NICOTINE - REPLACEMENT PRODUCTS IN SMOKING CESSATION: A REVIEW

F Alsagoff, H P Lee

ABSTRACT

Smoking cessation programmes have gained greater prominence in Singapore in the face of growing desire among smokers to stop smoking. There exists a whole plethora of different methods which are employed in smoking cessation; this reflects the fact that smoking is a compulsive habit which is difficult to stop. Most attempts at smoking cessation fail, and the failure is largely attributable to the addictive properties of nicotine, which causes a withdrawal syndrome when the body is deprived of it. A host of medications have been used in the past in an attempt to alleviate this withdrawal syndrome. Of these products, perhaps the most promising are the nicotine-replacement products. These products consist of nicotine which is delivered through contrasting delivery systems viz polacrilex gum, transdermal patches, nasal sprays and inhalers. A review of recent clinical trials assessing the efficacy of the nicotine gum and the transdermal nicotine patch was conducted. Of the two products, the transdermal nicotine patch seems to have superior pharmacokinetics and fewer side-effects, and may well be the product of choice.

Keywords: smoking, cessation, nicotine, gum, transdermal

SINGAPORE MED J 1993; Vol 34: 505-510

INTRODUCTION

From the time of first publication of the subject in 1950[1], the causal relationship between smoking and lung cancer has now been well established. Since then, there has been growing public knowledge of the dangers of smoking, with a consequent shift in popular perception of the cigarette. A greater interest in smoking cessation has emerged in the face of the "wellness" culture now sweeping across the developed world, particularly the United States. Smoking cessation clinics have become a common feature of American worksite health promotion programmes. According to the Corporate Wellness Programs 1987 Biennial Survey Results conducted in the United States by the Health Research Institute, smoking cessation programmes were offered in 86.5% of the companies surveyed which carried out worksite health promotion of any sort[2].

Interest in smoking cessation in Singapore has also risen greatly in recent years. Smoking cessation clinics are currently run by the Singapore Cancer Society, Youngberg Wellness Centre, the Singapore Armed Forces, as well as some government hospitals.

AN OVERVIEW OF SMOKING CESSATION METHODS

There exists a whole plethora of different methods employed in smoking cessation. While it would be beyond the scope of this paper to present a detailed discourse on the various methods, a brief overview at this juncture would be useful.

Broadly speaking, the common methods employed in smoking cessation are[3]: (i) Self-care, (ii) Smoking cessation clinics and groups, (iii) Hypnosis, (iv) Acupuncture, (v) Physician counselling, (vi) Mass media and community programmes.

Department of Community, Occupational and and Family Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

F Alsagoff, MBBS
Senior Tutor

H P Lee, MBBS, MSc (Public Health), FAMS, FFPHM (UK)
Associate Professor and Head

Correspondence to: Dr F Alsagoff
Medical Executive Officer
TOUCH Community Services
66/68 East Coast Road
#07-00 GRTH Building
Singapore 1542

Self-care means simply being able to do for yourself things that maintain your health. It involves a personal choice by the individual to quit, although he may be aided by self-help guides or over-the-counter medication.

Smoking cessation clinics involve a group approach, facilitated by one or more leaders. Specific approaches may vary but generally such clinic programmes would include awareness talks on the dangers of smoking, and coping mechanisms for nicotine withdrawal. Success depends a great deal on the communicative skills of the counsellors and the degree of mutual support obtained for clinic participants. Clinics may or may not employ medication to attempt to lessen withdrawal symptoms. In the "5 Day Plan" run by the Seventh Day Adventist Church since 1960, no medication is advised. In Singapore, the Youngberg Wellness Centre offers this package, while the Singapore Armed Forces offer a modified "5 Day Plan" to its personnel.

Hypnosis and acupuncture have not been widely used and their efficacy have also not been validated. Physician counselling arises during usual doctor-patient consultations. When a smoking history is elicited, the patient is counselled by the attending physician to stop smoking. This exchange is brief and is not usually detailed, and success rates are not very high. However, as the number of doctor-patient interactions each day is great, it provides an excellent means by which smoking cessation may be encouraged.

Examples of mass media and community programmes would include the smoking control campaign in Singapore held in 1991 which included a street party as well as a smoking cessation programme aired over television. It would be expected that there exists a great diversity in the nature and intensity of such programmes.

