

REVIEW

Regulation of nicotine replacement therapies (NRT): a critique of current practice

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Abstract

Nicotine replacement therapy (NRT) describes a group of products delivering nicotine that are licensed for the relief of withdrawal as an aid to smoking cessation. This paper examines areas where public health considerations suggest changes should be made to the current indications and characteristics for NRT products. It is argued that the current regulatory framework restricts access to NRT without adequately considering that the likely consequence is continued dependent use of a far more harmful and widely available version of the same drug: tobacco. The paper argues that minors, pregnant smokers and smokers with cardiovascular disease (CVD) be allowed to use NRT. NRT use for smoking reduction, to support temporary abstinence, for long-term use should also be enabled and NRT products should be made as widely available as cigarettes. This paper also recommends that regulators encourage the development of less harmful forms of nicotine delivery devices to compete with cigarettes. Although this paper is written largely with reference to the UK medicines regulatory framework, these issues also apply to many other countries.

Introduction

Nicotine replacement therapy (NRT) products are licensed for the relief of withdrawal as an aid to smoking cessation. The rationale is that NRT eases withdrawal symptoms by providing an alternative source of nicotine. The attempt to stop smoking is broken into two stages. Initially the smoker continues with a reduced dose and speed of nicotine supply while overcoming the loss of the behavioural side of the dependence. Subsequently the smoker breaks the nicotine dependence by stopping using the NRT product.

There are currently six NRT products available that differ in nominal dose and the method and speed of delivery of nicotine. All are on the

market in England: gum (2 mg and 4 mg, different flavourings), transdermal patch (16 hours and 24 hours in varying doses), nasal spray, inhalator, sublingual tablet and lozenge. All the products are available from pharmacies and recently also became available on NHS prescription. In 1999 the 2 mg gum became available on a general sale category (GSL) and the Medicines Commission recently also made the 4 mg gum, patches and lozenges available on GSL. The products have various restrictions, contraindications and cautions about their use.

In all countries NRT products are regulated within the country's medicines regulatory framework. In the United Kingdom the medicines

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regulatory framework consists of the Medicines Commission, the Medicines Control Agency, the Committee on Safety of Medicines, the Medicines Act and the Secretary of State for Health, in addition to relevant European Union regulation and EU-related bodies. Regulatory approval usually requires applications to be made by pharmaceutical companies, which must provide evidence to satisfy the regulators.

This paper argues that the framework in which NRT is regulated does not properly weigh the risks and benefits of NRT use in situations in which its use is qualified, restricted or contraindicated. In particular, there appears to be greater weight placed on the risks associated with NRT, compared to the risk associated with smoking that could arise when NRT is not used. Continuing smokers face a 50:50 chance of dying as a result of their smoking, whereas the risks associated with NRT use are orders of magnitude lower.

It seems likely that the reason for this is risk aversion on the part of the regulatory bodies, deriving from their institutional position as *pharmaceutical* regulators. Regulators have responsibility for the licensing of pharmaceuticals and focus on potential harm caused by the NRT product. They have no responsibility for the consequences of continued or additional smoking, which might arise where NRT is not used. Although the position of medicines regulators has changed recently with the advent of AIDS drugs, the smoking epidemic, despite its much greater public health burden, has not merited the same creativity and urgency. Warnings, limitations and contraindications included by the regulators transfer responsibility and liability to the medical professional advising the patient. Although there is a small chance of adverse consequences arising from NRT use, the medical professional is responsible—perhaps before a court—whereas there is no responsibility or liability for smoking-related harm. The effect of this imbalance is ultimately to transfer risk from the regulator and medical professional to the patient.

The regulatory inertia may also reflect an assumption by some regulators and health professionals that if smokers just had enough willpower they could stop by themselves. However, tobacco-delivered nicotine is highly addictive, to a degree similar or in some respects greater than addiction to drugs such as heroin or cocaine.

