 – 70 the SCHEER Opinion discusses the notion that e-cigarette consumption may play some role in initiating consumption of combustible cigarettes – especially amongst “young” people. In some of the studies that SCHEER survey “young” people are defined as being younger than 30 years of age. Very clearly, however, investigating whether minors are consuming combustible cigarettes is of public policy concern, and the notion that e-cigarettes may be a gateway to doing so is also of public policy concern.

The SCHEER Opinion spends some pages discussing flavours that are added to e-cigarette liquid and nicotine. It is only at page 66 that they begin to address the serious issue at hand. Here they introduce two hypotheses of interest: The Gateway Hypothesis, and the Renormalisation Hypothesis.

The Gateway Hypothesis is justified by reference to two studies (Bunnell et al., 2014; Kandel and Kandel 2014), while the Renormalisation Hypothesis is justified with reference to just one study (Fairchild et al., 2014).

It is difficult to ascertain precisely what is meant by the Gateway Hypothesis (and what the alternate hypothesis being tested might mean) as the Bunnell et.al study does not employ the word “gateway” anywhere in the paper². Indeed the word “hypothesis” does not appear in the paper. It simply does not articulate what the “Gateway Hypothesis” could mean. By contrast, Kandel and Kandel (2014) do discuss a “Gateway Hypothesis”³. Specifically they discuss how adults might transition from the use of combustible cigarettes to the consumption of marijuana and cocaine, and then onto other illegal drugs. This paper addresses the epidemiology of that transition. In their conclusion Kandel and Kandel (2014) speculate that nicotine delivered by e-cigarettes may have the same effect on the human brain as does nicotine delivered by combustible cigarettes. They do concede, however, that e-cigarettes have lower morbidity effects than do combustible cigarettes. Kandel and Kandel (2014) may well be correct – it is very likely that nicotine has a similar effect on the human brain irrespective of delivery technology. That must be true for any and all nicotine delivery technologies, be it lozenges or gum or sprays or any other harm reduction product. The SCHEER Opinion does not investigate whether individuals transition from either combustible cigarettes or e-cigarettes to marijuana or cocaine or any other illegal drug. Quite simply it does engage with the Gateway Hypothesis as defined and described by Kandel and Kan-

2. Bunnell et al., 2014. *Intentions to Smoke Cigarettes Among Never-Smoking US Middle and High School Electronic Cigarette Users: National Youth Tobacco Survey, 2011–2013*. *Nicotine & Tobacco Research*. Available at <https://academic.oup.com/ntr/article/17/2/228/2857952>

3. Kandel and Kandel 2014. *A Molecular Basis for Nicotine as a Gateway Drug*. *The New England Journal of Medicine*. Available at <https://www.nejm.org/doi/pdf/10.1056/NEJMsa1405092>

del (2014). To the contrary, what the SCHEER Opinion addresses can be best described as being a “Substitution Hypothesis” - that some individuals may substitute the consumption of either combustible cigarettes for e-cigarettes or vice versa. Given that some individuals may consume both combustible cigarettes and e-cigarettes, the SCHEER Opinion may be addressing a “Complementary Hypothesis”. Unfortunately the SCHEER OPINION never specifically spells out the hypotheses being discussed - the reader must simply fill in the gaps using their own prior beliefs, expectations, and prejudices. The Renormalisation Hypothesis is even more problematic. The word “renormalization” (US spelling) appears just twice in Fairchild et al. (2014)⁴. Once in the title, and once in the following quote:

The chief advertising officer of one e-cigarette company has spoken explicitly about the “renormalization” of smoking in the form of “vaping” — the popular name for e-cigarette use.

Unfortunately no reference is given for that claim; consequently, it is not possible to ascertain what it is the individual may have meant by that comment, or even whether that comment was ever made. It is clear, however, what Fairchild et al. (2014) mean by “denormalization”:

The once-widespread habit didn’t simply become denormalized or marginalized; it became highly stigmatized. The pervasive became perverse.

Denormalization, according to Fairchild et al. (2014), means that a significant minority of the population became marginalised, stigmatised, and labelled perverts. It is unclear, however, what renormalisation means. Are combustible cigarette smokers no longer stigmatised? Are they no longer perverts? How could such an hypothesis be tested? It is not clear from Fairchild et al. (2014) how the existence of e-cigarettes rehabilitates that stigmatised minority who consume combustible cigarettes. Interestingly the word “hypothesis” does not appear anywhere in the Fairchild et al. (2014) paper. The Renormalisation Hypothesis is not an hypothesis of any sort, there is no obvious test that can be performed to test this “hypothesis”, nor is one suggested, it is simply not a scientific concept. Notwithstanding the lack of any support in the academic literature that the SCHEER Opinion itself has cited, it defines the issue as follows (emphasis added):

... there remains concern if the expansion of electronic cigarettes may hinder tobacco control efforts and impact smoking rates as adolescents and young adults who were likely to never use any form of nicotine products start experimenting with electronic cigarettes and other forms of nicotine delivery.