PHARMACEUTICALS IN SMOKING CESSATION

The existence of such a diversity of smoking cessation methods underlie one fact: smoking is a compulsive habit which is difficult to stop. Data in 1978 from the National Centre for Health Statistics in the United States showed that 59% of all smokers studied had tried to quit[4]. This result is fairly similar to results obtained in a local study done in 1978 among residents in Telok Blangah, which showed that 57% of all smokers surveyed had tried to quit[5]. It is reasonable to expect the current percentage of smokers in Singapore that have tried to quit to be much higher, given the harsher legislative anti-smoking measures as well as the greater proportion of non-smokers present locally. Indeed, in a nation-wide study carried out in 1987 among Singaporean schoolchildren between the ages of 9 and 20, 70.7% of male

smokers and 54.6% of female smokers indicated a desire to stop smoking with most of these having already attempted cessation prior to the time of survey[6]. These findings are encouraging as the teenage years are usually the most vulnerable part of life for smokers to be initiated into smoking. Most attempts at smoking cessation, however, fail, and their failure to quit smoking is attributable in large part to the addictive properties of nicotine[7].

In about 80% of smokers, the cessation of cigarette smoking results in the development of a withdrawal syndrome[8,9]. The withdrawal syndrome has been attributed to nicotine[10-12]. Indeed, nicotine withdrawal syndrome has been recognised as a disease entity by the American Psychiatric Association in the "Diagnostic and Statistical Manual of Mental Disorders", third edition, revised (DSM-III-R, 292.00)[13]. The nicotine-seeking behaviour of smokers is described well by the World Health Organisation definition of drug dependence as "a behavoural pattern in which the use of a given psychoactive drug is given a sharply higher priority over other behaviours which once had a significantly higher value"[14].

Symptoms of the smoking withdrawal syndrome include a craving for tobacco, irritability, restlessness, anxiety, difficulty in concentrating, increased appetite and food intake, and weight gain. A host of medications have arisen in the past to alleviate or suppress the symptoms of withdrawal that smokers face with dread. These medications include anticholinergics, sedatives, tranquilizers, sympathomimetics and anticonvulsants. Results of success have been disappointing. Perhaps from the whole array of pharmacologic agents that have been used to date, the nicotine-replacement products hold the most promise.

NICOTINE-REPLACEMENT PRODUCTS

In recognising nicotine as the chemical reinforcer of the smoking habit, Ferno, Lichneckerts, and Lundgren first advanced the idea that it might be possible to develop a product that could replace nicotine[15]. This notion was supported by Gritz and Jarvik[16], Russell[17], and Schachter[18]. Ferno's further work subsequently resulted in the production of "Nicorette", a nicotine-containing polacrilex, or chewing gum.

Nicotine gum is a prescription drug in the form of a sugar-free chewing gum containing nicotine, obtained from the tobacco plant, which is bound to an ion exchange resin nicotine when chewed. The gum is available in 2 mg and 4 mg doses, and is chewed each time the patient feels an urge to smoke. Nicotine is released from the gum by the chewing action and is absorbed by the buccal circulation. Hence the rate of nicotine absorbed is not constant but is dependent on rate of chewing and proper chewing technique.

A more recently developed nicotine-substitution product is the Transdermal Nicotine System (TNS). Nicotine has the pharmacological property of being readily absorbed through the skin. That nicotine topically applied to the skin may be absorbed to significant levels systemically was shown by Rose et al in 1984[19]. TNS makes use of this property by incorporating nicotine in its free base form into a patch which can then be applied to the body. Muller et al[20] and Dubois et al[21] subsequently used the TNS in experiments to determine its pharmacokinetic properties. Ciba Geigy has produced a TNS which is marketed under the proprietary name "Nicotinell TTS". The product is available in three sizes: 10, 20 and 30 cm^2. The amount of nicotine released from the TNS per cm^2 is constant, with the dose delivered determined solely by the contact area of the system. The rate of nicotine delivery onto the skin for "Nicotinell TTS" is 0.7mg per cm^2 per 24 hours[22].

Two other forms of nicotine delivery are the nicotine nasal spray and the nicotine vapour inhaler. The delivery device for the nasal spray is essentially similar to that used to deliver steroid nasal sprays, such as intranasal beclomethasone. Both modes of nicotine delivery are fairly new and large-scale clinical trials are underway to test their efficacy.

EFFICACY OF NICOTINE GUM AND THE TRANSDERMAL NICOTINE SYSTEM

The efficacies of the two main nicotine-replacement products in smoking cessation were assessed by reviewing clinical trials done over the past five years, from 1987 to 1991.

Nicotine Gum

Nicotine gum has proven to be of some benefit when used in trials where behavioural support measures are also taught, as in cessation clinic settings. In a placebo-controlled, double-blind, 2-year prospective study involving 182 smokers given nicotine gum or a placebo, Blondal[23] obtained success rates of 44.6% of nicotine gum users still abstinent after 2 years, compared to 31.3% in the placebo group ($p < 0.05$).

