The future of nicotine replacement

MICHAEL A. H. RUSSELL

ICRF Health Behaviour Unit, Institute of Psychiatry, 101 Denmark Hill, London SE5 8AF, UK

Abstract
Following in the wake of progress forged by nicotine chewing gum, a new generation of nicotine replacement products will soon be available as aids to giving up smoking. These range from nicotine skin patches, which take 6-8 hrs to give very flat steady-state peak blood levels, to nicotine vapour inhalers which mimic the transient high-nicotine bolus that follow within a few seconds of each inhaled puff of cigarette smoke. Other products undergoing clinical trials include a nasal nicotine spray and nicotine lozenges. It is argued here that it is not so much the efficacy of new nicotine delivery systems as temporary aids to cessation, but their potential as long-term alternatives to tobacco that makes the virtual elimination of tobacco a realistic future target. Their relative safety compared with tobacco is discussed. A case is advanced for selected nicotine replacement products to be made as palatable and acceptable as possible and actively promoted on the open market to enable them to compete with tobacco products. They will also need health authority endorsement, tax advantages and support from the anti-smoking movement if tobacco use is to be gradually phased out altogether.

Introduction
Some time in the 21st Century we could see the rapid demise of tobacco smoking. How soon this can be achieved will depend on how soon we adopt rational policies. It is essential for policy makers to understand and accept that people would not use tobacco unless it contained nicotine, and that they are more likely to give it up if a reasonably pleasant and less harmful alternative source of nicotine is available. It is nicotine that people cannot easily do without, not tobacco.

It is timely that these issues be considered now. First, the clear statements in the 1988 US Surgeon General’s Report that tobacco use is addicting and that nicotine is the drug in tobacco that causes addiction, should ensure that these two facts are more widely accepted and will hopefully inform new policies. Secondly, the wide range of new nicotine delivery systems being developed by the pharmaceutical industry offers us, for the first time, the means for turning the virtual elimination of tobacco use into a realistic target. It is not so much their efficacy as temporary replacement to aid cessation, but their potential use for long-term self-administration which merits the most serious consideration.

In discussing these issues tobacco will be considered in pharmaceutical terms as a drug delivery system. This will facilitate comparison of alternatives on offer from the tobacco and pharmaceutical industries. It will be assumed throughout that our main concern is to reduce tobacco-related diseases and that moral objections to the recreational and even addictive use of a drug can be discounted provided it is not physically, psychologically or socially harmful to the user or to others.

Tobacco as a drug delivery system
By and large it is the impurities in tobacco and its smoke which kill, while nicotine provides most of the pleasure, stimulation, and relief from stress. Conventional tobacco products will in future be
regarded as archaic as the use of unrefined alkaloids in folk medicine appears now in comparison with the modern products of the pharmaceutical industry.

The principle for all drugs has been to purify them as much as possible. The tobacco industry is like a dinosaur in pharmaceutical terms and, with one notable exception, has signally failed to clean up the delivery of its drug, nicotine. Future historians will find it hard to understand how governments over many years went on allowing the manufacture, let alone extensive advertising and promotion, of such a dirty product containing an addictive drug alongside impurities that kill more people than die in wars. Much more could have been done much earlier to make cigarettes less harmful. To cap it all, when a tobacco company in the United States spends 300 million dollars to develop a sophisticated, virtually tar-free, and far less harmful cigarette (R. J. Reynolds Premier Cigarette, 1988) its sale is blocked by bureaucratic technicalities abetted by misguided pressure from health experts. Meanwhile Reynolds remain free to actively promote their more lethal conventional cigarettes to the 50 million US citizens who still smoke after decades of conventional anti-smoking policies.

Since people smoke mainly for nicotine and fail to quit because they are addicted, and since they die mainly from the tar, carbon monoxide and other harmful gases taken in alongside nicotine, and since they chew and snuff tobacco for nicotine but die largely from the nitrosamines and other carcinogens in tobacco, it seems logical to offer either a cleaner product or, better still, an acceptable source of purer, less contaminated nicotine.

The case for a cleaner product is perhaps best illustrated by a hypothetical analogy. If the source of an epidemic of lead poisoning were traced to alcoholic beverages, contaminated during the fermentation process, so that heavy drinkers were most at risk, would it be rational to try to eliminate all alcohol use to curb the epidemic? Or, failing that, would we exhort people to drink less alcohol, or place upper limits on the strength of alcoholic beverages? Obviously not, the solution would surely be to eliminate as far as possible the lead from the alcohol.

