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The 1988 U.S. Surgeon General's report 'Nicotine Addiction': How well has it stood up to three more decades of research?

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Running head: The 1988 Surgeon General's Report

Abstract

The 1988 U.S. Surgeon General's Report titled 'Nicotine Addiction' was a comprehensive treatise setting out the evidence that tobacco is addictive and showing that nicotine lies at the heart of this addiction. It likened tobacco to drugs such as cocaine and heroin, and provided a powerful rationale for combining public health and clinical approaches to prevent and combat tobacco addiction. The main conclusions of the report have stood up well to more than 30 years of further research, but there are areas where our thinking needs to be updated. In particular, we now know that different nicotine products are differently addictive and that different tobacco and nicotine products only partially substitute for each other, even when they deliver similar amounts of nicotine with similar rapidity. We also understand that addiction to nicotine products does not depend on development of physiological tolerance, pleasurable effects or need to relieve adverse mood and physical symptoms. The field of tobacco control needs to embrace a model of tobacco and nicotine addiction based on nicotine acting in concert with the means of ingesting it to generate cravings. The field also needs to go further in distinguishing between addiction to different tobacco and nicotine products. Crucially, tobacco policy globally needs to do much more to recognise the addictive nature of tobacco and benefits of treatment.

Key words: tobacco, addiction, nicotine

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It has been believed for centuries that tobacco is addictive and harmful to health. With the discovery of nicotine and its profound actions on the brain came the theory that this was the chemical primarily responsible for tobacco addiction (1). Yet, before the late 1980s, many people working in public health and addiction still regarded tobacco use as a lifestyle choice. In fact, the 1964 US Surgeon General's Report on smoking cessation used the term 'habituating' rather than 'addictive' (2) which may have had something to do with the fact that the tobacco industry had a representative on the committee writing it (3).

In the 1970s and 1980s, things started to change. Laboratory findings emerged that non-human species would demonstrate nicotine-seeking behaviours, such as pressing a lever to receive nicotine infusions (e.g., 4). It was found that smokers who switched to low-nicotine cigarettes would smoke each cigarette harder in an apparent attempt to compensate for the reduced nicotine yield (5). A cigarette withdrawal syndrome was characterised involving mood disturbance, increased appetite, difficulty concentrating, changes to the EEG and reduced secretion of cortisol and adrenaline (6). And it was found that withdrawal symptoms could be mitigated by ingesting pure nicotine (6). The scientific case was building for tobacco to be considered an addictive substance with nicotine as the active agent responsible for this. Then, after several years' meticulous work by a large number of the world's leading tobacco and nicotine researchers, the U.S. Surgeon General's Report titled 'Nicotine Addiction' was published. This 647-page magnum opus, arguably more than any other single document, made the concept of tobacco addiction mainstream. This paper reviews the conclusions of that report and examines how far they have stood the test of several decades of further research and the advent of a type of product that can deliver nicotine much like a cigarette but without burning tobacco: the e-cigarette.

The 1988 report

The 1988 report did not come out of nowhere. In fact, in 1979 a previous Surgeon General's Report had concluded 'it is no exaggeration to say that smoking is the prototypical substance-abuse dependency' (7). Yet this had seemingly not been enough to make the case for considering tobacco addiction alongside other substance addictions in the eyes of most policymakers and healthcare organisations. Since that report, a huge body of evidence accumulated that formed the basis for the 1988 report.

In the 1988 report, the case for considering tobacco to be addictive, and for nicotine to be the agent primarily responsible for this, came in multiple strands. Key supportive observations in the report related to the difficulties experienced when people tried to stop or limit their use. This included evidence that: 1) tobacco users, primarily cigarette smokers, mostly failed when they made a determined attempt to stop using, 2) tobacco users, again primarily cigarette smokers, experienced powerful urges to use their tobacco product, 3) there was characteristic tobacco withdrawal syndrome, including irritability, restlessness, depression, and difficulty concentrating, which typically lasts for up to four weeks, and increased appetite, which lasts for several months.