Hence, although two-thirds of smokers say they would like to quit, only about 0.5–3%¹ succeed in stopping each year, because most of them try to stop using willpower alone.

Following a discussion of safety, abuse and dependence potential of NRT products this review takes each constraint on NRT use in turn and weighs up the evidence from a public health viewpoint. In each case a suggested way forward is proposed. In cases where a change to the indication is recommended despite few research data, it may be prudent to indicate that the evidence is not conclusive so that the indication can be responsive to further research.

This paper proposes that a review of NRT in these areas should be carried out proactively by the regulators. Although changes to indications are made normally in response to requests from pharmaceutical companies, applications from the pharmaceutical industry are influenced by the anticipated responses of the regulatory bodies. The paper also makes recommendations, where appropriate, for the pharmaceutical industry.

Safety, abuse and dependence potential of NRT products

NRT products are much safer than cigarettes, which are exceedingly 'dirty' delivery systems for nicotine.² It is the tobacco, not the nicotine, which causes most of the harm.^{3–6} There exists a large body of evidence that nicotine is not a significant risk factor for cardiovascular events, does not cause cancer and does not cause respiratory diseases such as emphysema.^{3–6} Although there is some evidence from *in vitro* and *in vivo* studies with mice that some metabolites of nicotine can be transformed into nitrosamines⁷ or that nicotine might stimulate angiogenesis and promotes tumour growth and atherosclerosis in mice,⁸ there is no evidence of this happening in people using NRT. There is now a great deal of experience with NRT products in the United States⁹ and the United Kingdom and the evidence indicates clearly that the products are safe.¹⁰ Similarly, the epidemiological evidence from long-term use of Swedish *snus* (a form of smokeless tobacco) users is that nicotine intake does not cause an increase in oral/pharyngeal cancer,¹¹ and there is no conclusive evidence of an increased risk of myocardial infarction.¹²

There are, however, concerns about nicotine safety in pregnancy. Nicotine crosses the pla-

centa and is a potential fetal teratogen. Nicotine may contribute to obstetrical complications in pregnant women and has been implicated in low birth weight¹³ and in sudden infant death syndrome (SIDS).¹⁴

The abuse potential (defined here as the ability to facilitate dependence in non-users and using indicators such as pleasantness and satisfaction) of NRT products has been shown to be very low. We are unaware of any published reports of non-smokers becoming NRT users. Novice users generally perceive nicotine as moderately unpleasant.¹⁵ A comparative study of four NRT products found generally low ratings of pleasantness and satisfaction from using the NRT products for 4 weeks and concluded that the abuse liability for all four products was low.¹⁶ Surveillance in the United States following the release of the gum and patch on general sale showed no evidence of significant abuse.⁹

The speed of delivery of the different products affects their dependence potential (defined here as the ability to induce long-term use using standard definitions of dependence).^{2,16} Those products delivering relatively low doses of nicotine slowly are much less addictive than cigarettes. The patch releases nicotine slowly, typically reaching a plateau after 4–9 hours, whereas levels peak after 30 minutes of each gum/tablet/lozenge/inhalator use, and 10 minutes after a dose of nasal spray.¹⁷ This compares with a concentrated bolus of nicotine reaching the brain within 10 seconds of each puff on a cigarette.¹⁸

A small proportion of NRT users do become long-term users, ranging from as little as 3% of patch users who pay for their medication still using after 15 weeks¹⁶ to 43% of those remaining tobacco-free for a year and receiving the nasal spray free and still using it at 1 year.¹⁹ However, the evidence indicates that those who transfer their dependence to NRT were heavy smokers who would otherwise have remained dependent on their tobacco at far greater cost to their health.²⁰ Long-term use of NRT could therefore be seen as an extension of the treatment period rather than the development of a new dependence. Long-term use of NRT is discussed in more detail below.