In Tonnesen's[24] study of 113 smokers who were assessed using the Horn-Russell scale to be medium or low dependence smokers, the rates of abstinence for nicotine gum users versus placebo gum users were 38.3% and 22.6% respectively at one year, and 28.3% and 9.4% respectively at two years ($p < 0.001$).

In the same study, high dependence smokers were given gum containing either 2 or 4 mg of nicotine. The rates of abstinence for the 2 mg dose versus the 4 mg dose were 12.1% and 44.4% respectively at one year (95% confidence interval for difference 10-54%), and 6.1% and 33.3% respectively at two years (95% confidence interval for difference 7-47%). These results suggest that titrating the dosage of nicotine supplied is an important determinant in ensuring success.

Oswald's[25] study of 388 participants in a smoking cessation clinic where nicotine gum was used provided abstinence rates of 38% and 30% at 6 months and one year. There were no controls in the study design. Jensen's[26] trial involved 496 smokers in a randomised comparison of the effect of silver acetate, nicotine gum and placebo gum. After 12 weeks, he obtained abstinence rates of 59% in the nicotine gum group, 50% in the silver acetate group and 45% in the placebo group. These results were not statistically significant. All participants were given counselling and support on cessation. At 6 and 12 months, the success rates were similar for all three groups, 39.7% and 23.3% respectively. These results were not statistically significant.

Fortmann SP et al[27] carried out a trial which was named the "Stanford Stop Smoking Project". This was a randomised, double-blind, placebo controlled trial that sought to determine the effectiveness of nicotine gum combined with self-administered relapse prevention materials in maintaining smoking cessation. His success rates at 6 month follow-up were 31% for nicotine gum users (95% confidence interval 23-38%) and 22% for the placebo and no gum groups (95% confidence interval 16-30%). The criterion used for abstinence in the study was abstaining from smoking for a period of at least seven days, which would account for the fairly high rates for abstinence in a minimal intervention smoking cessation study. In his study involving 86 treated and 53 controls, Basler et al[28] obtained abstinence rates of 63.9% at three months, compared with 3.3% for the control group. At twelve months, abstinence rate for the treated group was 52.3% This study involved twelve weekly sessions that included behavioural modification techniques.

In trials that did not include counselling on coping skills, success rates were more modest. Sutton's[29] study involved the use of nicotine gum in a workplace setting. Out of 172 participants who were given the nicotine gum, 12% were still abstinent after one year, with biochemical validation. The control group

which had no intervention at all only had a success rate of 2% (95% confidence interval for difference 2-11%). In general practice settings, the success rates when nicotine gum is used appears to be less evident. Hughes'[30] study of 315 smokers produced rates of 10% for gum users abstinent for 11 months versus 7% in the control group (95% confidence interval for difference -3 to 10%). Gilbert's[31] randomised controlled trial of nicotine gum used in primary care settings (n = 223) produced results of 8.1% of the study subjects abstinent at one year follow-up, as compared to 9.8% in the control group (95% confidence interval for difference -9.3 to 6.4%). Shaughnessy's[32] trial of nicotine gum in a family practice setting similarly produced results that did not favour the use of the gum. Out of 99 subjects in his trial, 12.2% of nicotine gum users were abstinent at one year follow-up, as compared to 20% cessation rate for his control group.

Table I – Summary of results of smoking cessation trials using nicotine gum

Author	Study Setting	Cessation Rates		End Point
		Nicotine Gum Users	Control Group	
Blondal T	Specialised	44.6%	31.1%	2 years
Tonnesen P et al	Specialised	28.3%	9.4%	2 years
Oswald JS et al	Specialised	30%	–	1 year
Jensen EJ et al	Specialised	23.3%	23.3%	1 year
Fortmann SP et al	Specialised	31%	22%	6 months
Basler HD et al	Specialised	63.9%	3.3%	3 months
Sutton S et al	Workplace	12%	2%	1 year
Hughes JR et al	Medical Practice	10%	7%	1 year
Gilbert JR et al	Medical Practice	8.1%	9.8%	1 year
Shaughnessy et al	Medical Practice	12.2%	20%	1 year

The studies reviewed above suggest that nicotine chewing gum is of benefit mainly when used in a specialised clinic setting (Table I). When used in general practice, the results are not as encouraging. This conclusion is similar to Lam et al's[33] meta-analysis of randomised controlled trials of nicotine chewing gum. In his analysis, he found that in specialised clinics, subjects treated with nicotine gum had cessation rates of 27%, compared to 18% for the control group. At twelve months, the rates were 23% and 13% for nicotine gum users and controls respectively. In general practice settings, cessation rates were 17% and 13% over 6 months, and 9% and 5% over twelve months for nicotine gum users and controls respectively.

