

Comments and Critique

Skin Patches to Prevent Lung Cancer

SKIN PATCHES for transdermal delivery of the tertiary amine, (S)-3-(1-methyl-2-pyrrolidinyl)pyridine, have recently become available in Switzerland and Germany for the treatment of patients at high risk of lung cancer. In most European countries at least 30% of the population are at high risk, their risk being 10 times or more above that of the general population. Those at high risk are easily identified by asking people one or two brief questions followed by biochemical confirmation with a simple, inexpensive, breath test.

Present indications are that at the recommended dose of one patch per day for 3–4 months some 10–20% of subjects respond to treatment [1, 2]. No serious adverse effects have been reported, but about 5% experience local irritation or hypersensitivity of the skin which may lead to premature withdrawal from treatment. In those who respond, the risk of future lung cancer will be substantially reduced. Fortunately, the risks of cardiovascular disease are also reduced, as are the risks of a variety of other cancers. Although it is easy to identify those at high risk, only crude measures currently exist for identifying those cases most likely to respond to patch treatment. The treatment is, therefore, indicated in all high-risk patients who are well motivated and want to reduce their risks of lung cancer and cardiovascular disease.

For those who have not already decoded our thinly veiled language, we refer of course to cigarette smoking and to the potential of nicotine-containing skin patches in promoting smoking cessation. The importance of cancer prevention, alongside screening, early detection and the search for better cures, was emphasised in these columns recently by Fentiman [3]. He raised the interesting possibility that breast cancer might be prevented in some cases by use of tamoxifen for up to 10 years. He went on to outline plans for the large multicentre trial that would be necessary to detect the small, but worthwhile, effect anticipated, and added that tamoxifen might also decrease mortality from coronary heart disease.

There is little doubt that if tamoxifen were shown to be effective in preventing either breast cancer or coronary heart disease, its prophylactic use would be rapidly incorporated into the daily routine of good medical practice. Could the same be said for the use of nicotine skin patches to prevent lung cancer by helping people to stop smoking? Probably not. Had it been another compound that prevented cancer through a mechanism other than helping people to stop smoking, doctors would have jumped at using the drug. Indeed, some may have been attracted to this article through being unaware at first that it is concerned with stopping smoking.

Why doctors might be more willing to prescribe tamoxifen if it prevented breast cancer than nicotine patches to help people

stop smoking is a complex issue which cannot be fully addressed here. Breast cancer falls strictly within the medical domain while smoking is seen as a personal choice as well as a public health problem involving wider social, economic and political issues. Doctors rightly recognise that the control of smoking is a national problem, requiring major measures that affect the smoking population as a whole. Such measures include large-scale health education and public information campaigns, and regulations and restrictions to control advertising, cigarette yields and price, smoking in public places, the sale of cigarettes to children and so on. These are clearly the responsibility of governments and their health authorities rather than matters for individual doctors.

Despite the scale of the problem, intervention by doctors could have a major impact. Not only are they respected sources of health information and advice, but more importantly, they have repeated face-to-face contact with the great majority of smokers in the population. Some 75% of the population consult their doctor at least once in a given year. Most of these opportunities for intervention are wasted. Although cigarette smoking is generally recognised as far and away the major cause of preventable illness and premature death, no systematic procedure for intervention against smoking has ever been incorporated by the medical profession as an essential component of their routine care of patients. This contrasts with the situation regarding other preventive measures, such as immunisation and cervical smears.

Various reasons may account for the reluctance of many doctors to get involved with their patients' smoking. The lack of clearly effective treatments has engendered a feeling of powerlessness even in doctors deeply concerned by the harm caused by tobacco. Smoking has in the past been regarded largely as a behavioural problem for the individual to resolve by the use of "willpower". There has been no obvious application for specifically medical skills such as the use of drugs, laboratory tests or physical procedures. When advice to stop is given, its effect is usually too small to be perceived by the doctor and, when help with stopping is sought by the patient, the doctor in the past has had little to offer. Lack of time is probably not a fundamental issue and may be related to the doctor's perception of efficacy. Few doctors begrudge time spent on the effective use of the skills that their training and inclination have led them to acquire.

