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REVIEW

Pharmacological approach to smoking cessation

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ABSTRACT: At present, the possibilities of pharmacological intervention in smoking cessation remain limited. Some products, like smoking deterrants, lobeline, amphetamine and sedatives, definitely seem to have been rejected. The efficiency of other drugs aiming to treat the withdrawal syndrome (*e.g.* clonidine) or to eradicate the smoking habit (*e.g.* mecamylamine) must still be confirmed in large controlled trials. The same is true of the "cigarette substitutes" which have appeared recently. The only effective substitute treatment currently available is nicotine, presented as nicotine gum; other modalities of administration of nicotine are in preparation. Even if it has not fulfilled all the expectations of its promoters and of the smokers who hoped for a panacea, nicotine gum, when administered to highly dependent smokers motivated to stop, with the appropriate technique, effects a moderate increase not only in the cessation rate but also in the long-term abstention rate, in so far as the necessary psychological support is provided, either by the physician in medical settings, or by other health professionals, in smoking-cessation clinics or in industrial and community settings. The addiction to psychoactive nicotine presents only one facet of the smoking process in chronic smokers. They must also be helped to face the behavioural components of their habits, so individualized counselling remains essential, in addition to the prescription of the gum, in order to achieve satisfactory rates of long-term smoking cessation.
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In spite of the overwhelming evidence of health hazards resulting from smoking tobacco, many health professionals, including physicians, fail to treat smokers. This reluctance probably stems from an inadequate medical training in smoking cessation, together with a lack of awareness of behavioural literature on the subject. Most health professionals are adepts of the "will-power" theory of smoking, which should be replaced by a "supportive attitude". Most of them (up to 96%) believe that they cannot change the smoking habit, and even more, think that smokers' treatment is not their responsibility. Finally, the low success rates of nicotine gum in medical practice have had a discouraging effect on their prescribing attitude [1]. However, data from the 1983 Health Interview Survey (USA) indicate that physicians have contact with at least 70% of all smokers each year, and with 61% of smokers who consider themselves to be in excellent health. When attempting to give up smoking, many smokers (perhaps 10%) seek advice and assistance from their physicians [2], and recent studies have shown the importance of physicians' counselling [3, 4].

A medical intervention during an individual clinical approach (even due to reasons other than tobacco related diseases) appears to be a cessation strategy with an excellent cost/effectiveness ratio, especially among patients who are motivated to give up smoking (*e.g.* post-myocardial infarction patients, who have been given formal advice to stop smoking) [5], in so far as the physician has a comprehensive view of the motivations to smoke.

The smoking habit depends on two groups of determining factors: behavioural determinants inducing the psychological dependency, and pharmacological determinants inducing the physical addiction due to the psychoactive character of nicotine.

Among the behavioural determinants are social reinforcements (reinforcement: consequence which strengthens a behaviour pattern) [6] like peer pressure, (most important among young people), conviviality, gratifying peripheral stimulation of the senses (flavour, taste, deep tracheal stimulation, vision, touch) and conditioned reflexes (smoking initiated by the end of a meal, coffee drinking, driving in slow traffic, looking at TV, performance demands, anxiety and stress).

The rapid, transient and dose-related central nervous system (CNS) activities of nicotine are well known. Its biphasic activity pattern can be used by the smoker as an effective "coping response" to the demands of daily living: arousal, alertness during smoking followed by relaxation, particularly in stressful situations induce temporary improvements in task performance and memory, and in affect (anxiety relief, pain reduction). These positive reinforcements can be modulated by the smoker through voluntary variations of smoking pattern by taking more puffs, larger puffs or inhaling deeper than usual [7] resulting in repeated "shoots" of high cerebral nicotine

concentration, so that the smoker finally becomes nicotine-addicted [8]. Nicotine, stimulating the release of endogenous neuroregulators, like beta-endorphin, acetylcholine, catecholamines, dopamine, etc, which have important behavioural effects, can be used by smokers to regulate the body's normal adaptative mechanisms in response to stressful stimulation.

Once an addiction to nicotine has been acquired, the smoker needs a cigarette in order to be released from the withdrawal symptoms appearing when the cerebral nicotine level is falling (negative reinforcement) [9].

In most smokers, both behavioural and pharmacological determinants are interactive, and their relative strength can vary from smoker to smoker and, in the same subject, can vary with time, the central physical dependence usually becoming dominant with the passage of time [10]. Furthermore, nicotine dependence is becoming more prevalent in smokers, due to a selection process, the successful "quitters" being the less dependent on nicotine.