Transdermal Nicotine Systems

A total of 7 studies on the efficacy of TNS in smoking cessation done between 1989 to 1991 were reviewed. Abelin's[34] trial was a 3-month, placebo-controlled randomised double-blind study involving use of the TNS on 199 subjects from 21 general medical practices. The abstinence rates for the TNS group at the end of treatment was 36% while the placebo group had a success rate of 23% (p = 0.043). A subsequent study by the same group based on the same study design, but involving 311 smokers, was reported by Muller[35]. The same results were obtained.

The difference in efficacy of TNS when used continuously as opposed to its use only during wakeful hours was studied by Daughton[36]. This placebo-controlled trial involved 158 smokers. Abstinence rates at the end of the trial were 39% for the 24-hour nicotine delivery regimen group, 35% for the wakeful hour nicotine delivery regimen, and 13.5% for the placebo treatment group. The difference in quit rates were not found to be statistically significant. After 6 months, abstinence rates were 22%, 31% and 8% for 24-hour nicotine delivery regimen, wakeful hour nicotine delivery regimen and placebo treatment groups respectively. These results were not found to be statistically significant.

Rose's[37] randomised, double-blind trial involved 65 smokers. The study design also included a behavioural smoking cessation programme. Initial abstinence rates of the TNS and placebo groups were 55% and 34% respectively ($p < 0.05$). Three weeks later, the abstinence rates were 18% and 6% respectively. In another trial, Buchkremer[38] randomised 131 smokers into three groups: TNS users, placebo users and a non-intervention control group. All participants underwent behavioural training. At the end of 9 weeks, the abstinence rates were 69%, 51.2% and 44.4% respectively. A randomised double-blind placebo-controlled trial by Hurt[39] yielded abstinence rates at 6 weeks of treatment of 77% for TNS users, and 39% for placebo patch users (p = 0.002). He remarked, however, that beyond 6 weeks, a substantial relapse rate occurred in both groups. Finally, in a unique double-blind cross over study involving 13 psychiatric patients who were not trying to stop smoking, Hartman[40] found that these patients smoked significantly less cigarettes while receiving nicotine patches than when they received placebo patches.

Table II – Summary of smoking cessation trials using transdermal nicotine systems

Author	Study Setting	Cessation Rates		End Point
		TNS Users	Control Group	
Buchkremer G et al	Specialised	69%	52.2%	9 weeks
Rose JE et al	Specialised	55%	34%	4 weeks
Abelin T et al	Medical Practice	36%	23%	3 months
Hurt RD et al	Self Help	77%	39%	6 weeks
Daughton DM et al	Self Help	31%	8%	6 months

DISCUSSION

Difficulties in interpretation of results

A discussion based on the review of smoking cessation trials must surely begin with the problems faced in comparing trial results. For any study on smoking cessation to be meaningful, the parameter used to measure success must be uniform and standard. A reduction in the number of cigarettes smoked cannot then be used as a parameter since the amount of nicotine and tobacco products taken into the body system depends not just on the number of cigarettes smoked, but also on the depth of each inhaled puff. Hence the only acceptable end-point for measuring success of any smoking cessation trial should be total abstinence from smoking. In the review, therefore, reports based only upon decreased cigarette consumption were excluded.

Relapse rates for smoking cessation programmes are generally high and as such, the later the lapse before follow-up, the poorer would be the expected results. In the studies reviewed, there were marked variations in the length of follow-up in the different studies. Trials involving transdermal nicotine patches had particularly short follow-up periods, probably as a result of the relative newness of the product. In addition, the studies also incorporated different control designs. Both of these factors prevent meaningful comparison of results between each individual study. Conclusions can only be drawn by comparing the

abstinence rates between nicotine-replacement usage and placebo-controls within each study.

Herein lies yet another problem. Is it reasonable to expect that the efficacy of any smoking cessation product be reflected by permanent, or at least long term, abstinence? Consider the medical analogy of a patient with pneumonia due to penicillin-susceptible bacteria. Having been cured of his pneumonia, do we judge the antibiotic as ineffective if after twelve months, he again succumbs to pneumonia? In this situation, we clearly would not. In the case of cigarette addiction then, are we justified in assuming the smoking cessation method to be ineffective if after twelve months of successful cigarette abstinence, he relapses into smoking again? The issue here is to distinguish between initiating smoking abstinence and subsequent relapse prevention. In initiating smoking abstinence, nicotine replacement has a role to play in overcoming physiological dependency. However, relapse prevention requires the patient to overcome his behavioural dependency on the cigarette. Success in the long term would thus depend on effective behavioural modification. A clear distinguishing line between initiation of abstinence and relapse prevention has not yet been delineated, which is due to the marked inter-individual variation that exists among smokers.

