

SPECIAL COMMUNICATION

Toward a comprehensive long term nicotine policy

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Global tobacco deaths are high and rising. Tobacco use is primarily driven by nicotine addiction. Overall tobacco control policy is relatively well agreed upon but a long term nicotine policy has been less well considered and requires further debate. Reaching consensus is important because a nicotine policy is integral to the target of reducing tobacco caused disease, and the contentious issues need to be resolved before the necessary political changes can be sought. A long term and comprehensive nicotine policy is proposed here. It envisages both reducing the attractiveness and addictiveness of existing tobacco based nicotine delivery systems as well as providing alternative sources of acceptable clean nicotine as competition for tobacco. Clean nicotine is defined as nicotine free enough of tobacco toxicants to pass regulatory approval. A three phase policy is proposed. The initial phase requires regulatory capture of cigarette and smoke constituents liberalising the market for clean nicotine; regulating all nicotine sources from the same agency; and research into nicotine absorption and the role of tobacco additives in this process. The second phase anticipates clean nicotine overtaking tobacco as the primary source of the drug (facilitated by use of regulatory and taxation measures); simplification of tobacco products by limitation of additives which make tobacco attractive and easier to smoke (but tobacco would still be able to provide a satisfying dose of nicotine). The third phase includes a progressive reduction in the nicotine content of cigarettes, with clean nicotine freely available to take the place of tobacco as society's main nicotine source.

Deaths from tobacco use are high and rising. Peto¹ estimated 3 million annually in the mid 1990s rising to 10 million by 2030. These deaths are almost entirely due to the inhalation of tobacco smoke or its oral use, a process driven, in today's world, substantially by tobacco product marketing, and sustained by nicotine addiction. Whereas comprehensive tobacco control policy receives (rightly) much attention, and has achieved a reasonable degree of unanimity,²⁻⁴ a comprehensive policy towards nicotine is complex and elusive. There is now an adequate understanding of nicotine's role in tobacco use and disease which enables the postulation of long range nicotine based policy to reduce tobacco use and disease.

That nicotine addiction can be overcome is evidenced by the observation that ex-smokers in the USA constitute half of the ever-smokers. The same observation provides evidence that overcoming nicotine addiction is difficult, as illustrated by the fact that the USA has applied formidable resources to the problem resulting in a relatively modest change in adult smoking prevalence in the 1990s.⁵

Although many cigarette smokers are able to achieve abstinence from all forms of nicotine, many others achieve

abstinence from cigarette smoking by indefinite periods of use of other forms of nicotine such as nicotine gum and, in Sweden, smokeless tobacco products. Such nicotine product substitution appears to sustain the dependence on nicotine while reducing the risk of smoking related diseases. A policy that accepts only tobacco and nicotine abstinence as its goal flies in the face of the biology of tobacco addiction and would seem to condemn many tobacco users to their course toward premature death. Alternatively, a policy that too liberally promotes any form of nicotine as an alternative to smoking could increase overall nicotine addiction, a prospect worrisome to many in public health. Either extreme appears unacceptable from either a public health or a policy perspective. A realistic and long term approach must find a meeting ground between these two views but must include major elements of harm reduction.

Both specific nicotine policy and comprehensive tobacco policy need, to some extent, to be national rather than global, since tobacco use habits vary widely around the world. What is suitable for countries in which smokers are highly dependent on the cigarette is not necessarily suitable for those where smokeless tobacco, bidi, kreteks, and other habits are common.

The underlying objective of a national nicotine policy is improved public health by reducing tobacco caused death and disease. Because tobacco attributable disease is directly related to exposure to tobacco related toxicants, but not to nicotine per se, progress toward this objective will be made most profound by reduction in tobacco use, even if nicotine use persists. The World Health Organization Framework Convention on Tobacco Control (FCTC) should contribute to progress by encouraging tobacco products with lower levels of toxicants, and contributing to prevention and cessation of tobacco use. The possibility that alternative nicotine delivery systems may be substituted indefinitely for tobacco products by persons unable to totally abstain from nicotine is discussed later and is not an express part of the FCTC, but one which we urge consideration of in this paper.

