

Comment on a letter urging WHO to treat electronic cigarettes as tobacco products or medicines:

The importance of dispassionate presentation and interpretation of evidence

Following our letter to the Director General of the WHO of 26 May 2014¹ Professor Stanton Glantz organized a letter in response ('the Glantz letter')². While our letter concerned the broader issue of tobacco harm reduction and principles that should govern the policy approach to low risk alternatives to smoking, the Glantz letter attempted a scientific critique of e-cigarettes (EC).

Before moving to specifics, we would like to stress that our points about tobacco harm reduction remain valid and relevant, and that authors of the letter to Dr Chan stand by the principles set out in the text. We hope that WHO and the parties to the FCTC will respond accordingly.

As regards the specifics, it is a matter of regret that the Glantz letter repeated examples of misinterpretation of research data that had been already criticized by a number of commentators at the time of writing^{3,4}. We believe that researchers have a duty to make every effort to be objective in presentation of evidence and that studies cited should be relevant, properly interpreted and support the conclusions drawn.

In the following paragraphs we explain why conclusions drawn in the Glantz letter do not follow from the studies cited.

1. Contrary to the impression given, surveys have found that use of e-cigarettes by never smokers is negligible and smoking rates are declining among youth

The letter reports "... rapid growth in youth e-cigarette use, including disturbing rates among youth who have never smoked a cigarette". The CDC National Tobacco Youth Survey (NYTS) was cited in support of this statement.^{5,6} In fact, the CDC states "*During 2011–2012, among all students in grades 6–12... current e-cigarette use increased from 1.1% to 2.1% ($p < 0.05$), and current use of both e-cigarettes and conventional cigarettes increased from 0.8% to 1.6% ($p < 0.05$)*".⁶ Thus, prevalence was 0.5% among non-smokers

and some of these would have smoked in the past and now be using e-cigarettes instead. Moreover, current use was defined very broadly as any use of an e-cigarette in the past 30 days, not regular or daily use.

The letter also refers to a study in Korea, and they state that it showed “a rapid growth in youth e-cigarette use”.⁷ In fact, the study found that “... 4.7% were current (past 30-day) e-cigarette users (3.6% dual users and only 1.1% e-cigarettes)”. This percentage again was “any use in the last 30 days”. The authors of the Korean survey report: “It was rare for students no longer using cigarettes to be among current e-cigarette users”.

Clearly it is important to continue to monitor the trends but alarmist statements about dramatic rises in EC use are not warranted on the basis of the surveys cited.

Moreover, if potential smokers used e-cigarettes instead, this would clearly be a public health gain as long as they did not go on to smoke. On the other hand, the most serious issue would be if there was a rise in cigarette smoking through a ‘gateway effect’. In fact the CDC reports “...the prevalence of current tobacco product use among middle and high school students was 6.7% and 23.3%, respectively”, while for 2011 estimates were “7.5% for middle school and 24.3% for high school students”.⁶ Thus prevalence of youth smoking in the US is thus falling and the data offer no support for a ‘gateway’ from e-cigarettes to cigarette smoking.

2. The claim that dual use of e-cigarettes and cigarettes confers no benefit is not supported

Establishing the potential benefits or harms of dual use requires estimation of toxin intake compared with what it would be if the same smokers were not using e-cigarettes. Prospective studies are essential to control for the fact that it is heavier smokers are likely to try e-cigarettes as a means of cutting down (based on findings from licensed nicotine products). Furthermore, markers of toxin intake are required to assess whether use of e-cigarettes means that cigarettes are smoked less intensively because e-cigarettes are providing an alternative source of nicotine. Failure to acknowledge this is misleading. In addition, with licensed nicotine replacement therapy (NRT) it has been shown that dual use with smoking is linked prospectively with subsequent cessation of

cigarettes.⁸ Adequately powered studies need to be done with e-cigarettes before any claims about dual use can be made one way or the other.

3. The claim that e-cigarettes undermine cessation is not supported by evidence – which tends to support the opposite conclusion

The fact that the proportion of EC users is higher among smokers than ex-smokers is used in the Glantz letter to support the claim that EC use inhibits quitting. This is based on fallacious reasoning and misunderstanding of conditional probability. The relative proportions of EC users in smokers and ex-smokers can arise from many different factors, including EC users who stop smoking going on to stop EC use, and smokers using EC just to cut down.

Establishing whether EC use while smoking influences cessation requires a prospective study in which EC users at baseline are followed up to assess later cessation even when other confounding factors have been adjusted for. This could still be subject to unmeasured confounding but at least offers some prospect of addressing the issue. It will also be necessary to compare with cessation following NRT use because NRT use while smoking has been shown to predict subsequent cessation.

One study cited in the letter followed up 949 smokers from 2011 to 2012, and found no association between EC use (which was reported by 88 smokers) and smoking cessation.⁹ This study did NOT find that *“smokers who use ENDS are less likely to stop smoking”*. The statistical power to find an association, positive or negative, was low.