In this light, the extent to which behavioural support is given would also constitute a confounding variable in comparing between trials, unless there is uniformity in intensity and nature of the support. This was not so among the various trials reviewed.

Other confounders include demographic factors (such as age, sex, highest educational level achieved, socio-economic status and ethnicity), physiologic factors (such as strength of nicotine dependence, state of hepatic metabolism, severity of withdrawal symptoms, amount of weight gain), number of prior quit attempts, cultural factors (especially the cultural beliefs that shape the person's perception of smoking), and the motivation of the subjects to quit[41].

Another commonly encountered problem in smoking cessation trials lies in the validation of smoking cessation. Often, published success rates are based on patient self-reported information. This is often higher than objectively measured data[42]. Biochemical validation of smoking cessation is readily available; the markers which may be used are carbon monoxide, thiocyanate or cotinine. Carbon monoxide may be measured in the blood as carboxyhaemoglobin, or simply in expired air. It yields a sensitivity and specificity of about 90%. Thiocyanate can be measured in serum, urine or saliva but sensitivity and specificity are poor because of the long half-life and presence of thiocyanate in commonly consumed food products like leafy vegetables, nuts and beer. Cotinine can be measured in urine, serum and saliva, and has a sensitivity of 96-97% and specificity of 99-100%. It would be the marker of choice but the main disadvantage of using cotinine as a marker lies in its cost. For large scale studies, carbon monoxide provides an acceptable degree of discrimination and is considerably cheaper and simpler to apply[43,44]. Not all studies reviewed utilised objective biochemical validation.

Having mentioned all the difficulties inherent in comparing smoking cessation trials, it can only be deduced from the trials reviewed that nicotine replacement systems appear to be of some benefit in most instances. The use of systems appears to show the most benefit when incorporated as part of a multi-component therapy. Usage of these products also appear to give better results when the patients are motivated and highly nicotine-dependent. Results of nicotine replacement systems when used in general practice settings have been disappointing. These findings are consistent with a review of anti-smoking products by Gourlay[45].

The presence of so many confounding variables prevents a meaningful comparison of the efficacy of the two nicotine-replacement products in the review. The studies reviewed do suggest a trend, however, that transdermal nicotine systems are more efficacious. Perhaps the choice between using nicotine gum or the transdermal nicotine system may be better made based upon their different pharmacokinetics and side-effects.

Pharmacokinetics

The pharmacokinetics of nicotine delivery by the two nicotine-replacement products differ significantly. Nicotine is released from nicotine gum upon chewing. Ideally, the nicotine released is absorbed through the buccal circulation and enters the systemic circulation. In order that a stable plasma nicotine level be reached, the gum should be chewed regularly and slowly throughout the day. Failure in compliance leads to fluctuations in plasma levels. This commonly occurs when the patient chews the gum too vigorously or rapidly, resulting in a large dose of nicotine suddenly entering the systemic circulation. This may result in an increase in heart rate, blood pressure, stroke volume, cardiac output and coronary blood flow. There may be concomitant cutaneous and systemic venous vasoconstriction. Also when this happens, a significant amount of nicotine released passes into the gastrointestinal tract and is absorbed in the gut. The nicotine thus absorbed enters the portal circulation and undergoes first pass effect in the liver resulting in a systemic trough level of nicotine that is lower than expected based on analysis of nicotine in the chewed gum[46].

Failure to comply with instructions on proper usage of the gum is common due to the difficulty in chewing the gum and its unpalatable taste. Plasma nicotine levels also dip significantly during sleep when the gum cannot be used resulting in a low plasma nicotine level when the patient awakes. This is significant as a low plasma nicotine level is suggested to be the cause for early morning cigarette craving. For heavy smokers attempting to stop smoking, these early morning cravings were felt to be especially severe[47]. Nicotine deficiency symptoms which are alleviated by nicotine-supplying behaviour (chewing gum) serves also as a positive reinforcement to nicotine seeking and nicotine addiction may thus not be extinguished[48].

Transdermal nicotine systems have the advantage over nicotine gum in not requiring an active response by the patient in order to attain nicotine release. Nicotine is released across the skin into the systemic circulation through passive diffusion. The rate of diffusion is constant and depends only on the contact surface area. Furthermore, the patch can be used over 24 hours, thereby ensuring constant plasma nicotine levels throughout the day. The early morning nicotine dip is also avoided.