A key issue is the relative doses delivered by the various sources of tobacco nicotine and clean nicotine alternatives. Dose depends on both choice of delivery system (product), and on the way it is used. Current ways of measuring dose for packet labelling purposes, particularly for cigarette smoke, are misleading.⁶

THE SPECTRUM OF HARMFULNESS OF NICOTINE DELIVERY SYSTEMS

The epidemiology tells us that tobacco products delivering nicotine vary considerably in harmfulness. Within each

Abbreviations: FCTC, Framework Convention on Tobacco Control; FTND, Fagerstrom test for nicotine dependence; NDSS, nicotine dependence syndrome scale; NRT, nicotine replacement therapy; PREP, potential reduced exposure product; SACTob, Scientific Advisory Committee on Tobacco Product Regulation; TCM, tobacco control community

product category there is a (sometimes wide) variation of dose and manner of use, but the extreme ends of the spectrum differ in harmfulness by orders of magnitude.

Cigarettes

The cigarette is by far the most routinely dangerous form of nicotine delivery device leading to premature death in approximately half of its long term users.⁷ Although cigarette composition varies between countries,^{8–10} over time the mortality outcome per pack year has varied little.¹¹ The danger of the modern cigarette is potentially increased because it is highly sophisticated and addictive. The development of the modern cigarette is well chronicled by industry documents^{12–13} suggesting that its addictive properties may have been enhanced over recent decades. Furthermore the widespread use of ventilated filters facilitates compensatory smoking.¹⁴

Cigars and pipes

Cigar smokers experience much lower mortality ratios for coronary heart disease, chronic obstructive lung disease, and lung cancer than do cigarette smokers. They experience about half the risk of laryngeal cancer and similar risks of oral and oesophageal cancer. As expected, daily dose and inhalation patterns modify this difference to the degree such that an inhaling smoker of five cigars daily experiences the same lung cancer risk as a one pack per day cigarette smoker.¹⁵ Less information is available for pipe smokers, who often are classified with cigar smokers and may have mixed habits,¹⁶ but the mortality outcomes are substantially less than those associated with cigarettes.^{17–19} The lower risks associated with primary cigar smoking probably reflect the fact that many such smokers are satisfied by buccally absorbed nicotine and do not develop the habit of inhaling the smoke into the lungs.

Smokeless tobacco

Smokeless tobacco use in India and South Asia is associated with increased risk of cancers of the oropharyngeal area.²⁰ Risks vary greatly according to the dose and form of tobacco mix used. Relative risks for oral cancer were one- to fivefold, for oesophageal cancer two- to threefold. Tobacco use habits are very diverse and an increased risk of other oral disease is seen, as might be expected. A review of US studies concluded that snuff use increases risk of oropharyngeal cancers.²¹ Another study reported increased risk of oral cancer and high relative risks for cancer of the buccal mucosa and gums among snuff users.²² Use of Swedish snus has not been associated with increased risk of oropharyngeal cancer.²³ The latter may be related to lower levels of tobacco specific nitrosamines in Swedish snus compared to many US smokeless tobacco products.

Other products

There is a galaxy of other tobacco products that can be presumed to be dangerous but for which quantitative epidemiological data are not reliable. These vary from the hookah type waterpipe to reverse smoking of cheroots, to bidi and kretek and to mixtures such as nass and gudarkhu.²⁴ There is also the question of the harmfulness of those new tobacco products that heat but do not burn tobacco (potential reduced exposure products (PREPs)).²¹ Their place on the spectrum of harmfulness must await more data.

Nicotine replacement therapy

Nicotine replacement therapy (NRT) products such as gum, patches, lozenges, inhaler, and nasal spray, do not contain the various toxicants and contaminants of tobacco products and they must meet standards for purity and safety set by regulatory authorities in each country or region in which they

are marketed (for example, US Food and Drug Administration; European Drug Regulatory Agencies). They are not without harm or risk, but their risks are well characterised and are very low compared to tobacco.^{21–25} Although there is wide variation in the actual permitted uses of the products, the primary basis of approval and use is for a few months to treat tobacco dependence and thereby promote smoking cessation. Long term use to sustain tobacco abstinence in former tobacco users has been suggested and appears to carry a highly favourable benefit to risk ratio but has received relatively little study.^{21–26–28}

There exists a broad spectrum of nicotine replacement products with respect to dosing characteristics and form. However, a broader spectrum is possible and warranted to accommodate the broad diversity of needs and preferences of tobacco users. For example, there is no true inhaler which delivers nicotine to the lung in the same way as the cigarette does. There is no oral nicotine delivering product which can compete with the 10 mg nicotine containing, highly buffered oral tobacco products that are popular among smokeless tobacco users.^{29–30} Whether a clean nicotine product such as gum, lozenge, patch, or inhaler (by “clean” we mean free enough of tobacco toxicants to pass regulatory approval) can or should be made to deliver nicotine as efficiently and palatably as tobacco products is an unresolved question; however, it appears crucial that the range of options be expanded considerably in the long run.