The behavioural anti-smoking strategy of the physician facing a smoker includes emphasizing the risk of smoking and its reversibility, and the relationship between current symptoms and smoking, simple advice to stop, the loan of self-help guides, asking the patient for a commitment to stop smoking, eliciting a firm date for giving-up, if necessary prepared by a short period of brand-switching towards low nicotine cigarettes or of nicotine-fading [11], emphasizing the transient character of the withdrawal symptoms, and sometimes, extensive counselling with scheduled follow-up, if necessary by telephone contacts, or finally referral for more intensive treatment in specialized facilities like 5-day plans or smoking cessation clinics [12].

These interventions, focusing on the psychological component of tobacco dependency, obtain valuable although modest results in the clinical setting, personal encouragement having been shown to improve the success rate of those who try to give up smoking on their own [13]. A 20% average success rate for all smoking cessation methods was reported by HUNT and BESPALEC [14], with relapse rates of 70–80% within 1 yr.

At least, some of these numerous failures with habitual smokers are due to the physical dependence on nicotine, the intake of which averages 1 mg per cigarette, and which possesses all the characteristics of addictive substances: immediate pharmacological reward, rapidly increasing tolerance, abstinence symptoms on withdrawal and a strong tendency to relapse.

In the remainder of this paper, we shall address the issue of pharmacological treatment of smoking dependency.

Drugs used in smoking cessation

Smoking deterrents

They produce an unpleasant metallic taste in the mouth of individuals who consume tobacco products in conjunction with them. Formerly, several astringent mouth washes were prepared mainly from silver nitrate, copper sulphate and potassium permanganate. Silver citrate was also used in the form of a lozenge. It induced argyrism in 2 cases using up to 50 times the recommended dosage [15, 16]. When used as a chewing-gum (Tabmit®), the safety of silver acetate seems established [17]. Its efficiency as a method of giving up smoking, suggested in ROSENBERG's controlled study involving 60 smokers, (11 quitters out of 30 after 2 weeks with Tabmit® *vs* 5 quitters out of 30 with placebo) is not definitively established, since that study relied entirely upon smokers' own reports for outcome measures [18].

MALCOLM *et al.* [19] have recently assessed the efficacy of silver acetate chewing-gum in a double-blind placebo controlled study involving objective measurements of subjects' levels of smoking prior to treatment, after three weeks of treatment and at four month follow-up. Among 400 subjects recruited through advertisements in local media, 285 attended an initial visit, were instructed to chew the "Tabmit®" chewing-gum, containing 6 mg of silver acetate 6 times per day, to continue to smoke for the first week, to choose a stop-smoking date between day 8 and 17, and were controlled at day 21 and day 150 (carboxy haemoglobin (HbCO) blood measurements and nicotine plus cotinine urine measurements). The subject drop-out rate was 45%. There was minimal medical or psychological intervention. After 3 weeks, there were 1.1% quitters (15 out of 136) with silver acetate *versus* 4% (6 out of 146) with placebo. After 4 months, the abstention rate was 7% (9 out of 136) after silver acetate and 3% (4 out of 146) after placebo. Adverse effects observed among the "completers-group" of 155 subjects were more frequent with silver acetate than with placebo for gastrointestinal complaints (nausea, heartburn, abdominal cramps) and oral complaints (bad taste with foods, dry mouth, a green tinted tongue). No subjects demonstrated any evidence of argyrism.

These results are evidently modest in the context of giving up smoking. Perhaps the aversive conditioning mechanism of silver acetate action is better suited to preventing recidivism. Perhaps also the results might be more encouraging if the product was used in a setting of more intensive multi-component aversive conditioning strategy.

Pharmacological treatment of nicotine dependence

Nicotine dependence, like any other drug dependence, can be basically treated by three types of approach [20].
1) *Substitution therapy.* A more manageable form of the drug is provided, according to a pre-arranged maintenance protocol (*e.g.* methadone for opiate dependence). If some of the difficulty in stopping smoking is due to withdrawal of nicotine, then its temporary replacement should help [21].
2) *Blockade therapy.* The effects of the abused drugs are blocked by pre-treatment with an antagonist (*e.g.* naltrexone for opiate dependence), so that an 'extinction' of the drug use can be expected.
3) *Non-specific supportive therapy.* Symptomatic treatment of withdrawal symptoms (*e.g.* benzodiazepines during alcohol detoxification).

Substitution therapy

Lobeline. Lobeline sulphate, a partial nicotinic receptor agonist, pharmacologically related to nicotine, is no more effective than a placebo [14, 22], probably since it cannot mimic the full range of pharmacologic actions of nicotine [2, 23]. Lobeline exists in over the counter preparations: Nikoban®, Bantron®, Lobidan®, (lozenges or chewing-gum of 2 mg).