At high doses nicotine can intoxicate, but this is very rare because of the rapid development of tolerance and the fact most nicotine products are designed to minimize acute overdosing.³

Age restrictions

Current position

There are inconsistencies in the advice given for different NRT products in the United Kingdom regarding their use by young people. For example, the Summary of Product Characteristics (SPCs) for some products (nicotine inhaler and the nasal nicotine spray) include a contraindication for children, recommending that the sublingual tablet should not be used by under 18-year-olds, whereas for others (patch, sublingual tablet, gum) the SPCs state that they are not to be administered to individuals under 18 years of age except on the advice of a doctor. Sometimes there are differences in the advice given in the SPCs and the Patient Information Leaflets (PILs) for the same products.

Public health position

To date, there are very few data on the use of NRT by under-18-year-olds, although there is a high level of smoking among adolescents and most adult smokers take up smoking during adolescence. One study of 22 adolescent smokers using nicotine patch therapy concluded that this seemed safe for use with adolescent smokers.²¹ A second study involved 101 adolescents in a non-randomized open-label trial and concluded that nicotine patch therapy did not appear to be effective with this target group.²² It has been suggested that even low abstinence rates in adolescents (11% at 6 weeks) could translate to a public health benefit²³ although the rates were within national cessation rates among adolescents.²⁴ However, only minimum behavioural therapy was given in this study and it may be that other acute forms of NRT may be more effective with this age group.

A seminar held with British and American experts under the auspices of the then Health Education Authority (HEA) in September 1999²⁵ concluded that NRT is less harmful than cigarettes, so should not be discouraged as a replacement to them and as a cessation aid for this age group. NRT would certainly be a safer form of nicotine delivery than cigarettes.

The limit of 18 years does seem to be arbitrary. For most other medicines, 12 years or age of puberty are the cut-off limits. There is good evidence that many adolescent smokers are already inhaling cigarette smoke, absorbing

significant doses of nicotine and showing signs of being dependent on their cigarettes.²⁶

Suggested way forward

We endorse a conclusion of the HEA seminar,²⁵ that experts should 'explore, with the Department of Health, the Medicines Control Agency and the pharmaceutical companies, how to develop a research programme capable of demonstrating whether existing NRT or other, new nicotine replacement products are effective in helping young people to stop smoking'. We encourage the pharmaceutical companies to develop proposals for this research in the first instance.

In the meantime, we suggest that health professionals should assess motivation and readiness to quit and dependency with adolescent smokers similar to their assessment of adult smokers before offering treatment. Dependence in adolescent smokers may be harder to assess than in adults, as there may be constraints on time to first cigarette of day and daily cigarette consumption, two of the standard dependency measures used with adults; nevertheless, these questions plus additional questions such as difficulty perceived in going without cigarettes, should give some indication of dependence. Adolescent smokers reporting signs of dependence and who are ready to quit should be offered the best available treatment, which should include NRT. Age should not be used as a criterion: there is no evidence base or justification for denying NRT to a young dependent smoker who wants to quit. In addition, we agree with the experts cited above who concluded that NRT should be offered as a replacement for cigarettes to adolescent smokers. The cut-off age should be lowered accordingly to 12 years to be consistent with other medications.

Pregnancy advice

Current position

Again, there are inconsistencies in the advice given for different products. Some forms of NRT are contraindicated in pregnant women. Others can be used on medical advice, or following a medical assessment of the risk/benefit ratio, if the pregnant woman has tried and failed to give up without nicotine substitution.