The issue then is this: individuals who were never likely to ever consume any nicotine product do consume nicotine products as a result of e-cigarettes being available on

4. Fairchild et al. 2014. *The Renormalization of Smoking? E-Cigarettes and the Tobacco “Endgame”*. *The New England Journal of Medicine*. Available at: <https://www.nejm.org/doi/full/10.1056/nejmp1313940>

the market. Presumably SCHEER means that individuals become regular consumers of nicotine product as a result of e-cigarette consumption. This is a challenge to interpreting the SCHEER Opinion; not only is it unable to reference what it means by the terms Gateway Hypothesis and Renormalisation Hypothesis, it is unable to clearly define those terms itself.

The SCHEER Opinion cites a meta-analysis undertaken by Soneji et. al (2017) as its primary evidence in favour the Gateway Hypothesis⁵. This study was financed by the (US) National Cancer Institute, the US Food and Drug Administration Center for Tobacco Products, and the National Institute on Drug Abuse. One of the authors has been involved in litigation against the tobacco industry as a paid consultant, and the lead author, Samir Soneji, also co-authored two of the seven papers employed in one part of the analysis. It is not clear how, if at all, the SCHEER Opinion has considered these biases and conflicts of interest in their interpretation of the Soneji et. al (2017) results.

Conducting a meta-analysis of seven studies Soneji et. al (2017) report that there is a 23.2% probability that e-cigarette users would initiate combustible cigarette consumption compared to a 7.2% probability to non-e-cigarette users would initiate combustible cigarette use. The underlying studies control ex post for covariates associated with the likelihood of combustible cigarette consumption – none of them specifically model and control for that likelihood on an ex ante basis. Nonetheless the association that Soneji et. al (2017) report is statistically significantly different from zero, and appears to be quite large.

As I explain below, the methodology employed in those underlying studies is contrived to deliver that very result. The second paper that the SCHEER Opinion relies upon is Glasser, et al. (2019)⁶. Glasser, et al. (2019), however, caution against drawing strong conclusions:

Concerns have been raised that e-cigarettes appeal to youth who would otherwise not use other tobacco products, leading directly to smoking cigarettes. The current evidence does not permit firm conclusions in this regard, nor does it allow us to determine whether, as some have hypothesized, e-cigarette use might discourage cigarette smoking among some youth who would have smoked cigarettes anyway. Our conclusions differ from the recently published report from the National Academies of Sciences, Engineering and Medicine, which asserts that there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and [Young Adults].

5. Soneji et. al 2017. Association Between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: A systematic review and meta-analysis. *JAMA Pediatrics*. Available at <https://pubmed.ncbi.nlm.nih.gov/28654986/>

6. Glasser, et al. 2019. Patterns of E-Cigarette Use Among Youth and Young Adults: Review of the Impact of E-Cigarettes on Cigarette Smoking. *Nicotine & Tobacco Research*. Available at <https://academic.oup.com/ntr/article-abstract/21/10/1320/4998820>

It should be noted that the SCHEER Opinion does not report Glasser, et al.'s (2019) own misgivings about their results. The SCHEER Opinion also refers to a paper by Aladeokin and Haighton (2019)⁷. This study examines three underlying papers. Importantly for our purposes, both Glasser, et al. (2019) and Aladeokin and Haighton (2019) include a paper by Best et.al (2018) in their analysis⁸. Glasser, et al. (2019) state in their summary discussion:

We do not deny that there is a detectable association between use of e-cigarettes and subsequent smoking, but the nature of this association is clearly not simple and direct, and is likely the result of a combination of indirect influences. We also cannot rule out the possibility that methodological shortcomings in most of the studies could have unknown effects on their findings.

As I explain in this section, methodological choices drive the “detectable association between use of e-cigarettes and subsequent smoking”. Those methodological choices are profound, fundamental, and deliberately misleading.

That methodological choice is best illustrated by referring to the paper authored by Best et al. (2018)⁹. This study examined whether a cohort of “Never Smoker” Scottish high school students had taken up the use of combustible cigarettes in 2016 conditioned on whether they had consumed e-cigarettes in 2015. The table below is reproduced from Best et.al’s (2018) table 2. Note carefully, however, how the consumption of combustible cigarettes is contrasted with the consumption of e-cigarettes. Even just a puff (or two) is sufficient to label a student as a “smoker”. This creates an upward bias in the number of students likely to be categorised as having become a smoker.

