Occasional Review

Clinical use of nicotine chewing-gum

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Summary and conclusions

Nicotine chewing-gum has recently become available to doctors in Britain for use as an aid to giving up smoking. It produces blood nicotine concentrations similar to tobacco smoking and so relieves symptoms of nicotine withdrawal. Owing partly to the slower rate of absorption of nicotine through the buccal mucosa, however, it does not reproduce the pleasure of cigarette smoking. Indeed, in the early stages it is usually slightly aversive. Optimal use is a skill requiring practice and careful instruction. Since it is an aid rather than easy cure, its use is limited to smokers who want to stop. Earlier trials showed modest advantages over placebo, but improvements in the gum and more experience in its use suggest that long-term success rates of 40% or more can be obtained. It requires little time to administer and is therefore a feasible method for busy doctors.

Introduction

On 9 June 1980 a new product, nicotine chewing-gum (Nicorette), was released in Britain as a prescribable drug to help people give up tobacco smoking. Is it just another short-lived gimmick? Or does it really work? If so, how does it work? For how long should it be given? What kind of smoker is it likely to help most? Do smokers simply become addicted to the gum instead?

Doctors will no doubt receive information from the manufacturers. But, since we have had some experience of its use in clinical trials¹ (M Raw *et al*, unpublished observations) and have also studied blood nicotine concentrations produced by the gum,^{2,3} we thought it would be timely at this stage to consider these questions and to give some practical guidance and suggestions on how the gum might best be used. Definitive answers must await further experience and research.

The product

The nicotine chewing-gum was developed and is manufactured by Leo and Co, Helsingborg, Sweden, but is marketed in Britain by Lundbeck Ltd, Luton, Bedfordshire. It is available in two strengths—4 mg and 2 mg nicotine in each piece of gum. The nicotine is bound to an ion exchange resin which allows it to be released slowly as the gum is chewed. About 90% of the

nicotine is released after 30 minutes of chewing, the rate of release depending on the vigour and rate of chewing.⁴ The nicotine is absorbed through the buccal mucosa and, since the rate of absorption is pH dependent, the gum contains a buffer that keeps the pH in the mouth at about 8.5 as the gum is chewed. Nicotine that is swallowed is largely wasted. Although absorbed in the gut, it is rapidly metabolised in its first passage through the liver to cotinine and nicotine-N-oxide, which are pharmacologically inert.⁵

Nicotine absorption

As fig 1 shows, absorption of nicotine from the gum is slower than from a cigarette. This is partly caused by the slow release of nicotine—30 minutes against 5-10 minutes for a cigarette—but mainly by the small surface area of the mouth compared to the lungs. The gum, however, compares very

Fig 1—Blood nicotine concentrations after chewing one piece of 4-mg gum compared with smoking a cigarette (1.2 mg nicotine) and a large Havana cigar. At least 12 hours' abstinence before testing.

favourably with non-inhaled smoking of a large Havana cigar. This is because the buffer in the gum is more effective than the buffering capacity of cigar smoke in keeping the saliva at an alkaline pH. The rate of nicotine absorption from the gum falls about mid-way between inhaled cigarette smoking and non-inhaled cigar smoking.

Despite the slower rate of absorption, fig 2 shows that with repeated use the 4-mg gum soon builds up blood nicotine

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concentrations similar to cigarette smoking. Several studies have shown that the 4-mg gum produces blood nicotine concentrations and cardiovascular effects, such as increase in heart rate and blood pressure, similar to those produced by cigarette smoking, but that the effects of 2-mg gum are proportionately less^{1-3, 6, 7} (C Nyberg *et al*, unpublished observations). With clinical use, however, the 2-mg gum seems to be satisfactory for most smokers. When allowed to chew according to their own needs (when necessary) they average eight 2-mg gums a day, and this produces blood nicotine concentrations of about half the peak concentrations obtained just after a cigarette¹ (M Raw *et al*, unpublished observations).

Fig 2—Comparison of blood nicotine concentrations while subject smoked one cigarette an hour or chewed one piece of nicotine gum an hour. Urine controlled at acid pH. (Data from Russell *et al*.²)

Theoretical aspects

The purpose of the gum is twofold—firstly, to provide a substitute oral activity during cigarette withdrawal, and, secondly, to provide nicotine by an alternative route to allay those withdrawal symptoms attributable to lack of nicotine. In this way the object is to facilitate cigarette withdrawal by enabling the smoker to tackle it in two stages—a first stage of breaking the smoking habit without at the same time having to overcome nicotine dependence, which is then faced at a later stage by gradual withdrawal of the gum. The two very different plasma nicotine profiles illustrated in fig 2 suggest that the gum is more likely to allay nicotine withdrawal symptoms than to substitute for the effects of the rapid intravenous-like plasma nicotine peaks of inhaled cigarette smoking. It is thus similar to treating heroin addicts with oral methadone. Although oral methadone prevents withdrawal symptoms, it does not produce the positive pleasures of intravenous heroin.