Public health position

Expert opinion is that despite the risks of nicotine in pregnancy outlined above, NRT is considerably safer than continued smoking in pregnancy²⁷ which also exposes the fetus and mother to many other toxins in addition to nicotine. NRT also generally provides lower doses of nicotine than smoking (typically around one-third of the nicotine concentrations),²⁷ a finding corroborated by a small-scale study with pregnant women using the 2 mg gum²⁸ but not in a study of transdermal nicotine (8-hour use of 21 mg patch) use in a sample of pregnant women, which found similar nicotine levels to those during smoking.²⁹ The only published placebo-controlled trial of transdermal nicotine in pregnancy did not find a significant improvement in tobacco abstinence rates at 1 year. Despite this, the group allocated nicotine patches had significantly higher birth weight babies than the women allocated to placebo patches.³⁰

The decision about appropriate use of NRT in pregnancy is a trade-off between the benefits to those that use NRT and stop smoking as a result, compared to the risks to those that use NRT but would have been able to stop without. In making this assessment the following considerations are relevant:

- Low rates of smoking cessation before and during pregnancy. A recent study among pregnant women found that only 7% of pregnant smokers receiving a midwife intervention 12 weeks into their pregnancy had quit by the birth and only 3% were still abstinent 6 months later.³¹
- The known efficacy of NRT in raising smoking cessation rates in adults.
- The much greater toxic exposure associated with continued smoking compared to NRT use.

This balance of risk and benefit would suggest that there is a strong argument in favour of wider use of NRT in pregnancy. However, strong warnings in the SPCs are likely to deter health professionals from advising in favour of the use of NRT.

This type of advice is given on other medicinal products; for example, the SPC for disulfiram (Antabuse) tablets recommends that the risk-benefit ratio in assessing the adverse effects of alcoholism in pregnancy should be taken into account when considering the use of disulfiram in pregnant patients.

Suggested way forward

The Royal College of Physicians' recent report on nicotine² recommended that NRT products should be able to be used by pregnant women for whom non-pharmacological interventions have failed. This would have the maximum public health impact if health professionals made their assessment of this in the early stages of pregnancy based on smoking history and previous attempts at quitting. The approach of requiring a pregnant smoker to try stopping without NRT first, with pharmacological support only as an option where this fails, should be discouraged. This risks continued smoking throughout the pregnancy, as motivation to quit may be diminished following a failed quit attempt.

The contraindication on NRT in pregnancy should therefore be removed. Pregnant smokers should be advised to use NRT following an early assessment of their prospects for quitting without it. The implementation and impact of greater use of NRT in pregnancy should be monitored.

Smokers with cardiovascular disease*Current position*

All NRT products contain some sort of cautionary statement about their use with patients with cardiovascular disease (CVD).

Public health position

Most smokers who develop CVD are still smoking a year later yet stopping smoking will slow the progression of the disease and reduce the risk of it recurring.² The safety of NRT use in patients with CVD is widely documented^{32,33} and current research indicates that withholding NRT for use in smokers with CVD is not warranted.³³ Evidence indicates that NRT can be used safely by smokers with less severe CVD.³⁴ New guidelines comment that: 'There may well be no discernible risks involved, but even in the most cautious scenario where some degree of risk is assumed, this is far outweighed by risks of continuing smoking.'⁷

There is some concern about the use of NRT in those with recent myocardial infarction, or unstable angina, severe arrhythmias or refractory angina³⁴ although again continued smoking will be far more harmful.

Suggested way forward

We support recommendations from the new guidelines³³ that NRT 'can normally be recommended to smokers with CVD who tried and failed to quit without such help'. The cautionary statement for medical advice with stable CVD should therefore be removed. The guidelines make a number of helpful suggestions regarding how NRT should be recommended (for example oral products rather than transdermal nicotine patches) and what precautions to take. We would also endorse the view that NRT should be able to be used with smokers with severe or recent CVD episodes under the advice of a specialist physician, but with a strong exhortation that the physician makes a proper risk-benefit analysis that includes the likelihood and consequences of continued smoking.

Use of NRT to reduce and control cigarette consumption

There is good evidence that smoking-related morbidity and mortality are highly related to the dose or amount of smoking. However, there is also some evidence (e.g. from studies of the effects of passive smoking) of a non-linear relationship between dose and health effects.³⁵ Studies on the health impact of reducing smoking would take many years because most tobacco-related diseases take many years to develop. Given the evidence from short-term and cross-sectional studies³⁶ it is reasonable, in the absence of evidence to the contrary, to assume that a reduction in toxin intake will lead to a reduction in health risk, although the exact nature of this relationship is not well defined.³⁷

Two strategies for smoking reduction are discussed below: the use of NRT for periods of temporary abstinence and the use of NRT as an aid to a reduction in cigarette consumption.