Nicotine skin patches are certainly not a panacea, but should not be regarded as just another quick gimmick. They are the current front runner among a wave of new nicotine replacement treatments that have followed in the wake of nicotine chewing gum. Other new preparations include nicotine lozenges, a nasal nicotine spray and a nicotine vapour inhaler, all in phase III trials. All are based on the results of research over the last decade which has led to better understanding of the nature of cigarette

smoking as a drug-taking activity and as an addiction. This is well documented in the 1988 US Surgeon General's Report, significantly entitled *Nicotine Addiction* [4]. The report's three main conclusions were that tobacco use is addictive, that nicotine is the drug in tobacco that causes addiction, and that the underlying processes are similar to those that determine addiction to heroin and cocaine.

The evidence supporting these conclusions is compelling. Most smokers absorb sufficient nicotine to obtain pharmacological effects. Nicotine influences mood and performance. It acts as a primary reinforcer, induces tolerance, and physical as well as psychological changes occur on withdrawal. Chronic exposure increases the number of nicotinic receptors in many parts of the brain [5, 6], indicating the presence of structural as well as functional changes in the central nervous system of smokers. These may play some part in the difficulties of giving up smoking.

One way to ease these difficulties is to provide nicotine from an alternative and less harmful source. Nicotine chewing gum has been a major advance in treatment for smokers. 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 gum or behavioural methods alone [7].

Several pharmaceutical companies have nicotine skin patches at various stages of testing and they are already licensed for use in two countries. Current patches give blood nicotine levels similar to those of the gum from about 4 h after application, but it is easy to produce higher levels with larger patches or by using more than one patch. Although the patch may not prove more effective than the gum in specialised clinics where intensive support and supervision are available, it will probably have a major impact in medical practice settings, especially primary care. Here the gum has been less successful possibly due to lack of time available to give the instructions necessary to secure compliance. In contrast, use of the patch requires only brief explanation, dosage is easily controlled and compliance is not a problem. Early trials indicate that with relatively brief support, long-term success rates of 10–20% may be achieved among the 50% or so of smokers who are well motivated to stop but go on smoking due to a high degree of dependence [1, 2]. Success rates of this order would have a major cumulative impact. Success rates of 30–40% could be obtained by doctors who wish to give more intensive support. In general, a doctor's time would be better spent giving less support, but treating more patients.

A widely disseminated medically-based treatment strategy is most applicable in countries where the antismoking campaign is "mature" with a majority of smokers who want to stop, but are held back by their dependence. Public awareness of the smoking problem varies widely across Europe, and in some countries close to 50% of doctors still smoke [8, 9]. In these instances the need is for the medical profession to begin with itself.

In conclusion, cigarette smoking is a form of drug dependence requiring medical intervention. Nicotine dependence is clearly an adverse condition involving acquired structural and functional changes which impair voluntary control of smoking

behaviour. The state of nicotine withdrawal after stopping smoking is officially listed in the US (DSM-III-R) as a "nicotine-induced organic mental disorder" [10]. The condition is treatable by temporary nicotine replacement. If treatment is neglected or withheld, the condition tends to persist for many years and carries a high mortality (1 in 4). Quantitative assessment and feed-back to motivate patients and to monitor progress can be obtained instantly by measuring expired-air carbon monoxide (Bedfont, £300) [11]. A more specific and highly accurate measure of exposure is provided by cotinine concentrations (a metabolite of nicotine with a 20 h half-life) in samples of serum, saliva or urine [12, 13] and is sufficiently sensitive for quantitative work at passive smoking levels [14]. In any combination of tests used for comprehensive health screening, serum or saliva cotinine (cost about £5) could prove the most important single measure for predicting the risks of future illness and early mortality. Intervention by doctors against smoking has the scope for achieving real progress in the prevention of many cancers.

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