As a drug delivery system, tobacco is so dirty that it eventually kills one in three people who go on using it (RCP 1977). It could and should be rapidly replaced by cleaner, less harmful sources of nicotine. This notion is a logical extension of current low-tar programmes for product modification. Unfortunately these programmes fail to take adequate account of the smoker’s need for nicotine. Proposals to allow for this and focus on lowering tar to nicotine ratios have gone largely unheeded (Russell, 1974, 1976). It is ironic that when Reynolds produces a near-perfect low-tar cigarette, the tar is so low and the smoke so clean that it is regarded as a nicotine delivery system and forced to withdraw from sale as a tobacco product. Amazingly the American Medical, Heart and Lung Associations and the American Cancer Society all clubbed together to petition against the product (US House of Representatives Subcommittee Hearing, 1988). This does not augur well for regulatory authority approval of nicotine replacement as a long-term substitute for smoking.

Health risks of nicotine

While it is patently obvious that nicotine alone must be less harmful than nicotine plus tar plus noxious gases, decisions about policies for opening the market to cleaner nicotine replacement products and gradually phasing out tobacco will depend crucially on the health risks of nicotine. As mentioned earlier, it is assumed that there is no great objection to drug use and addiction per se. Nicotine addiction is not harmful. Unlike many other addictive drugs, nicotine does not disturb consciousness, impair judgement or social behaviour and, if anything, it enhances rather than impairs cognitive and psychomotor performance and the capacity to work. The key question is the extent to which nicotine or its metabolites contribute to the harmfulness of tobacco.

Nicotine has no role in tobacco-related cancers, which are responsible for 30% of all cancer deaths, neither is it implicated in chronic obstructive lung disease. The possibility of endogenous formation of carcinogenic nitrosamines from nicotine metabolites has been suggested (Hoffmann, 1989). However, it has not been demonstrated and, if it occurs, the amounts would be negligible compared with those present in tobacco and formed when it is burned.

It is likely that nicotine is implicated in the cardiovascular risks of cigarette smoking and that carbon monoxide also plays a part. However, to date no definitive epidemiological studies have identified the cardiovascular risks of individual smoke components. Nicotine activates the sympathetic nervous system and increases circulating levels of adrenaline, noradrenaline and vasopressin. Through these mechanisms it causes peripheral vasoconstriction and may also contribute to atherogenic and throm-
bogenic processes. It probably increases the adverse consequences of ischaemic heart disease. Propranol largely abolishes the deleterious effects of smoking on mortality following a first heart attack (Jafri et al., 1990) indicating that adrenergic mechanisms are involved. This strongly implicates nicotine which is the only smoke component with effects on adrenergic systems.

In contrast with cigarette smoking, the cardiovascular risks are negligible in primary pipe and cigar smokers who have never smoked cigarettes and who tend not to inhale deeply (Doll, 1983). It is not clear whether the difference is due to the slower rate of buccal absorption from non-inhaled pipe and cigar smoking, to lower steady-state nicotine levels, or to lower CO levels. Similarly the lack of evidence that use of smokeless tobacco poses a cardiovascular risk is open to various interpretations.

In summary, nicotine has no part in tobacco-related cancers and chronic obstructive lung disease, two of the major causes of tobacco-related premature deaths. There is some evidence that it contributes to the overall cardiovascular risks of smoking. These risks appear to be most evident when nicotine is rapidly absorbed through the lungs. However, it must be said that the evidence is discounted by two experts more competent than I am to assess it. They state: “That nicotine has a role in the cause of cardiovascular disease has its adherents, but the evidence is not compelling” (Froggatt & Wald, 1989).

**Nicotine replacement**

The term, nicotine replacement, refers to the use of pure nicotine to replace that which would otherwise be obtained from tobacco use. The acceptability of nicotine as a substitute for smoking was first noted by Johnston (1942) who gave subcutaneous injections of nicotine to 35 volunteers. Non-smokers found it unpleasant, but “smokers almost invariably thought the sensation pleasant and, given an adequate dose, were disinclined for a smoke for some time thereafter”. However, Johnston failed to recognize any therapeutic or other practical implications and some 10 years later was still advocating willpower as the only cure for tobacco smoking (Johnston, 1952). It was Ove Ferno and his colleagues in Sweden who first considered the therapeutic implications (Ferno et al., 1973). I cannot do better than to quote Ove Ferno, the undisputed father of nicotine replacement, referring to the development of nicotine chewing gum.