The side-effects for nicotine-replacement products can be broadly divided into two categories: those which are due to nicotine and is systemic in effect, and those which are due to the mode of nicotine delivery, which is local in effect. The symptoms of nicotine intoxication, such as nausea, vomiting, pallor, weakness, dizziness, lightheadedness, headache, and sweating, are possible side effects for both nicotine gum and the transdermal nicotine patch. Nicotine gum has, in addition, some inherent disadvantages. Chewing gum may not be socially acceptable to every smoker willing to give up the habit. The nicotine released by the gum can irritate oral and gastric mucosa, cause indigestion, eructations, anorexia, hiccups, and impair the sense of taste[49,50]. Hence nicotine gum is contraindicated for smokers with oral or pharyngeal inflammation or with a history of oesophagitis or peptic ulcers[51]. Chewing the gum may also lead to muscular jaw ache, and is not suitable for smokers with temporomandibular joint disease. Smokers with artificial dentures would have to renounce this type of nicotine-replacement completely[52]!

Transdermal nicotine systems, by virtue of its mode of delivery, are free of the mechanical and gastrointestinal side

effects inherent in nicotine gum. Apart from putting on the patch, the smoker does not require any other active involvement. The patch also does not restrict his daily activities in any way. The main side effect of using the TNS, apart from possible nicotine intoxication, is erythema and pruritus of the skin at the contact area. In a clinical study of 183 TNS users, it was found that 53% of the patients developed pruritus, and 39% developed erythema. Most symptoms were slight or moderate in severity. However 6 patients developed genuine contact allergy (type IV, delayed type reaction), which proved in 5 cases to be induced by the nicotine contained in the patches[53]. Skin erythema and pruritus thus produced may be minimised in most cases by rotating the site at which the TNS is applied. However it is best to avoid its use in cases of hypersensitivity of the skin to nicotine and systemic skin disease.

The superior pharmacokinetics of the transdermal nicotine system over nicotine gum, its greater ease of application (which would ensure greater patient compliance) and fewer and less severe side effects would form the basis for the author's choice of the transdermal nicotine system as the more suitable form of nicotine substitution product. However, longer follow-ups in trials are needed to assess long term efficacy, especially when the patient has stopped using the TNS completely.

Nicotine Addiction and Nicotine-Replacement

The role of nicotine replacement in treatment of nicotine addiction may seem unacceptable to some. However, literature seems to suggest that they work, for which several explanations are possible. The prescription of nicotine medication would involve a health professional in the treatment process, which may motivate greater efforts put in by the patient as he would be accountable to someone. Furthermore when the risk is personalised, a change in behaviour is more likely[54]. The physician in charge would also be able to tailor the dosage and frequency of nicotine delivery to suit the individual. These factors would enhance the pharmacological effects of the nicotine present in nicotine-replacement products.

In the final analysis, though, the addiction to psychoactive nicotine presents only one facet of the smoking process in chronic smokers[55]. The smoker must also be helped to face the behavioural components of his habit, so individualised counselling remains essential. It is logical to assume that a smoker is not completely free of his cigarette addiction until he is successfully abstinent without the use of any forms of nicotine at all. Nicotine replacement products have an adjuvant role in therapy in allowing the body to cope with the physiological aspects of nicotine withdrawal. They cannot be the mainstay of treatment, as all trials involving only the use of such products have yielded very poor results. In the end ,while the use of nicotine- replacement may be helpful in tapering off the physiological components, the behavioural component must be decisively altered to ensure a lasting cessation. Perhaps the role of nicotine-replacement products would thus be in highly motivated, highly dependent smokers, to facilitate the behavioural coping process, so that the patient would then be more capable of dealing with the nicotine withdrawal process which must inevitably come when the nicotine replacement product is removed.

CONCLUSION

Nicotine-replacement products have an adjuvant role to play in smoking cessation. Their greatest efficacy is obtained when used in highly motivated, highly dependent smokers, in a specialised cessation clinic where behavioural support is the mainstay of treatment. Of the two nicotine-substitution products reviewed, the transdermal nicotine system seems to have superior pharmacokinetics and fewer side-effects, and may well be the product of choice.