Use of NRT to support temporary abstinence*Current position*

In the United Kingdom and most of the world, NRT product indications do not specify for use during temporary abstinence, but instead for the relief of withdrawal symptoms only as an aid to complete smoking cessation.

Currently most smokers who are prohibited from smoking in certain situations (e.g. in the

work-place, on public transport, in hospital) or choose not to smoke (e.g. in front of their children) do not use nicotine replacement to control withdrawal symptoms. Instead, they take regular cigarette breaks³⁸ and smoke heavily before and immediately after entering the smoking-restricted situation.³⁹

Norway and Austria recently agreed to an additional indication for NRT and temporary abstinence.

Public health position

There is good evidence that the signs and symptoms of nicotine withdrawal (i.e. worsening of mood and cognitive performance, slowing of frequencies on the EEG) occur within a few hours of abstinence.^{40,41} NRT can be utilized in periods of temporary abstinence as a means of treating the nicotine withdrawal syndrome and so help the smoker to abstain successfully for a period of time where this is perceived as necessary or desirable. For example, a smoker who took an adequate dose of NRT during a smoke-free work shift, flight or hospital stay could substantially reduce the severity of nicotine withdrawal-related bad mood, poor concentration and tobacco craving.^{42,43}

The ultimate public health objective is, however, to reduce exposure to tobacco smoke. Compensatory smoking tends to increase over time after implementation of a smoking ban and reduces the potentially large health gains from reduced toxin consumption due to work-place and other smoking bans.⁴⁴ Given the evidence supporting the interpretation of smoking behaviour as nicotine self-administration,² it should be assumed in the absence of evidence to the contrary that use of NRT should reduce compensatory smoking from heavier smoking before and after the forced abstinence.

The use of NRT for periods of temporary abstinence may also result in the smoker learning that they can manage without tobacco for several hours and might help encourage later cessation attempts. Advocating NRT for withdrawal relief should not therefore require a dilution of the clear message on cessation, but there are some concerns that an indication of NRT for temporary abstinence may reduce the motivation to quit.

Fewer cigarettes smoked before and after abstinence will mean less environmental tobacco

smoke (ETS), which is an added public health benefit. Furthermore, by offering an alternative to smokers, an NRT indication of 'temporary abstinence' should ease the implementation of policies that offer protection from ETS. These policies not only achieve a direct public health benefit for non-smokers, but have also been shown to trigger higher levels of cessation.

Suggested way forward

We believe that NRT should be provided routinely and free of charge in certain situations where the smoker has no choice but to remain in such an environment (e.g. hospital inpatients, prisoners, members of the armed forces) as a treatment for the resultant withdrawal syndrome. An example of this comes from New Jersey in the United States, where the State has made it a licensure standard that all free-standing residential addiction treatment services become completely tobacco-free not only inside the buildings but also in the grounds. Given that some of these institutions do not allow new patients off the grounds for over a month, this policy could only be implemented humanely alongside the provision of free NRT.⁴⁵

Smokers should be informed that NRT can be used to prevent the mood and performance deficits that result from relatively short periods of nicotine abstinence. The implementation of this change in the indication on NRT products to enable their use for temporary abstinence should be monitored for adverse effects on quitting behaviour. Research should be carried out on the effects of NRT during temporary abstinence on compensatory smoking.

Although the evidence that repeated temporary withdrawal is a significant motivator for cessation is unclear, it is a plausible assumption. However, we believe that there are ethical problems with denying smokers relief from temporary withdrawal symptoms, on the basis that this repeated unpleasant experience is a driver to smoking cessation. Such an approach has an overly coercive prescriptive dimension, and could be viewed as a violation of the rights of people who, for whatever reason, continue to smoke.