THE SPECTRUM OF NICOTINE DEPENDENCE AND ADDICTION

For the purposes of this discussion, “nicotine” is taken to mean nicotine and its salt forms—for example, nicotine tartrate and nicotine base—as variously used in nicotine replacement products. Regarding the terms dependence and addiction we believe that the convention used with other addictions is appropriate and useful. Specifically, we use the term addiction as the broad umbrella term for the compulsive, generally harmful, pattern of drug self administration as is characteristic of most cigarette smokers and many users of other tobacco products. This is equivalent to the term “dependence” as used by the WHO (*International classification of disease*, 10th revision (ICD-10), 1991) and American Psychiatric Association.³¹

Furthermore, we recognise the appropriateness of the distinction made between harmful “out of control” drug use such as frequently occurs with heroin or tobacco, and controlled relatively safe and preferable use of replacement therapies such as methadone and nicotine, respectively. In the case of long term replacement therapy users, the person may be physically dependent upon the drug but the harm is minimal, and use is considered an appropriate and desirable alternative to relapse to the originally addicting substance. As we will discuss further on, a long range policy option will be to reach the point that few people are using the most deadly forms of tobacco based nicotine delivering products even though many people may be chronically using clean nicotine products.

Nicotine: addiction in the user

Russell³² wrote in 1978 “cigarette smoking is probably the most addictive and dependence producing form of object specific self administered gratification known to man”. While this is probably true, the spectrum of nicotine addiction, and addictiveness between products, is broad. The degree of product addictiveness is very dependent on the pharmacokinetics and pharmacodynamics of the form of nicotine chosen. Russell, and others,^{33–34} make a persuasive case that the rapid absorption of nicotine bolus provided by the cigarette

makes it more addictive than other forms of tobacco usage.^{35 36}

Nevertheless smokers of cigarettes differ considerably in the amount of nicotine they take in and in their degree of dependence. The blood concentrations of nicotine that are achieved reflect the degree of dependence of the user and correlate reasonably well with psychometric tests such as the Fagerstrom test for nicotine dependence (FTND)³⁷ and the nicotine dependence syndrome scale (NDSS).³⁸ Both correlate reasonably well with the ultimate test, the difficulty of stopping smoking. However, there is individual variation in the relation between nicotine intake, or blood concentrations, and the level of dependence, reflecting the complexity of the addiction process.

Jarvis³⁹ showed that, on average, smokers took in approximately the same amount of nicotine regardless of whether they were smoking "low" or "high" nicotine cigarettes, but the same study revealed substantial numbers of smokers who achieved very low blood concentrations and substantial numbers who achieved high values. This was seen in smokers of both low and high nicotine yield cigarettes.

NRT is not known to be attractive to non-tobacco users and for most tobacco users who use the therapy, premature discontinuation is common, with use longer than six months occurring in only a small percentage of persons who initiated treatment.^{40 41} However, it is telling that among people who successfully quit smoking using NRT, extended use (that is, 6–24 months) is more frequent (10–20%), suggesting that extended use may benefit many people. This suggests that increased smoking cessation might be promoted by efforts to enable more people to use NRT for longer periods, such as with more attractive products and more flexible regulatory policies governing use. There are a range of options for product modification and regulatory evolution which have been discussed elsewhere and these include making products and their allowed uses more attractive to enable more ready compliance and tobacco abstinence.^{26 27 42–44}

POLICY ISSUES: A THREE PHASE POLICY

Many aspects of tobacco control policy aimed at reducing death and disease through tobacco product modification, and enhanced prevention and cessation, have been discussed in recent years.^{3 21 45 46} There has been some discussion of policy to enhance the attractiveness of NRT products.²⁶ What has received less discussion is a comprehensive regulatory policy covering all nicotine delivering products at various stages in the future. Below, we outline a forward looking nicotine policy which considers reduction of tobacco death and disease as the primary priority. Critical means to this end would remain preventing tobacco use and fostering tobacco cessation. The comprehensive nicotine policy would provide the additional potentially powerful public health tools of shifting recalcitrant tobacco users from the deadliest forms of nicotine to less deadly forms, ultimately leading to the virtual end of the status quo in which the deadliest forms of nicotine dominate use, choice, and life.