		Have you ever smoked cigarettes or roll-ups, even if it is just one or two puffs? (2016)		
		No	Yes	Total
E-cigarette use (2015)	I have never used an e-cigarette	1693	249	1942
		87.20%	12.80%	100%
	I have only used them once or twice	104	65	169
		61.50%	38.50%	100%
	I use them sometimes (monthly)	3	5	8
	37.50%	62.50%	100%	
I use them often (weekly)	2	4	6	
	33.30%	66.70%	100%	
Total		1802	323	2125

7. Aladeokin and Haighton. 2019. Is adolescent e-cigarette use associated with smoking in the United Kingdom?: A systematic review with meta-analysis. *Tobacco Prevention & Cessation*. Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7205081/>

8. Best et al. 2018. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. *Tobacco Control*. Available at <https://tobaccocontrol.bmj.com/content/27/4/373>

9. This argument draws on a discussion in a companion paper written in response to the e-cigarette debate in Australia.

Best et.al (2018) interpret the table as follows: Of the 2125 students in the sample, 183 students consumed e-cigarettes (169+8+6). Of those 183, 74 students also consumed combustible cigarettes. Therefore, according to Best et.al (2018), 40.4% (74/183) of Never Smokers who had consumed e-cigarettes went on to consume combustible cigarettes. By contrast, only 12.8% of Never Smokers went onto consuming combustible cigarettes (249/1942). That is one interpretation of the data.

That interpretation, however, is highly misleading. It artificially partitions the students into combustible cigarette consumers and e-cigarette consumers, and then investigates any overlap. It assumes that which is yet to be proven. The Gateway Hypothesis suggests: those individuals who had consumed e-cigarettes are more likely to subsequently become consumers of combustible cigarettes. The important distinction here is: more likely than whom? There are four groups of students in the sample. Those students who never consumed either a combustible cigarette or an e-cigarette. Then we have students who consumed combustible cigarettes who never consumed e-cigarettes. The existence of these two groups of students provide evidence against the Gateway Hypothesis. Then we have a group of students who consumed e-cigarettes who had never consumed (even took a puff or two) of a combustible cigarette. The existence of this group of students is, at least, inconsistent with the Gateway Hypothesis. To the extent that any of these students may well have become combustible cigarette consumers, but did not, this group of students would provide evidence that rejects the Gateway Hypothesis. Unfortunately, due the casual empiricism (discussed below) that interpretation of the data is not tested by Best et.al (2018) or any other researchers in the field. Finally there is a group of students that consumed e-cigarettes that went on to consuming combustible cigarettes (or, at least, had a puff or two of a combustible cigarette).

To better illustrate those four groups of students, I have summarised Best et.al's (2018) table 2 as below:

		Ever Smoked a Cigarette (2016)		
		No	Yes	Total
I have used an e-cigarette (2015)	No	1693	249	1942
	Yes	109	74	183
Total		1802	323	2125

Of the 2125 students in the sample, 1693 had never consumed either a combustible cigarette or an e-cigarette - that is 79.67% of all students.

249 students had consumed a combustible cigarette, but had not consumed an e-cigarette – that is 11.73% of all students. Over half of all the students who did consume combustible cigarettes (even just a puff or two) had never consumed an e-cigarette.

Then 109 students had consumed e-cigarettes; but had not consumed combustible

cigarettes (not even a puff or two) – that is 5.13% of all students.

Then 74 students had consumed both combustible cigarettes and e-cigarettes – that is 3.48% of all students.

Yet by carefully partitioning the student sample, Best et.al (2018) are able to inflate a figure where 3.48% of students use e-cigarettes before combustible cigarettes into a result consistent with the Gateway Hypothesis. If we look back to the original Best et.al (2018) table, we see that only four students who had regularly consumed e-cigarettes (weekly) went onto having had a puff (or two) of a combustible cigarette. That is 1.2% of all combustible cigarette consumers and 0.19% of all students. Who can even tell if those four students had gone on to being regular combustible cigarette consumers? The Best et.al (2018) summary statistics are too opaque to reveal that (important) detail.

When viewed in this light, the “evidence” for the Gateway Hypothesis is very weak. The analysis that shows otherwise, is contrived to show a result that simply cannot be supported by the data. The Best et.al (2018) study, however, is not an outlier. It is not somehow an anomaly. It is typical of the literature.

To demonstrate this point I partially reproduce table 2 from Soneji et.al (2017) below. The first three columns are directly reproduced. The first column shows the study being referred to, the second column shows the probability of an e-cigarette user taking up the consumption of combustible cigarettes, while the third column shows the probability of a non-e-cigarette user taking up the consumption of combustible cigarettes. The results appear to be very similar to those reported in Best et.al (2018).