Early in 1968 work began in our laboratories based upon the idea that since nicotine is the chemical reinforcer of the smoking habit, it might be possible to produce a preparation containing pure nicotine, which would satisfy the smoker’s craving for nicotine without exposure to the other presumably more harmful ingredients of tobacco smoke.

Ove Ferno (1975)

**Nicotine chewing gum**

Nicotine gum has been a major advance in treatment for smokers and is now widely used in many countries. It reduces withdrawal effects, enhances success in short-term cessation, reduces relapse if use is not curtailed too soon, and roughly doubles long-term success rates compared with placebo and various psychological methods. More importantly, its clinical success, its use as a research tool, and the tendency for some smokers to transfer their dependence on cigarettes to dependence on the gum has provided new evidence that has contributed to wider recognition of the fact that smoking is an addiction. Indeed, it is unlikely that the 1988 US Surgeon General’s Report would have addressed this topic had it not been for Ove Ferno’s gum.

**Nicotine skin patch**

At least five pharmaceutical companies have patches at various stages of testing and in some countries they are already licensed for clinical use. Outcomes of placebo-controlled trials have been similar to those of nicotine gum (e.g. Abelin et al., 1989). Where the patch should have a major impact is in medical practice settings, especially primary care, where the gum has been less successful, possibly due to the lack of time available to give the instructions and support necessary to secure compliance. Besides the better compliance with patch use, a potential advantage may be the dissociation between reinforcement and self-administration. There are no repeated events of withdrawal relief following self-administration, no sensory or repetitive behavioural components to gain strength through conditioning, so that weaning may be easier for the subject and more amenable to control by the therapist. Current patches give blood nicotine levels similar to those of the gum from about 4 hrs after application, but it is easy to produce higher levels with larger patches or by using more than one patch at a time.
Other nicotine delivery systems

Despite the clinical success of nicotine gum, it fails with many smokers. Long-term success rates seldom exceed 30%, even when the gum is given as an adjunct to intensive individual or group treatments at specialized smokers clinics. On the premise that some smokers might find it more helpful to receive nicotine that is absorbed more rapidly, Ove Ferno initiated the development of a nasal nicotine spray which produces a blood nicotine peak about 5 min after dosage. This product is currently undergoing phase III trials.

It is only by absorption through the lung alveoli that the efficiency of smoke inhalation can be fully matched to give the intermittent high-nicotine boli that follow each inhalation. To extend the rapid absorption premise, a device was developed to deliver nicotine vapour from a porous plug contained within a cigarette-sized hollow plastic tube. It was briefly market-tested some years ago as a smokeless cigarette under the brand-name of Favor. Its success was limited partly by its low nicotine delivery (13 ug per puff compared with about 100 ug for a conventional cigarette), but more importantly by the slow rate of nicotine absorption, presumably due to its deposition in the mouth, throat and large airways (Russell et al., 1987). This problem has been overcome by a prototype nicotine vapour inhaler with a draw resistance sufficiently low for inhalation directly into the lungs without the pause of a preliminary puff. Moreover, the volume of the inhalation (1–2 L as opposed to a 50 ml puff) compensates for its low nicotine content. The pharmacokinetic profile indicates that nicotine is absorbed rapidly through the lung alveoli and closely resembles that of the Reynolds Premier cigarette (Feyerabend & Russell, 1990). Although the inhaler is only at a developmental stage, a Favor-type nicotine vapour puffer is starting Phase III trials.

A final product which may have scope as a potential competitor to the gum is a nicotine lozenge to be tucked in the cheek to dissolve slowly. Various lozenges based on tobacco extracts have been available in the past, but a new one meeting high pharmaceutical standards is almost ready for clinical trials.