Two studies have shown that the gum has an inhibitory effect on ad libitum smoking. One showed that it reduced the number of cigarettes smoked and the degree of inhalation

(measured by COHb) significantly more than placebo gum.¹ The other showed a significant dose-related inhibition of puffing behaviour.⁸ The fact that it inhibits smoking in smokers who are not trying to stop and that it produces satisfactory blood nicotine concentrations suggests that it should be clinically useful in helping people to give up smoking. As mentioned above, it is likely to provide a more effective form of nicotine replacement for the heavy, addictive type of smoker, who smokes mainly to avoid withdrawal symptoms. That it is theoretically less suited to the less addicted type of smoker who smokes mainly for pleasure should not be a serious disadvantage, since the less addicted smoker has less difficulty in giving up the habit.

Clinical trials

The findings on the clinical efficacy of the gum are at present only suggestive, and a final verdict must await further study. It has a powerful placebo effect, but most clinical trials have shown a modest advantage of active over placebo gum, which suggests that the presence of nicotine does make a specific contribution to enhancing the success rate. Out of five placebo-controlled trials⁹⁻¹¹ (W M Fee, M J Stewart at 2nd European Council on Smoking and Society, Rotterdam, 1978), three showed significantly better short-term success rates in those using the active gum^{9, 11} (W M Fee, M J Stewart). At follow-up after 6-12 months, however, there were no significant differences, although the results were invariably slightly better in the active groups. The long-term abstinence rates ranged from 23% to 35%, which is marginally better than the 15% to 25% range reported for other methods.¹² In two double-blind studies smokers rated the nicotine gum as more helpful than placebo gum¹ (W M Fee, M J Stewart). It was also rated as more satisfying and subjects were more "put-off cigarettes" by it.¹

The tendency to relapse after initial success is one of the main problems of giving up smoking. It is well known that the relapse rate is high over the first three months of abstinence but that it then tails off.¹³ Although other factors could account for this phenomenon,¹⁴ it possibly takes three to four months' abstinence for the strength of the habit to diminish sufficiently to make relapse less likely. In a recent trial in which more prolonged use of the gum was encouraged we have obtained a COHb-validated one-year abstinence rate of 38% for smokers using nicotine gum compared with only 14% for psychological methods such as rapid smoking (M Raw *et al*, unpublished observations). In a subgroup that used the gum for more than three months the long-term abstinence rate was 67%, which agrees with the findings of another long-term study that showed a four-year abstinence rate of 68% in those who used the gum for at least four months.^{14a} These longer-term chewers are obviously a self-selected sample. Also other factors, such as higher motivation and longer contact with the clinic, could have contributed to their greater success. These findings, however, do suggest that it might be worth encouraging smokers to persist with the gum for at least four months.

Another advantage of nicotine gum over other methods is that it is cost-effective in terms of the therapist's time. It takes only a few minutes to encourage the smoker, record progress at each visit, and prescribe the gum, whereas other less effective methods may take far longer. This makes it a more feasible method for busy doctors.

Effect on body weight

Increase in body weight can be a discouraging side effect of success at giving up smoking. Nicotine gum seems to reduce this tendency. In one study the average increase in weight at six-month follow-up was 1.7 kg in subjects taking nicotine gum

compared with 3.0 kg in those on placebo gum⁹; in another study the average weight increases at one-month follow-up were 0.6 kg and 1.2 kg respectively.¹⁰ Weight gain after giving up smoking is not a simple consequence of increased eating, but occurs even if food intake is kept constant. Nicotine has numerous metabolic effects of which the end result is to lower body weight.¹⁵ This effect could be used to enhance the clinical efficacy of the gum.

Adverse side effects

Very few smokers enjoy the chewing gum at first, though many grow to like it later. In the early stages it is usually slightly aversive. Dislike of the taste, irritation of the tongue, mouth, and throat, and occasional nausea are common complaints during the first week¹ (W M Fee, M J Stewart, Rotterdam, 1978) and may deter some smokers from continuing. This is partly caused by excessive chewing which releases the nicotine too rapidly and causes excessive salivation and swallowing of nicotine. Most of these side effects can be avoided by careful instructions (see below). In any case they tend to subside after a few days and are seldom a problem after the first week. Less common side effects are ulceration of the tongue, aching of the jaw due to chewing, flatulence, hiccups and epigastric discomfort, and, rarely, a feeling of faintness or dizziness. The incidence of side effects is now much lower than it was with the earlier forms of the gum. In a recent study in which careful instructions were given on how the gum should be chewed, only nine out of 69 subjects complained of side effects and these were all minor ones (M Raw *et al*, unpublished observations).