As well as allowing this indication for NRT, regulators also need to consider how such products will need to be packaged and marketed to appeal to the intended user.

Reducing smoke intake from tobacco by allowing concomitant NRT use and smoking

Current position

Smokers are frequently being advised to cut down despite the dearth of evidence supporting this as a useful strategy^{46,47} and indeed increasing evidence to the contrary.⁴⁸

The use of NRT alongside cutting down has not been recommended although there is some evidence supporting this (see below). Current indications for NRT products in the United Kingdom are that smokers should stop cigarette smoking before using the product as part of a cessation attempt. In Denmark it has been accepted that NRT can be an aid to smoking reduction, but only for short-term use as a prelude to cessation.¹⁰

Public health position

When smokers cut down their cigarette consumption they compensate for this by inhaling more from each cigarette, although compensation is not complete.³⁶ Reducing smoking does not appear to undermine cessation and may increase motivation for cessation,³⁶ although more evidence on this is needed.

The use of NRT alongside smoking reduction has been proposed^{49,50} as this would 'top up' nicotine levels and make compensation less likely. A few studies have demonstrated that the use of NRT can help with reduction and reduce the amount of compensatory smoking.^{49,51} One further study by Hurt and colleagues showed that short-term reduction in smoking had a mixed effect on various biomarkers of harm.⁵² This study involved the use of the nicotine inhaler alongside a structured cigarette reduction strategy in a group of smokers interested in reduction but not cessation. Although smokers who remained in the study reduced their smoking significantly, most had difficulty adhering to the cigarette reduction schedule. Use of the nicotine inhaler was low, which could explain this—indeed, in the Fagerstrom study⁴⁹ the nicotine inhaler was the least preferred NRT from the five NRT products available for use in this study.

A possible downside is a concern that total nicotine exposure could increase, as smokers would be obtaining nicotine from both sources.⁵⁰ The evidence from the Fagerstrom and Benowitz studies suggest that total nicotine intake (as measured by saliva cotinine) remains broadly stable

when smokers use NRT to reduce their smoke intake^{49,50} (while cigarette consumption and carbon-monoxide levels decrease). Further, experts have proposed that the additional harm associated with higher nicotine exposure, but no extra 'tar' exposure, is not great.⁴⁹

Finally, a reduction in the number of cigarettes smoked will again decrease ETS.

Suggested way forward

We believe that regulators should remove labeling that implies that there is a grave risk from using NRT while not completely tobacco-abstinent, as at present the balance of evidence does not support this and the risks are low. There is no evidence that this is harmful, and there is some evidence that it facilitates smoking reduction. The implementation of this should be monitored to investigate the effect it has on motivation and further attempts to quit. Consideration will also need to be given to marketing and packaging when this indication change is made.

Use for long-term maintenance

Current position

NRT is supposed to be taken for a relatively short time, usually coinciding with the first 3 months of the cessation attempt. It is not intended for indefinite use in which the user continues to obtain nicotine from use of the NRT product.

Public health position

There is a relatively small proportion of highly dependent smokers who are able to stop smoking with the help of medication and many more who may be more likely to remain abstinent in the long term if they continue to use NRT. The ongoing use of NRT seems likely to represent a defence against relapse. Long-term use (dependence potential) appears to be more likely with faster delivery products (e.g. the nasal spray), but in conditions where the patient is required to pay for the NRT, only around 10% were still using the spray 4 months after attempting to quit smoking.¹⁶ When intensive support and free NRT are provided under the optimum clinic use setting, then up to 25% of those who remain free of tobacco for a year may continue to use the

gum²⁰ and 43% the spray for that year.¹⁹ The available evidence on long-term use of NRT supports the idea that extremely heavy smokers are more prone to becoming long-term NRT users.²⁰