Further evidence came from observations relating to the behaviour itself. The report noted that it was highly repetitive and apparently compulsive. Thus there was evidence that almost all smokers smoked multiple cigarettes each day and rarely went a day without smoking. In addition, smokers who attempted to reduce the number of cigarettes they smoked each day rarely succeeded for long, and their overall nicotine intake typically remained undiminished. Furthermore, tobacco users persisted in their behaviour despite being fully aware of the harmful consequences.

Evidence for the role of nicotine came from research that people would report a positive experience from ingesting pure nicotine, that smokers of cigarettes whose smoke contained low concentrations of nicotine increased the depth and frequency of puffing in a way that meant that their nicotine intake was similar to smokers of higher-yielding cigarettes. When smokers reduced their cigarette consumption they typically increased the intensity with which they smoked each cigarette, apparently to maintain their level of nicotine intake. It was found that nicotine acted on parts of the brain that had been found to be implicated in addiction to other drugs, most notably the ventral tegmental area. Moreover smokers developed physiological 'tolerance' to the pharmacological actions of nicotine such that these actions were weakened after repeated exposure. Compelling evidence for the role of nicotine came from the fact that ingesting pure nicotine from chewing gum or skin patches could alleviate the tobacco withdrawal symptoms and increase smoker's chances of remaining abstinent.

To counter the argument that smoking cannot be addictive because so many smokers manage to stop without assistance, the report noted that the same was true for other addictive substances such as heroin and alcohol. Another key argument that smoking could not be addictive was that only a proportion of youngsters who tried smoking would go on to become regular smokers and the report noted that this too was true of other substances widely acknowledged to be addictive. Thus a substance could still be addictive if some users did not become addicted and some addicted users recovered without assistance.

The report also noted that psychological and social factors are important drivers of tobacco use while stating that this was outside its scope.

It is worth noting that the vast majority of the research involved cigarette smoking rather than other forms of tobacco use and that the only non-tobacco nicotine products available at the time were limited in how rapidly they could deliver nicotine into the bloodstream.

The core propositions in the 1988 report have stood the test of time and been confirmed by subsequent research. However, the detail has needed to be refined or modified. The advent of e-cigarettes that can deliver nicotine in doses and with a rapidity similar to cigarettes has provided an opportunity to differentiate nicotine and tobacco. We will consider emerging evidence about e-cigarettes later; first, we summarise other strands of evidence.

Subsequent evidence emerging from studies on tobacco use and nicotine products

A substantial body of evidence has emerged since 1988 that has provided a more complete and nuanced picture of tobacco addiction and the role of nicotine.

Evidence has emerged that smokeless tobacco products are as addictive as smoked products. Thus, self-report measures of addiction to smokeless tobacco, derived from ones used to assess cigarette addiction, appear to show similar levels of addiction to cigarettes (8) and success rates when attempting to stop smokeless tobacco use appear to be no greater than those for cigarette smoking (9,10).

However, it appears that different tobacco products do not substitute well for each other, even when they deliver nicotine in broadly similar ways. For example, clinical trials have found that smokeless tobacco appears to be no more effective than pure nicotine replacement products in aiding smoking cessation (11–13), with the large majority of smokers relapsing to smoking. Surprisingly, pharmacological interventions, including nicotine replacement therapy, appear to be less effective for smokeless tobacco cessation than smoking cessation (9,10).

Evidence subsequent to the 1988 report has cast doubt on some of the presumed mechanisms of action of tobacco addiction. Thus evidence suggested that pure nicotine may not be as rewarding as had been supposed. For example, nicotine self-administration by non-human animals is not as robust as for drugs of dependence such as cocaine and is highly dependent on the presence of cues associated with nicotine delivery (e.g., 14). Cigarette craving and relapse to smoking following a quit attempt appear not to be correlated with the enjoyment smokers receive from smoking (15), making it unlikely that the positively rewarding effects of smoking mediate addiction. In addition, enjoyment of smoking appears to act primarily as a deterrent to make an *attempt* to quit smoking (15).

Evidence has also emerged that some smokers can transition to cigarettes that are able to deliver only a small fraction of their previous nicotine intake, whereas others do not appear able to do so (16).