REFERENCES

1. Doll R, Hill AB. Smoking and carcinoma of the lung: Preliminary report. Br Med J 1950; 2:739-48.
2. Health Research Institute. Corporate Wellness Programs: 1987 Biennial Survey Results. Participant report. Dec 1987
3. Schwartz JL. Review and evaluation of smoking cessation methods: The United States and Canada, 1978-85. NIH publication no 87-2940 April 1987:11-3.
4. Moss AJ. Changes in cigarette smoking and current smoking practices among adults; United States, 1978. U.S. Department of Health, Education, and Welfare, Public Health Service, National Centre for Health Statistics. Advance data from vital and health statistics, 1979 September 19; publ. no 52:15.
5. Lee HP, Ng KS, Chan KH, Liang HL. Smoking in a local community in Singapore. Singapore Med J 1979; 20:323-9.
6. Emmanuel SC, Ho CK, Chen AJ. Cigarette smoking among school children in Singapore. Part III – Knowledge and attitudes towards smoking. Singapore Med J 1991; 32:233-7.
7. Benowitz NL. Drug therapy: Pharmacologic aspects of cigarette smoking and nicotine addiction. N Engl J Med 1988; 319(20):1318-30.
8. Hatsukami DH, Hughes JR, Pickens RW, Svikis D. Tobacco withdrawal symptoms: an experimental analysis. Psychopharmacology (Berlin) 1984; 84:231-6.
9. Hughes JR, Hatsukami DK. Signs and symptoms of tobacco withdrawal. Arch Gen Psych 1986; 43:289-94.
10. Hatsukami DK, Gust SW, Keenan RM. Physiologic and subjective changes from smokeless tobacco withdrawal. Clin Pharmacol Ther 1987; 41:103-7.
11. Hughes JR, Hatsukami DK, Skoog KP. Physical dependence on nicotine in gum. JAMA 1986; 255:3277-9.
12. Hughes JR, Hatsukami DK, Pickens RW, Krahn D, Malin S. Luknic A. Effects of nicotine on the tobacco withdrawal syndrome. Psychopharmacology (Berlin) 1984; 83:82-7.
13. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). 3rd ed. rev. Washington D.C.: American Psychiatric Association. 1987:136.
14. Edwards G, Arif A, Hodgson R. Nomenclature and classification of drug and alcohol-related problems: A shortened version of a WHO memorandum. Br J Addict 1982; 77:3-20.
15. Ferno O, Lichtneckert S, Lundgren C. A substitute for tobacco smoking. Psychopharmacologia 1973: 201-4.
16. Gritz ER, Jarvik ME. Pharmacological aids for the cessation of smoking. In: Proceedings of the 3rd World Conference, Vol II, op. cit. ref. 58, 1977: 575-91.
17. Russell MAH. Smoking addiction: Some implications for cessation. In: Schwartz JL ed. Progress in smoking cessation, op, cit. ref. 49, 1978: 206-22.
18. Schachter S. Nicotine regulation in heavy and light smokers. J Exp Psychol 1977; 106:5-12.
19. Rose JE, Jarvik ME, Rose KD. Transdermal administration of nicotine. Drug Alcohol Depend 1984; 13:209-13.
20. Muller P, Imhof PR, Mauli D, Milovanovic D. Human pharmacological investigations of a transdermal nicotine system. Methods Find Exp Clin Pharmacol 1989; 11:197-204.
21. Dubois JP, Sioufi A, Muller P, Mauli D, Imhof PR. Pharmacokinetics and bioavailability of nicotine in healthy volunteers following single and repeated administrations of different doses of transdermal nicotine system. Methods Find Exp Clin Pharmacol, 1989; 11:187-95.
22. Ciba-Geigy Limited, Basle, Switzerland. Nicotinell TTS product information for patients. Mar 1990.
23. Blondal T. Controlled trial of nicotine polacrilex gum with supportive measures. Arch Intern Med 1989; 149:1818-21.
24. Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnersen AB, Forchammer H, et al. Effect of nicotine chewing gum in combination with group counselling on the cessation or smoking. N Engl J Med 1988; 318:15-8.
25. Oswald JS, Worden WL, Cox JL. The efficacy of nicotine gum in group-centred smoking cessation therapy in a family practice. J Fam Pract 1988; 27:179-83.
26. Jensen EJ, Schmidt E, Pedersen B, Dahl R. Effect of nicotine, silver acetate and ordinary chewing gum in combination with group counselling on smoking cessation. Thorax 1990; 45:831-4.
27. Fortmann SP, Killen JD, Telch MJ, Newman B. Minimal contact treatment for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: initial results of the Stanford Stop Smoking Project. JAMA 1988; 260:1575-80.
28. Balser HD, Brinkmeier U, Buser K, Gluth G. Nicotine gum assisted group therapy in smokers with an increased risk of coronary disease - evaluation in a primary care setting format. Health Ed Res 1992; 7:87-95.
29. Sutton S, Hallett R. Randomised trial of brief individual treatment for smoking using nicotine chewing gum in a workplace setting. Am J Public Health 1987; 77: 1210-1.
30. Hughes JR, Gust SW, Keenan RM, Fenwick JW, Healey ML. Nicotine vs placebo gum in general medical practice. JAMA 1989; 261:1300-5.
31. Gilbert JR, Wilson DM, Best JA, Taylor DW, Lindsay EA, Singer J, et al. Smoking cessation in primary care. A randomised controlled trial of nicotine-bearing chewing gum. J Fam Pract 1989; 28:49-55.
32. Shaughnessy AF, Davis RE, Reeder CE. Nicotine chewing gum: effectiveness and the influence of patient education in a family practice. J Fam Pract 1987; 25:266-9.
33. Lam W, Sze PC, Sacks HS, Chalmers TC. Meta-analysis of randomised controlled trials of nicotine chewing gum. Lancet 1987; ii (8549): 27-30.
34. Abelin T, Buchler A, Muller P, Vesanen K, Imhof PR. Controlled trial of transdermal nicotine patch in tobacco withdrawal. Lancet 1989; i (8628):7-10.
35. Muller P, Abelin T, Ehrsam R, Imhof P, Howald H, Mauli D. The use of transdermal nicotine in smoking cessation. Lung 1990; 168 Suppl: 445-53.
36. Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, et al. Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomised placebo-controlled double-blind study. Arch Intern Med 1991; 151:749-52.
37. Rose JE, Levin ED, Behm FM, Adivi C, Schur C. Transdermal nicotine facilitates smoking cessation. Clin Pharmacol Ther 1990; 47:323-30.