Amphetamines. D-amphetamine is a non-catecholamine sympathomimetic drug also acting on the CNS and mimicking the CNS stimulating effect of nicotine. When administered to smokers, it enhances the pleasure gained by smoking and increases the smoking behaviour: it is thus not an adequate substitute for nicotine [24]. Acute increases in cigarette smoking were reported as a function of dextroamphetamine administration [22, 25].

Sedatives. Sedatives and anxiolytics mimicking the sedative effect of nicotine are ineffective aids to cessation (diazepam, phenobarbital, hydroxyzine, meprobamate) in either in the acute or longer term [26–30].

Nicotine. The combined dual (stimulating and sedative) action of nicotine seems essential for the reinforcement of smoking. In order to satisfy the nicotine-dependence of the smoker, nicotine seems irreplaceable at present but should be administered by a vehicle other than smoking. Given the very high toxicity of nicotine (lethal dose 40–50 mg *per os*), tablets, lozenges or injectables cannot be used, on account of the risk of nicotine poisoning, since the product must be administered by the patient himself.

Nicotine chewing-gum (Nicorette®). Mixing nicotine with a resin ion-exchanger chewing-gum allows a slow release of small doses of nicotine which are readily absorbed *via* the buccal mucosa thanks to the bicarbonate buffer. Some regulation of the nicotine intake is allowed by modifying the intensity of chewing, in the same way that cigarette regulation is obtained by modifying the smoking pattern. The use of this sugar-free nicotine chewing-gum was first proposed by FERNO *et al.* [31]. The risk of intentional or accidental nicotine poisoning is limited, since nicotine once swallowed, is fully metabolized during its first passage through the liver to pharmacologically inert derivatives. Furthermore, the extraction of nicotine from nicotine gum is incomplete, averaging 53% and 72% from 2 mg and 4 mg gum respectively, and highly variable (more than two-fold) in different people [32].

Efficacy of nicotine chewing-gum. Among 14 studies concerning nicotine chewing-gum, submitted to the Food and Drug Administration (FDA) by the producer, twelve were rejected either for lack of efficacy or for critical flaws in design, conduct or analysis, the two remaining studies showing some evidence of the efficacy, but being insufficient to meet the standards for FDA approval [33]. After 2 new studies [34, 35] had been submitted, the FDA admitted that nicotine gum increased the likelihood of smoking cessation among participants in acceptable counselling programmes.

The study of JARVIS *et al.* [34] included 116 heavy smokers, attending a hospital based anti-smoking clinic: this study population was probably not representative of all smokers, and shows an extraordinary degree of compliance (more than 90% of the participants at the one year follow-up visit!). Furthermore, the clients were followed by an experienced therapist! The abstinence rates with nicotine gum are 48% at 1 month and 31% at one year, compared with 24 and 14% respectively in the placebo group.

In the study of CHRISTEN *et al.* [35], 208 cigarette smokers recruited from the Indiana University Campus and nearby community by posters and newspaper advertising, and reporting a desire to stop smoking, were included and randomly distributed into an experimental group (nicotine gum 2 mg) of 105 and a placebo group of 103 (gum without nicotine). The smokers' own reports of giving up were checked by an expired breath CO value of less than 8 ppm. The 51 dropouts were considered as failures. Success rates were 34.2% and 12.4% for nicotine gum at 6 and 15 weeks respectively *versus* 10.7 and 4.8% for the placebo group. The difference between nicotine gum and placebo was more marked in heavily dependent subjects (46%) than in less dependent subjects (29%). The modest success rates must be interpreted in the setting of a minimal, impersonal stop-smoking cessation programme.

Recently [36], trials were conducted comparing maintenance treatments with nicotine gum alone, behavioural therapy, and both combined. The abstinence rates, biochemically verified, were 23%, 30% and 50% respectively after 10.5 months in the Stanford Trial and 37%, 28% and 44% after 52 weeks in the University of California trial. Nicotine gum combined with considerable psychological support thus produces high long-term abstinence rates, certainly better than either method in isolation.

Those studies do not concern patients examined in medical settings. A recent work of TONNESSEN *et al.* [37, 38] addresses smokers consulting the clinic of the department of Pulmonary Diseases of the Gentophe Hospital in Copenhagen, where smokers were recruited through a poster in the waiting room. Of 292 initially interested people, interviewed by a physician, 202 returned questionnaires, and 173 were enrolled in the study. The degree of nicotine dependence was assessed through a modified Horn-Russel rating scale based on answers to nine questions; smokers with scores of 19 or more were classified as highly dependent, the others as having medium or low dependence on cigarettes.