Moreover, most aspects of the nicotine withdrawal syndrome, including mood disturbance, difficulty concentration and increased appetite, are at best weakly predictive of relapse to smoking during attempts to stop (17). Chronic pharmacological tolerance appears to occur only to the aversive effects of nicotine, particularly its emetic effects (18). It does not appear to be the case, as has been proposed for other addictive drugs, that smokers need to escalate their dose in order to obtain sought after positive effects.

Subjective urge to smoke has emerged as a key mediator of tobacco addiction. Thus, urges to smoke are predictive of short-term relapse (17) and strength of urges to smoke while still smoking, i.e., prior to the start of the quit attempt, are at least as predictive of relapse during the quit attempt the leading measure of cigarette addiction, the Fagerstrom Test for Cigarette Dependence (19). The drugs varenicline and cytisine, both partial agonists acting on the alpha-4-beta-2 nicotinic acetylcholine receptor, substantially increase smokers' likelihood of success at stopping smoking, and this appears to be mediated through a reduction in urges to smoke and the satisfaction obtained from smoking (20,21) even though these drugs have no rewarding properties of their own. Their effect on urges to smoke appears to be greater than their effect on symptoms of nicotine withdrawal (22).

The role of the behaviour and speed of nicotine delivery in tobacco addiction has been called into question by the fact that nicotine transdermal patches, which release nicotine very slowly and involve no repetitive behaviour, appear as effective as some faster-acting nicotine products (nicotine gum, nicotine inhalator and nicotine nasal spray) that involve repetitive behaviour at aiding smoking cessation even though the latter promote higher levels of addiction in users (23). On the other hand, using nicotine transdermal patches together with one of the faster-acting forms of nicotine replacement, such as nicotine gum, has been found to be more effective in aiding smoking cessation than using any one single form of nicotine replacement (24).

Thus, while the addictiveness of cigarettes has been confirmed and the fact that nicotine plays a crucial role in this has also been confirmed, it has become apparent that we need to rethink the precise mechanisms involved.

It seems unlikely that either the pleasurable effects of nicotine or the withdrawal symptoms are prime drivers of cigarette addiction, although enjoyment of smoking may deter attempts to quit. It also appears that different forms of tobacco do not readily substitute for each other, and so 'tobacco addiction' cannot be considered to be an addiction to tobacco per se but to a particular form of tobacco, whether it be cigarettes or some form of smokeless tobacco. The finding that pharmacological treatments appear to be less effective for smokeless tobacco use than for

cigarettes is surprising and suggests a significant gap in our understanding of tobacco addiction. It also seems that some nicotine users can tolerate quite a large variation in the amount of nicotine they ingest, whereas others cannot. Finally, it is apparent that physiological tolerance may not contribute directly to the drive to smoke, although tolerance to the adverse effects of nicotine may enable smokers to ingest more nicotine than they would otherwise have been able to.

Evidence emerging from e-cigarettes

When e-cigarettes first came onto the market, their nicotine delivery was no greater or more rapid than products such as an inhalator or nicotine gum (25). However, technological developments have subsequently led to products that can provide as much nicotine as a cigarette as rapidly as a cigarette (26). Many millions of smokers have tried these products. A proportion of these have switched to them completely, whereas others have continued to smoke cigarettes and use e-cigarettes as well (e.g., 27). However, most have continued to smoke cigarettes and stopped using e-cigarettes (e.g., 27).

If cigarette addiction was completely or largely a matter of ingesting nicotine rapidly into the bloodstream, most people should find it easy to switch from cigarettes to e-cigarettes, but they do not. It is true that historically e-cigarettes have not delivered nicotine as effectively or efficiently as cigarettes, but in countries such as the U.K. and U.S., smokers now have access to e-cigarette brands that do deliver nicotine in a way that is similar to tobacco cigarettes. Yet most people who try to switch completely to these products do not succeed.

Evidence from the most recent e-cigarette trials shows that they are more effective in helping smokers to stop smoking than licensed nicotine products such as transdermal patches and chewing gum (28), but even with psychological support, the majority of smokers who are motivated to use them to stop smoking relapse to cigarettes (e.g., 29). This must mean that for a majority of smokers, they do not adequately substitute for cigarettes and therefore that there must be something about cigarettes that is missing.