Abuse and addiction

The aversiveness of initial use without instructions and the fact that it does not reproduce the pleasure of smoking means that nicotine chewing-gum is most unlikely to be abused or used illegally to any serious degree. Because the absorption of nicotine is slower it is far less addictive than cigarette smoking. Though about 10% of heavy smokers develop some degree of dependence on the gum during clinical use this is not a serious problem¹ (M Raw *et al*, unpublished observations). Most can be encouraged to withdraw gradually without relapse to smoking. Accidental swallowing by small children would not be hazardous as little of the nicotine would be released and any that was absorbed would be mostly metabolised before reaching the general circulation.

Guidelines for clinical use

At this early stage there is no rigid protocol for optimal clinical use. Some basic principles, however, are suggested by the limited experience gained so far. The four most important issues are the selection of subjects, the detailed instructions on how to chew the gum, the dosage, and the duration of treatment.

SELECTION OF SUBJECTS

There is obviously not much point in offering the gum to smokers who do not want to stop. Even if they took it and stopped smoking they would probably relapse later. Since the gum is in no way a panacea or easy cure for smoking and since it is initially aversive rather than pleasurable, its use should be restricted to smokers who are well motivated to give up smoking. For the theoretical reasons discussed earlier one would expect the gum to help heavy smokers more than light smokers, and this was indeed found in one study.⁹ The gum also has a powerful placebo effect, however, which some doctors might

wish to use. Until the issue is clearer it is probably worth trying the gum in all but the lightest smokers—that is, in those who smoke 10 cigarettes or more a day, provided of course that they want to stop smoking and are willing to persevere with the gum.

INSTRUCTIONS ON USE OF THE GUM

Many patients will have unrealistic hopes that the gum will satisfy them in the same way as cigarettes and that it will enable them to give up smoking easily with little effort on their part. It is most important that these false expectations be corrected. They should be warned that the gum will provide little positive pleasure and that it is designed rather to ease withdrawal symptoms; that the taste of nicotine may seem irritating and unpleasant for the first few days until they get used to it; and that success at giving up smoking will depend mainly on their own efforts with no more than a little help coming from the gum. The mechanism of release and absorption of nicotine should be explained. They should be instructed to chew gently to avoid excessive salivation and if the taste gets too strong to stop chewing for a while, leaving the gum in their cheek, until the irritation passes and gentle chewing can be resumed.

We recommend that subjects practise chewing two or three gums a day for a few days to get used to it before their target day for giving up smoking. On their target day they should stop smoking abruptly rather than cut down gradually. The gum should then be used as necessary whenever the urge to smoke is strong, and they should be warned not to expect the urge to subside immediately but that it may take 15–20 minutes. In some instances, if they expect that the urge to smoke will be strong, it may help to start chewing a gum 15 minutes beforehand.

DOSAGE AND DURATION OF TREATMENT

Treatment should start with the 2-mg gum, chewed as necessary as described above. Most smokers manage on about eight pieces of 2-mg gum a day so that a box of 105 pieces should last one to two weeks. Only those who exceed 15 pieces a day need be offered the 4-mg gum. Such smokers are relatively rare, and even among heavy smokers attending our clinic only about 5% require the 4-mg gum.

For reasons discussed above, we believe smokers should be encouraged to continue using the gum for four months even if their daily consumption of gum is low. After four months the gum should be reduced gradually, but only if this is achieved without undue difficulty. Most subjects will find this quite easy, but they should still have a supply available for an emergency and be encouraged to carry it with them, probably for as long as a year. In the few who find it difficult to give up the gum it would be wiser to delay applying pressure to withdraw before about one year.

Smokers who fail to stop within two weeks are unlikely to succeed, at least on the current attempt. If they have not stopped smoking completely after four weeks there is little to be gained by continuing to prescribe gum. It should be used as an aid to cessation and not simply as a means to enable the smoker to reduce cigarette consumption.

CONTRAINDICATIONS

There are no strictly rational contraindications with the possible exception of patients prone to peptic ulcers. Blood nicotine concentrations when it is used as necessary are usually around half the smoking concentrations, and there are no carbon monoxide or other harmful smoke constituents. Although nicotine may have a role in heart attacks and other thrombo-occlusive disorders as well as harming the fetus, the use of gum is if anything less likely to cause harm than continued smoking.