Recognising that implementation of policy change will change opportunities and needs for subsequent policy, we recommend planning for staged policy implementation in which each stage is accomplished over an approximately 5–10 year time frame (although phase 1 should be shorter than this). This does not imply a simple sequential process because even as initial short term policy is being implemented, the ground work towards medium and long term policy should be under development. Many aspects of the medium and long term policy would be impossible to predict before the experience that will be developed with shorter term policy changes; however, we believe that it is essential to initiate the

comprehensive nicotine policy with a plausible framework for medium and long range strategies under consideration.

Short term policy

The immediate need is to capture all nicotine into a regulatory system. Only with comprehensive regulation of all nicotine delivering products can serious progress be made toward levelling the playing field between development and marketing of medicinal nicotine and tobacco nicotine. This might be accomplished by giving pharmaceutical regulators a new mandate to regulate tobacco or by setting up a special unit for the purpose. The priority issues are related to measurement systems; definition of what constitutes "dose" for regulatory purposes; development of rules to cover the marketing of all forms of nicotine with the objective of establishing a market in which clean nicotine is at least as available as tobacco; and standards to be set for the other toxicants that are inhaled with nicotine. At this time a monitoring programme would be needed to provide ongoing assessment of any increase in overall nicotine usage, especially among youth and former smokers.

There are many ways of making clean nicotine more widely available including reduced prices, variable size packages, and more outlets including vending machines. By contrast, tobacco availability should become progressively less easy.

This process is likely to take some years, as suggested by the report of the Scientific Advisory Committee on Tobacco Product Regulation (SACTob) of the WHO.⁴⁷ During this time research should be undertaken to understand further the determinants of the rate and extent of nicotine absorption from tobacco products and to clarify the role of additives in this process. It will be important to include adequate monitoring of effects of the policy and trends on all forms of nicotine development, marketing, and use, to enable corrections in the policy and provide a guide towards medium and long range policy goals.

Medium term policy

The objective is to continue to diminish the tobacco nicotine market and increase, relatively, the market for less toxic or non-toxic sources of nicotine. This means that non-tobacco nicotine sources need to be made more competitive with tobacco sources, with the objective that they could, over time, replace tobacco as the dominant source of the drug. This might involve regulatory measures, taxation measures, and research to improve the spectrum of clean nicotine products on the market.

During this period attempts should be made to simplify tobacco delivery systems by eradication of most additives, particularly those that make the tobacco easier to use/smoke, those which facilitate nicotine absorption, and those which provide attractive flavourings. Thus an adequate nicotine dose could be provided but the "attractiveness" of the products should be reduced while at the same time competitive clean alternatives should be developed and marketed.

When the market includes a spectrum of clean nicotine sources that are cheap, widely available, and effective in providing the required nicotine "fix", consideration might be given to options such as gradually reducing the availability of nicotine from cigarettes as proposed in 1994⁴⁸ and more fully developed in a report endorsed by the American Medical Association.⁴⁹ This approach involves a progressive reduction of the nicotine content of cigarette tobacco. The anticipated results would be a lower likelihood that experimental tobacco use in adolescents would progress to addictive use, and that already addicted smokers would be gradually weaned off nicotine and their level of addiction diminished. A lower level of addiction would make cessation easier. There have been

concerns that smokers may be exposed to greater toxic exposures while smoking such cigarettes as they smoke them more intensively or smoke more of them in order to maintain nicotine intake. However, recent research with such low nicotine content cigarettes indicates that, at least in the short term, smokers do not increase their smoke consumption and do not increase toxic exposures despite substantial reductions in nicotine intake.⁵⁰ The ready availability of clean nicotine would also allow addicted smokers who do not obtain adequate nicotine from their reduced nicotine cigarettes to supplement their nicotine intake so as to prevent unpleasant and disruptive nicotine withdrawal symptoms. Such dual use would be better than the current sole reliance on tobacco for nicotine intake, because it would reduce exposure to tobacco smoke toxins.