It is plausible that what is missing is the sensory experience of smoking that has been conditioned to CNS effect of nicotine. Thus, years of smoking may have established the unique smell and taste of cigarette smoke and the look and feel of cigarettes as powerful conditioned reinforcers which smokers come to need. It is also possible that there are important primary reinforcers that act additively or synergistically with nicotine to create a total package that is what most smokers seek. It is also possible that there are chemicals in cigarette smoke that potentiate the addictive properties of nicotine. One such family of chemical comprises monoamine oxidase inhibitors (30). At this stage, it is not clear which of these hypotheses is correct. All three mechanisms may play a role.

Despite potentially being effective nicotine delivery devices, e-cigarettes do not appear to be as addictive as tobacco cigarettes. Thus young people try e-cigarettes are much less likely to go on to regular use of these nicotine delivery systems than those who try cigarettes are to become regular smokers and show much less evidence of dependence (31). In addition, self-report data suggest that e-cigarette users, on average, may be less addicted to their products than cigarette smokers are to theirs (32).

It has been proposed that the addition of flavouring to the e-liquids used in e-cigarettes adds to their addictive properties (33). If true, this could be an additive or synergistic effect. Still, it does not appear to be enough to make these products as addictive as cigarettes or to act as a satisfactory substitute for cigarettes in most cases.

What can we conclude about tobacco addiction today?

Findings that have emerged since the 1988 report reinforce the key proposition that tobacco products are addictive and that nicotine plays a central role in this addiction, but it also points to a more nuanced and multi-faceted model of tobacco addiction (34). In particular, three important new insights appear to have emerged:

1. Tobacco is addictive, with people becoming addicted to specific forms of tobacco that *only substitute for each other to a small degree*.
2. Addiction to tobacco does not appear to be principally caused by positive subjective effects of smoking, physiological tolerance to those effects, or the need to prevent adverse withdrawal symptoms, but *subjective urges to smoke do appear to play an important role*.
3. Nicotine ingestion plays a central role in causing that addiction, but *pure nicotine delivery products do not appear to be as addictive as tobacco and only partially substitute for tobacco*.

In addition to this, it is worth noting that the context has changed considerably. In many high income countries tobacco use, and particularly smoking, has declined substantially and the decline has been greater in people with higher than lower socioeconomic position. This appears to have increased associations between tobacco dependence and different aspects of inequality (35).

What does this mean for tobacco control?

The 1988 report acknowledged that addiction involves more than drug-seeking behaviour and that tobacco addiction is not nicotine addiction. Since it was published, the important role played by nicotine in tobacco addiction has been confirmed, as has the distinction between nicotine use and tobacco use. Considerable progress has been made in the science underpinning tobacco control, but that science has not been applied optimally.

Globally, many tobacco control advocates have failed to make the distinction either between different tobacco products or between tobacco and nicotine. Some major funders of tobacco control have failed even to take on board the main message of the 1988 report that tobacco is addictive; they have steadfastly refused to fund programmes that would assist the hundreds of millions of tobacco users worldwide to recover from their addiction. Treatment for tobacco addiction, in terms of public finance, has remained a Cinderella subject. It has been left mainly to pharmaceutical companies to develop effective treatments. This has put these treatments out of the reach of the majority of tobacco users. And when an extremely inexpensive treatment, cytisine, is available, there has been little or no interest in ensuring that this is made available to tobacco users at low cost.

There is much talk about an 'endgame' for tobacco, but the value of the global tobacco market continues to rise and is currently worth an estimated \$780 billion (36), with one-fifth of the adult population worldwide using tobacco products (37). The failure of the key players in tobacco control to take the main messages of the 1988 report seriously has arguably led to many hundreds of thousands more deaths and exacerbated inequalities from tobacco than need have been the case. Now would be a good time to develop policies and interventions based on the science of nicotine and tobacco. These would be policies to ensure that those people addicted to tobacco had ready access to affordable treatments.

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