Litigation, however, is not always based on reason, so that caution is advisable in those who are pregnant or have vascular disease, even though reason would suggest that its use is strongly indicated if these patients continue to smoke. Although not a contraindication, many people with false teeth find it difficult to chew the gum.

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MATERIA NON MEDICA

Disposal of the dead

The disposal of the dead is now a well regulated affair. It was not always so, at least not down here in Devon. A glance through parish registers reveals irregularities that could hardly have been expected at the time of death. Sometimes the body was buried in the wrong place, because the authorities were unsure of the proper site for it or interfering relatives preferred that it should lie elsewhere. On occasion, it was exhumed for a time or was not buried at all.

In June 1646 plague struck the village of Hemyock and killed 58 of the inhabitants. All but one of them were given a Christian burial during the following two months, the exception being Elizabeth Marks, who was consigned by her step-father, Mr Gregory Blakemore, to a dung heap ("heed vp in Dung"). Why? The most likely reason would seem to be parsimony, since many people then resented having to pay the registration fee. On the other hand, the county was in a turmoil during the closing stages of the Civil War and a sharp outbreak of plague in a small town ordinarily caused the panic exodus of all who had somewhere else to go. In this instance the rector may have fled, for the burial services were held after the epidemic had subsided. Yet Blakemore was presumably there when Elizabeth died, as he arranged her sinister disposal. Was he moved by hate or spite or just a confused state of mind in trying circumstances? On the face of it, he shows up rather poorly, but he could still be exonerated if a more charitable explanation comes to light from some obscure documentary source.

Twenty years later in South Pool, a remote village near the south coast, a very different situation arose. The rector, the Rev William Streat, died and was buried in June, having previously promised marriage to a Miss Dorothy Ford. In November of the same year his body was exhumed and a marriage ceremony was performed. He was not reinterred until nearly two years later, in August 1688. The parochial archive states: "The surname 'Ford' is still a much respected one in the parish." While the exhumation can be easily explained, no record exists of the whereabouts of the rector before he was finally laid to rest.

It is difficult to feel other than sympathetic towards Mr William Austin, who, in 1711, pleaded guilty at Colyton to "stealing goods to the value of 42 shillings, together with six-and-twenty cups and two buckets." He was duly hanged at Heavy Tree gallows and was interred nearby. Somebody must have had second thoughts about him as he was subsequently removed and given a decent burial in the churchyard. In 1832, again in Colyton, a plaintive call from beyond the grave was unexpectedly answered, so it appears. According to the Bishop's register, the remains of a woman were removed because "the deceased

desired to be buried with her father and mother in the family vault at Crediton church."

Such procedural deviations seem not to have been permitted since the Registrar-General undertook responsibility for the registration of deaths in 1837.—NEVILLE C OSWALD (retired consultant physician, Thurlestone, Devon).

Memento mori

Cities and thrones and powers
Stand in time's eye,
Almost as long as flowers,
Which daily die;

Measured in feet the crest is not high and in metres it seems nothing until, that is, you walk up it. The bostal which begins in front of the house winds up the steep northern side but is so cut up by one of the plagues of this age—fat little girls on ponies—that it is pleasant to climb only in times of drought or hard frost. Near the top are three thorn trees, and, if you walk up there on Christmas Day, you will find two bunches of flowers hidden among the dried grass at the foot of one. Each year since the war, except in 1977, the flowers have been placed there on Christmas Eve. Always the same—three pink carnations, three yellow chrysanthemums, a little bunch of freesia, a sprig of box, a spray of fir—all carefully pegged down. There they lie under the frost and snow until in a few weeks the rain will wash them away.

There is something Teutonic about the evergreen, but I have really no idea how the flowers get there each year. More than one crippled plane in the war crashed near the spot and young men died. One year, inspired by a vulgar curiosity, I climbed up each day. On the 23rd there were no flowers but the next day there they were at the foot of the same tree. Only a dark-haired middle-aged man was on the crest and, when I asked him about the flowers, he clearly thought that I was crazy and hurried away. Now I accept the mystery and keep some fantasies. Like Robert Frost, "I could say 'Elves' . . . but it's not elves exactly . . ." Perhaps a white-haired lady in a landau, the arthritic coachman climbing down and taking from her hands the two bunches. Or perhaps a widow, no longer young, brings her two grown-up children. They stop for a minute to look along the crest to where the sheep graze and the tractor turns under a cloud of gulls and where once were only the anti-aircraft guns and the searchlights.

So each age creates its legends, though ours may be less lasting than the tumuli and giant stones of our ancestors.—DENIS PIRRIE (retired psychiatrist, Hants, Sussex).