The longer term

The longer term policy goal may seem unrealistic when considering the current state of tobacco and nicotine use. However, as public health efforts advance through scenarios even remotely related to our proposed short and medium term strategies, we believe that the seemingly radical longer term strategy may be inevitable. Essentially, the longer term goal is the virtual elimination of tobacco use as it is presently known.⁵¹

The days in which the most deadly forms of nicotine were preferred (from the perspective of regulation, marketing, and consumer utilisation) would be past, and may begin to appear as archaic.

The most toxic remaining products, which might still include tobacco, would be the most restrictively marketed and the prevalence of tobacco use would be diminished greatly. Essential to achieving and maintaining this scenario would be ensuring that legitimate "demand" for nicotine or nicotine-like drugs could be met by readily accessible and acceptable products. In this phase increasing attention might be turned towards reducing overall nicotine utilisation, but this must be approached cautiously so as not to spur renewed demand for tobacco. Finding the balance between nicotine access so as not to foster unnecessary nicotine use should be guided by science and public health, and not commercial interests. The scenario whereby nicotine delivering products are treated with as little public health concern as are caffeinated beverages today, does not appear desirable since nicotine appears to carry greater health risks compared to caffeine, particularly during child and adolescent development, pregnancy, and in persons with heart disease. Nonetheless, if the science has progressed as the partner that it should be in public health policy development, we should have a better understanding of these issues in the coming decades.

CONCLUSIONS

These suggestions represent a pragmatic attempt to look and plan into the future in a policy area where there is a significant vacuum. Nothing here is intended to sidetrack efforts to reduce tobacco initiation or cessation. Nor is it an attempt to suggest that nicotine addiction is benign. The ultimate objective of reducing mortality and morbidity will only be achieved by reducing tobacco use. This will require stronger policies aimed at boosting cessation and reducing initiation, and at reducing overall tobacco related harm. Alternative and better sources of clean nicotine should be developed. Regulation and research should lead to reduction of the attractiveness and eventually the addictiveness of nicotine delivery systems based on tobacco.

The question of whether nicotine addiction can be eradicated is highly speculative and lies far in the future.

What this paper adds

This paper attempts to fill a policy vacuum. There is no consensus over long term nicotine policy. This paper proposes a three phase policy for implementation when the time of tobacco smoke constituent regulation comes. It considers the need for more efficient clean nicotine sources, in parallel with the view that the nicotine content and addictiveness of cigarette smoke should be progressively reduced. In addition it reviews the relative harmfulness of the various nicotine sources and the spectrum of nicotine dependence and addiction.

However, short and medium term nicotine policy can be developed on the basis of what we know and can do now.

It would be foolish to pretend that our proposal does not carry political ramifications, both within and without the tobacco control community (TCM). We recognise that there is a substantial body of opinion that does not condone drug addiction for a variety of reasons, and we believe that consensus will only be established by extensive discussion within the TCM, as no united political effort can be made without this. Recent divisions in the USA over potential legislation to regulate tobacco illustrate that the TCM becomes ineffectual when not united.

The legislative changes required for execution of the recommended policies are less complex than those which have been applied to marketing practices. In most countries tobacco escapes constituent regulation because it carries a special categorisation as neither a food, nor a cosmetic, nor a drug. Defining tobacco as a drug could, in many jurisdictions, bring it within the purview of orthodox drug regulation systems that are designed to deal with poisons and drugs that produce side effects. From that point on the nicotine policies we propose can be implemented. The pace of implementation would be at the discretion of professional experts, informed by experience. Cross fertilisation of ideas and experience would naturally occur, as it recently did following the experiences of New York and Ireland with smoke-free workplaces.

We believe that regulation of nicotine according to the policy proposed here is feasible.

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Competing interest statement: Boyle, Connolly, Gray, Jarvis. No competing interests. Dr Benowitz has consulted for several pharmaceutical companies that market smoking cessation medications. He has received research grant support in the past from GlaxoSmithKline Consumer Healthcare. Dr Benowitz has been a paid expert witness in litigation against tobacco companies. Karl Olav Fagerstrom: "I have consulted for most companies with an interest in smoking cessation medicines. I also owe a minority of shares in a company with an interest in developing nicotine replacement medications." Carolyn Dresler was the Medical Director for Research and Development for GlaxoSmithKline Consumer Healthcare working on nicotine replacement therapy products for five years before joining the International Agency for Research on Cancer. Jack Henningfield provides consulting services regarding

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