As more smoking cessation medications become available over the counter from pharmacies or on general sale it will be left more to the consumer to decide how long to continue taking the NRT. There is little research in this area, but the available evidence suggests that the problems may be more to do with under-dosing and use of NRT for too brief a period (e.g. less than 3 weeks) rather than large numbers unnecessarily becoming long-term users.¹⁶

Suggested way forward

We argue that smokers should continue to be advised to try to cease NRT use within the first 3 months of smoking cessation, if they are confident they will not relapse. They should also be informed that longer-term use is an option if they feel it would help them to stay off tobacco and that the health risks of this are very small and far less than those associated with continued smoking. The prime concern in deciding when to stop using NRT should be avoidance of relapse to smoking rather the risks arising from nicotine exposure through NRT.

NRT combinations

Current position

All the NRT products caution that the patient should stop smoking when using the product and most also state that the patient should also stop using other sources of nicotine. This advice effectively cautions the smoker against using more than one type of NRT at a time.

Public health position

There is a growing body of evidence in support of improved smoking cessation efficacy with combination treatments. For example, the use of patch and gum together may give the smoker additional control over withdrawal—both a steady supply during the day, and the ability to increase in response to cravings or stressful situations. Research has demonstrated that combining NRTs was more effective than a single NRT in reducing the withdrawal syndrome.^{43,53} Most

research has suggested that combining the patch with other forms of NRT is both safe and effective,^{54–57} although increased efficacy has not always been found.⁵⁸ There is no evidence that combination treatments are harmful.

Suggested way forward

We support the recommendation from the updated English Smoking Cessation Guidelines⁵⁹ which states: ‘There is no scientific basis for disallowing different forms of NRT to be combined and there may be some benefit to combinations.’ The US Tobacco Dependence Clinical Practice Guidelines indicated that combining the patch with an acute form of NRT was more efficacious than monotherapy and should be encouraged if the smoker is unable to quit using a single type of a first-line pharmacotherapy.⁶⁰

We would recommend that advice cautioning smokers from using different sources of nicotine be removed from the product information advice for all NRT products.

Wider availability of NRT products

Current position

The UK government recommended recently that the Committee on Safety of Medicines be asked to consider allowing all NRT products to be available on general sale (GSL), i.e. available from any outlet, provided the premises are lockable and the product supplied in an unopened manufacturer’s pack.⁶¹ Following applications from companies, the 4 mg gum, the lozenge and nicotine patches with a maximum daily dose of 21 mg nicotine were approved for general sale. The 2 mg gum has been on general sale in the United Kingdom since 1999.

Public health position

The potential public health benefit from NRT is determined by how many people use it which is determined by how many restrictions are placed on its sale and marketing by its licensing status. There is also an ethical argument that cigarettes should not be more widely available than NRT.

The most credible argument advanced against wider GSL status for NRT is that its efficacy increases in relation to the intensity of support and counselling provided to the smoker. It is

argued, therefore, that there is a benefit in limiting the availability of NRT to those settings where support is available, for example the pharmacy, general practice or smoking cessation services. We do not accept this argument. While high levels of support may be desirable, we do not believe they should be a *condition* of ready access to effective pharmaceutical treatment. Smokers may obtain support from a variety of credible sources outside established smoking cessation services and pharmacies. In addition, there is some evidence from trials using simulated over-the-counter (OTC) settings of effects similar to those in settings where more intensive behavioural support is offered,⁶² although the simulations involved more contact than would occur in a typical OTC setting.

Evidence from the United States has demonstrated public health benefits from increased availability of NRT with no significant abuse or dependence potential.⁹ The estimated number of quit attempts increased from around 3 million during 1993–95 to approximately 6 million in 1996, coinciding with the availability of nicotine gum and the nicotine patch as OTC products (equivalent to the UK General Sale category).⁶³ In the United Kingdom sales of the 2 mg gum increased since going GSL and this increase appears to have occurred without cannibalizing the pharmacy market, where sales have also increased.⁶⁴

If the products do change to GSL status, there is still a need for health professionals to be involved in advising smokers to stop and offering pharmacological treatments, as overall cessation rates increase when more support is given.⁶⁰

Suggested way forward

The RCP report² recommended the following: ‘NRT should be available to all smokers through reimbursable prescriptions, and also be widely available and affordable for general sale.’