	Probability of cigarette initiation %		Combustible cigarette users	Ever e-cigarette user	Never e-cigarette user
	Ever e-cigarette user	Never e-cigarette user			
<i>Miech et al</i>	31.1	6.8			
<i>Spindle et al</i>	29.4	10.6	230	45	185
<i>Primack et al</i>	37.5	9.0	87	6	81
<i>Barrington-Tri mis et al</i>	40.4	10.5	75	59	16
<i>Wills et al</i>	19.5	5.4			
<i>Primack et al</i>	37.5	9.6	71	6	65
<i>Leventhal et a</i>	8.8	3.1	249	67	182
Total	23.2	7.2	712	183	529

In order to establish the veracity of those data I investigated the summary statistics of each of the seven papers. In the case of Miech et.al, interpretable summary statistics were not included in the study. Similarly in the case of Wills et.al, I could not sensibly interpret the summary statistics that they did report. In the other five instances, understanding and interpreting the summary statistics was a non-trivial task. I submit that the reporting on summary statistics is deliberately opaque in order to mask the underlying reality that consuming e-cigarettes is not a gateway to the consumption of combustible cigarettes. In each study I attempted to establish the number of combustible

cigarette users, the number of e-cigarette users, and the number of non-e-cigarette users. The results of that exercise are shown in the final three columns of the table.

Looking at the totals row, across the five studies where I was able to get meaningful summary data, 712 individuals became combustible cigarette users, of those 183 had initially consumed e-cigarettes ($183/712 = 25.7\%$). That means that 74.3% of individuals who became combustible cigarette users did so directly without first consuming e-cigarettes. That result, however, is distorted by Barrington-Trimis et. al. This is the only underlying study that actually provides unambiguous support for the Gateway Hypothesis. This study has an astonishing small sample size of 298. In the absence of that outlier study the percentage of individuals who became smokers after having consumed e-cigarettes falls to 19.5%. That means that over 80% of individuals who become combustible cigarette consumers did not do so after consuming e-cigarettes.

Casual Empiricism

As I argued above, the hypotheses being tested in the underlying papers are vague. While it is true that readers can have an intuitive understanding of what a Gateway Hypothesis might mean, the scientific method requires precision. It is necessary to specify precisely what the hypothesis being tested is, and what the alternate hypotheses are. The analysis being conducted in the underlying studies is lazy and poor practice. The approach is to suggest some vague notion; that the consumption of e-cigarettes results in the consumption of combustible cigarettes. The alternate hypothesis is unspecified, but presumably is the converse: that the consumption of e-cigarettes does not result in the consumption of combustible cigarettes. That approach would be entirely appropriate when studying statistics at a first year level.

The authors of the underlying studies (and by extension the authors of the meta-analyses) are looking for evidence consistent with their prior beliefs. As I demonstrated in the previous section, they are prepared to generate and manipulate statistics that manufactures that evidence. What they fail to do, however, is specify a research method that rules out alternate hypotheses.

An alternate hypothesis, for example, could be that individuals who would otherwise have become smokers anyway, do not become smokers because they continue to consume e-cigarettes. In the underlying studies a large number – usually a majority – of e-cigarette consumers never become combustible cigarette users. The authors of the underlying studies never test that hypothesis. Indeed they have no framework to test that hypothesis, because they have no *ex ante* theory to predict who could become a smokers, they simply rely on *ex post* empirics to control for those factors.

A uniform problem across all the studies is that the hypotheses are poorly defined, the alternate hypotheses unspecified, the summary statistics opaque and often misleading, the models being tested are not set out, and the conclusions pre-determined. The authors have all very much followed a “have data will regress” research strategy.

Conclusion

Investigating possible relationships between initiating combustible cigarette consumption and e-cigarette consumption is a valid public health question. It deserves to be extensively studied, and properly studied. Unfortunately that has not occurred. The extant literature, while large, is uniformly of poor quality. The research that has been conducted simply reinforces pre-existing prior beliefs of the researchers. The data have been manipulated to arrive at the conclusion that e-cigarettes lead to the consumption of combustible cigarettes.

Rather than simply mechanically quote the literature on e-cigarettes, the SCHEER Opinion should engage with that literature on a scientific basis – it is, after all, a scientific committee. The underlying studies are scientifically flawed; they exhibit methodological flaws, and bias. The possible health benefits that flow from consumers substituting from combustible cigarettes to e-cigarettes, or consuming e-cigarettes to the exclusion of combustible cigarettes, are likely to be huge. It is important that the quality of the public health research be of the highest standard to reflect the importance of the issue at hand. Unfortunately the SCHEER Opinion does not reflect that importance.

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