With regard to a study by Vickerman et al.,¹⁰ which is cited as supporting the view that e-cigarettes discourage smoking cessation, the authors have pointed out: *“The recently published article by Dr. Katrina Vickerman and colleagues has been misinterpreted by many who have written about it. It was never intended to assess the effectiveness of the e-cig as a mechanism to quit”*.¹¹

As with other citations used in that section of the letter, the study by Popova and Ling did not find that smokers were less likely to quit by using e-cigarettes.¹² The authors themselves state: *“Because this was a cross-sectional study, we could not determine whether use of alternative tobacco products resulted in cessation attempts or whether*

those who were trying to quit—for whatever reason—were using alternative tobacco products”.

The only studies that were specifically designed to assess e-cigarette effectiveness as quitting aids were mentioned in the letter but discounted. The ASCEND study¹³ was reported of being biased against NRT because vouchers were sent to the participants assigned to nicotine patches, to get them for free from the pharmacies. The authors explained that such bias was unlikely because both the per-protocol and the intention-to-treat analysis showed similar results, so failure of NRT users actually to acquire the product was an unlikely explanation of the finding. The study showed that a first generation e-cigarette (which delivered minimal nicotine) had broadly similar efficacy to nicotine patches in smoking cessation. In fact the study had limited power to detect anything other than a large difference.

A study by Brown et al.¹⁴ evaluated the real-world effectiveness of e-cigarettes when used as an aid for smoking cessation. The study found that smokers who used e-cigarettes to quit were more likely to report continued abstinence compared to those who used a licensed NRT product bought over-the-counter or no aid to cessation. The Glantz letter criticized this study by stating that 80% of the smokers who used e-cigarettes did not quit; they added that no comparison was made with *“well-supervised approved cessation therapies”*.

Unaided quitting rates are typically less than 5% at 12 months. The fact that a majority of people who use a particular method of quitting do not succeed has been taken by some people (presumably as a polemical device since the logic is faulty) to show that the method is ineffective. The correct comparison, of course, is with unaided quitting. Therefore, the fact that a high proportion of smokers who use e-cigarettes to stop smoking fail to stop and continue to use e-cigarettes has no bearing on the question of whether they aid cessation. What is needed is a comparison with quitting rates in those not using EC after adjustment for confounding variables. So the fact that majority of smokers fail to quit with a given method does not mean that the method does not improve success rates. This is a basic error of interpretation.

The study authors noted that it could not look directly at e-cigarettes versus supervised quitting because of lack of statistical power but noted that on average best results have been achieved with specialist stop smoking services available in the UK. The critical issue is whether there is evidence that the growth in use of e-cigarettes for smoking cessation has been at the expense of potentially more effective methods and the evidence indicates that this is not the case.

4. Failure to quantify the relative risk compared with tobacco creates a misleading impression to non-experts.

It is misleading to make an issue of the presence of toxins e-cigarette vapor without showing how these compare both to levels in cigarette smoke and to routine exposure. Thus the letter states that nitrosamines are present in e-cigarette vapor , but does not state that the level of daily exposure is some 1800 times lower compared with tobacco cigarettes.¹⁵ The presence of heavy metals¹⁶ is similarly reported in a way that creates a misleading impression of the risk. The US Pharmacopeia has established safety limits for the daily exposure to heavy metals through inhalation for medications.^{15,17} In the case of lead and nickel (Pb and Ni), the safety limits are 6 times higher than the expected daily exposure from e-cigarettes while for chromium (Cr) the difference is more than 70 times. Reference is also made to ‘ultrafine particles’ as though it is particle size that governs risk to health. In fact the lowest size particles are water vapor¹⁸, which carries no health risk. What matters most is the chemical composition of the particulate matter – and this differs completely between tobacco smoke and e-cigarette vapor.

Similarly, it is misleading to report cases of accidental poisoning without providing appropriate reference points or quantification.^{19,20} The number of cases is very small compared with, for example, household cleaning products, cosmetics or medicines.²⁰

The basic proposition of harm reduction is not that the alternative nicotine products are *harmless* but that they offer reductions in risk of 95 per cent or more compared to cigarettes, and provide a viable alternative to smokers who cannot or do not wish to quit using nicotine. The challenge is to find an appropriate framework for realizing the significant public health opportunities this offers while managing residual risks.

In conclusion, we are concerned about what appears to be an attempt to influence policy through misrepresentation of evidence. We understand that signatories to the Glantz letter share our concern about anything that could undermine efforts to reduce the burden of disease and premature death caused by tobacco, and we should work together in good faith with that aim in mind. However, it is imperative that trusted scientists discharge their duty with care and make every attempt to be objective when presenting and interpreting evidence and recommending policies. Policy-makers need to be discerning users and critics of scientific reasoning, whether advanced by scientists, activists or interest groups.

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Note: this comment is endorsed by all the original signatories of the letter to Dr Chan of 26 May who were contactable and available to review this document by 26 June 2014. Please see the original letter for affiliations.