We support this and believe that all NRT products should be allowed to compete with tobacco products on general sale in the open market unless a convincing case can be made on public health grounds to restrict availability compared to cigarettes. We also agree that it is perfectly sensible that National Health Services or Health Insurance Systems should continue to cover effective medications such as NRT when they have become available OTC.

Possibility of tobacco competitive nicotine delivery devices for recreational use

Current position

NRT is currently treated much like any other medication with a fairly cautious approach to the issues of efficacy, safety and abuse potential. If a food or pharmaceutical company could create a nicotine delivery device that competed with cigarettes in terms of satisfaction and speed of nicotine delivery, it is likely that medicines regulators would refuse it a license on the grounds of its higher dependence potential, abuse liability, possibly higher risk of intoxication (although as with cigarettes they could be designed to minimize this) and possible cardiovascular toxicity compared with other NRT products. Meanwhile, tobacco products with equal addictiveness and much greater respiratory, cardiovascular and carcinogenic toxicity will continue to be freely sold. Non-tobacco nicotine products, if they were acceptable to consumers as alternatives to tobacco and widely marketed, could make very substantial public health gains by reducing the harm caused by recreational tobacco use. Given the likely failure of such products to surmount the regulatory hurdles provided by the medicines regulators, there is little incentive for companies to develop and produce them.

NRT products are designed from the outset to minimize the risk of abuse and dependence, and therefore do not offer smokers a ‘satisfying’ alternative to cigarettes. The current generation of products do not compete with tobacco for the recreational nicotine market. Standard medicines regulation ensures that new non-tobacco nicotine products, which could compete directly with tobacco, are unlikely to be developed and marketed widely, and effectively guarantee the market for recreational nicotine to the most harmful delivery system. Because of the regulatory imbalance between cigarettes and NRT products, it could be said that the pharmaceutical regulatory systems unwittingly support the favoured position in society of the tobacco product—the cause of the projected one billion tobacco-related deaths in the 21st century.⁶⁵

Public health position

The regulatory framework works against public health. The production and widespread availability of more satisfying forms of nicotine delivery might lead to a greater number of people

being addicted to nicotine, but many fewer would fall ill or die from their use.

Paradoxically, the imbalance in regulatory control between tobacco and pharmaceuticals may lead to new tobacco products being marketed as a way of taking nicotine with reduced harm—for example, oral tobacco products or products treated to reduce particular carcinogens. While there may be a plausible public health case to allow or encourage the tobacco market to evolve in this way, there cannot be a justification for preventing the pharmaceutical nicotine market also extending into this area.

Suggested way forward

Regulators need to consider how to reverse this perverse regulatory framework without relaxing standards for medicines. We believe that urgent consideration needs to be given to setting up a single regulatory framework for all nicotine products that can encourage the development of more tobacco-competitive nicotine delivery devices. At the same time, claims for harm reduction in tobacco products need to be assessed and regulated. If pharmaceutical products develop to provide a more psychoactive 'hit' of nicotine while tobacco products evolve to cause less harm, it seems likely that a single regulatory authority would need to take responsibility for the converging market in recreational nicotine.⁶⁶

Conclusion

The current regulatory framework restricts access to NRT without adequately considering that the likely consequence is continued dependent use of a far more harmful, and widely available product: tobacco. Regulators should review the licensing conditions for NRT products taking a broader overview of the public health consequences of any restrictions on availability.

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WHO Partnership Project is funded largely by three pharmaceutical companies that manufacture treatment products for tobacco dependence, but managed by WHO Europe and a steering group which included government representatives and many public sector organisations.

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