Rate of absorption spectrum

It may be helpful to consider the range of nicotine replacement products in terms of the relative rates of nicotine absorption obtained from their use, and to compare these with traditional tobacco products (see Fig. 1). The products shown range from nicotine skin patches, which take 6–8 hrs for steady-state blood levels to reach a very flat peak, to a nicotine inhaler giving rapid absorption through the lung alveoli, similar to the intermittent high-nicotine boli that follow within a few seconds of each inhaled puff of cigarette smoke. Nicotine concentrations in these boli, measured in arterial blood, are 3–4 times higher than the levels found in mixed venous blood soon after smoking. Position along the spectrum from inhaled cigarette smoking to slow absorption from nicotine skin patches may have some bearing on issues such as addiction potential, health risks and potential for replacing cigarettes, either for short-term therapy on the way to total abstinence or for long-term replacement. Combination therapies to secure smoking cessation prior to weaning off all nicotine may be suggested by position on the spectrum. Other factors may determine the abuse potential. For example, it would be easier to overdose with nicotine lozenges than with the gum or puffer, although the rates of nicotine absorption are similar. But there is no point in further speculation here. Clinical experience and the results of numerous trials will be available very soon.

The case for promoting replacement

The strength of the case for promoting nicotine replacement is based on what it seeks to replace, namely tobacco. It is not suggested that nicotine use be presented as something good, but rather as something far less bad than tobacco. But the verb, promote, is used deliberately. It is not proposed that it will be sufficient to grudgingly sanction long-term nicotine replacement. The case advanced is that selected nicotine replacement products be made as palatable and acceptable as possible and actively promoted on the open market to enable them to compete with tobacco products. Those deemed sufficiently safe should be easily accessible without medical prescription, probably initially at pharmacies. Everything possible should be done to give them a competitive edge over tobacco, for they may not be as pleasant or palatable and will depend on other incentives. They should be advertised and actively promoted even after advertizing of tobacco has been banned. There should be health authority endorsement to enable exploitation of their health advantages, and taxation should be adjusted to give them a clear price advantage over tobacco products.
RATE OF ABSORPTION SPECTRUM

<table>
<thead>
<tr>
<th>TOBACCO PRODUCTS</th>
<th>NEW DELIVERY SYSTEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAPID ABSORPTION</strong></td>
<td></td>
</tr>
<tr>
<td>Inhaled smoke →</td>
<td>Premier cigarette</td>
</tr>
<tr>
<td>Nasal snuff →</td>
<td>Nicotine inhaler</td>
</tr>
<tr>
<td>Oral snuff →</td>
<td>Naal nicotine spray</td>
</tr>
<tr>
<td>Chewing tobacco →</td>
<td>Nicotine puffer</td>
</tr>
<tr>
<td>Non-inhaled</td>
<td>Nicotine lozenge</td>
</tr>
<tr>
<td>pipe &amp; cigar</td>
<td>Nicotine chewing gum</td>
</tr>
<tr>
<td></td>
<td>Nicotine skin patch</td>
</tr>
</tbody>
</table>

**SLOW ABSORPTION**

Figure 1. Tobacco products and new nicotine delivery systems can be positioned roughly on a spectrum based on the rate of nicotine absorption obtained from their use.

There may be instances of children, who in defiance of the law, obtain a nicotine replacement product and try it before trying a cigarette. If so, it is unlikely to be as addicting as the first 3-4 cigarettes. Moreover, pharmacists are likely to be more responsible than tobacconists have proved.

The main point in favour of nicotine replacement is the overwhelming health advantage compared with tobacco use. An important bonus is the freedom of non-users from passive exposure. Until they have thought it through, those in the anti-smoking movement may fear that their clear simple message will be complicated and undermined. It need not be changed. There is only one fight and that is against tobacco and tobacco-related disease.

It is important that this battle is maintained. Nicotine replacement could not compete unless awareness of the health risks of tobacco remains high. Availability of substitutes for tobacco will help the anti-smoking message to be heeded. The pharmaceutical industry could become a powerful ally. As tobacco is gradually phased out the battle could shift to avoiding nicotine, if by then it proves to pose an unacceptable burden to health.

In conclusion, few countries have so far achieved a sustained decline in smoking prevalence in excess of 1% per year. It is difficult to see how active promotion of nicotine replacement will do anything but help to accelerate this process. On the contrary, can we afford to quibble and delay, in view of the
horrendous estimates of 10 million premature deaths throughout the world each year during the next century as a result of tobacco use (Peto, 1990).

References


This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.