38. Buchkremer G, Bents H, Horstmann M, Opitz K, Tolle R. Combination of behavioural smoking cessation with transdermal nicotine substitution. Addict Behav 1989; 14:229-38.

39. Hurt RD, Lauger GG, Offord KP, Kottke TE, Dale LC. Nicotine replacement therapy with use of a transdermal nicotine patch - a randomised double-blind placebo-controlled trial. Mayo Clin Proc 1990, 65:1529-37.

40. Hartman N, Leong GB, Glynn SM, Wilkins JN, Jarvik ME. Transdermal nicotine and smoking behaviour in psychiatric patients. Am J Psychiatry 1991; 148:374-5.

41. Sachs DPL, Leischow SJ. Pharmacological approaches to smoking cessation. Clin Chest Med 1991; 12:735-53.

42. Ohlin P, Lundh B, Westling H. Carbon monoxide blood levels and reported cessation of smoking. Psychopharmacology (Berlin) 1976; 49:263-5.

43. Jarvis MJ, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Comparison of tests used to distinguish smokers from nonsmokers. Am J Public Health 1987; 77:1435-8.

44. Schwartz JL. Review and evaluation of smoking cessation methods: The United States and Canada, 1978-1985. NIH publication no 87-2940; April 1987:8-9.

45. Gourlay SG, McNeil JJ. Anti-smoking products. Med J Aust 1990; 153(11-12):699-707.

46. Benowitz NL, Jacob P, Savanapridi C. Determinants of nicotine intake while chewing nicotine polacrilex gum. Clin Pharmacol Ther 1987; 41:467-73.

47. West R, Hajek P, Belcher M. Time course of cigarette withdrawal symptoms while using nicotine gum. Psychopharmacology (Berlin) 1989; 99:143-5.

48. Hughes JR. Dependence potential and abuse liability of nicotine replacement therapies. In: Pomerleau OF, Pomerleau CS. eds. Nicotine replacement: a critical evaluation. Progress in clinical and biological research. Vol 261. New York: Alan R Liss 1988:261-77.

49. Merrell Dow Pharmaceuticals., Inc. Nicorette (Nicotine resin complex): Summary of safety and efficacy, NDA #18-612, undated.

50. Merrell Dow Pharmaceuticals., Inc. Nicorette: Instructions for use. Included in chewing gum package.

51. Merrell Dow Pharmaceuticals., Inc. Physician's guide for nicorette, 1984.

52. Buchkremer G, Minneker E. Efficiency of multimodal smoking cessation therapy combining nicotine substitution with behavioural therapy. Methods Find Exp Clin Pharmacol 1989; 11:215-8.

53. Eichelberg D, Stolze P, Block M, Buchkremer G. Contact allergies induced by TTS-treatment. Methods Find Exp Clin Pharmacol 1989; 11:223-5.

54. Peters JA. Nicotine replacement therapy in cessation of smoking. Mayo Clin Proc 1990; 62:1619-23.

55. Prignot J. Pharmacological approach to smoking cessation. Eur Respir J 1989; 2:550-60.