The treatment consisted of six group counselling sessions (psychological counselling with nonspecific support and encouragement) led by a physician during the first four months, for groups of 12–15 members, mixing smokers of 3 treatment groups: placebo, 2 mg and 4 mg nicotine gum. For the 60 highly dependent smokers, the study was a dose-response one, the smokers being given either gum containing 4 mg of nicotine at first, followed after 6 weeks by gum containing 2 mg of nicotine (n=27),

or gum containing 2 mg of nicotine for the entire test period (n=33). The 113 smokers with medium or low dependence were given gum containing 2 mg of nicotine (n=53): this was a blind placebo controlled study since the different gums did not differ in appearance and taste. The recommended dose (free of charge) was 6–14 pieces per day for the first 2 months, with gradual reduction thereafter. Subjects' abstinence from smoking was validated by CO monitoring of the expired air during each session and at 12 and 24 months. Plasma nicotine and cotinine were also controlled at the first session. The Horn-Russel rates scoring correlates with the concentration of CO in expired air and with the plasma nicotine and cotinine concentrations. In highly dependent smokers, the percentage of abstinence at 12 months was 44% with the 4 mg gum and 12.1% with the 2 mg gum, and at 24 months, 33.3% and 6.1%, respectively (differences significant at the 5% level). Similar one year success rates are reported for smokers highly dependent according to the FAGERSTRÖM questionnaire (>6), namely 46% for users of the 4 mg gum, and 18% for users of 2 mg gum [39]. In smokers with medium or low dependence, the success rate at 12 months was 38% with 2 mg gum and 22.6% with the placebo gum (not significant), but at 24 months 28.3% and 9.4%, respectively (significant at the 5% level). Nicotine gum had no influence on weight gain.

This dose-response and placebo controlled study conducted in a medical setting has important implications. It shows the usefulness of grading the nicotine dependence for the choice of treatment, the use of 4 mg nicotine gum being imperative in highly dependent smokers. It confirms the former success rates of FAGERSTRÖM [39] showing a larger difference between nicotine gum and placebo in highly dependent *versus* less dependent smokers. It shows that nicotine gum (2 mg) (associated with nonspecific psychological group counselling) has more than a placebo effect in medium and low dependent smokers. It shows that nicotine gum, associated with group counselling, is useful even in medical settings, and not only among the highly selected population consulting smoking cessation clinics. Finally, the nicotine gum appears to help not only in the initial phase of giving up, probably as a treatment of the withdrawal syndrome, but also in the long-term, with clinically significant abstinence rates at 1 and 2 yrs.

The results of TONNESSEN *et al.* [37] contrast with those of the British Thoracic Society [40] conducted in 95 different hospitals or chest clinics, where smokers mostly with medical conditions related to smoking, were entered into the study, conducted in the course of routine clinical work. The very low overall success rate at 1 yr (9.7%) seems to indicate that with or without nicotine gum, isolated routine medical advice of smoking cessation can be of some help [3], but does not by any means reach the level obtained after an organized cessation programme, reinforced by nicotine gum in patients willing to participate. Apparently, many of the patients of that trial received instructions from doctors with minimal experience in the use of the gum [41]. Furthermore, the number of gums used per day is not mentioned, and 90% of the smokers claim they still use the gum at three months, although most are still smoking, evidently an inadequate treatment. Finally, the conclusions of a study including patients with smoking-related diseases cannot appropriately be extrapolated to the predominantly healthy general-practice population [42].

The only controlled trial of the gum in 6 general practices concerning 24 physicians was inconclusive: it showed a non-significant advantage for nicotine gum over placebo at six months (13.9% *vs* 11.1%) [43]. Its conclusions are subject to criticism since, with the size of the sample (200), the likelihood of detecting a difference at the 5% level of around 10% against 5% is only 40% [44].

LAM *et al.* [45] concluded from their meta-analysis of randomized controlled trials of nicotine chewing-gum that the proper use of nicotine gum in specialized clinics increases the rate of patients stopping smoking; the use of the gum in general medical practices remains questionable. In these practices, attending patients do not necessarily wish to stop smoking, and are probably less dependent on nicotine than the clients attending smoking cessation clinics, who all wish to stop. The psychological advice is also less specialized than in smoking cessation clinics. Both factors can contribute to the difference in results in both settings [11, 46].

In a community health setting (North Karelia project), PUSKA *et al.* [47] conducted a 4 mg nicotine gum - double-blind placebo controlled trial. Subjects receiving nicotine gum succeeded in stopping smoking more frequently than those receiving placebo gum (quit rate 70% *vs* 55%). The difference in abstention rate persists, but not significantly, at 6 months (35% *vs* 28%).

A smoking cessation trial with nicotine gum but without psychological support was conducted in 161 of 1500 men aboard HMS Hermes, who received an unlimited supply of cheap cigarettes: at 3 months and 1 year, 11% only were abstinent [48].

Recently (1987), KORNITZER *et al.* [49], working in an industrial setting, showed that the highly dependent smokers reached at one year a significantly higher abstention rate when starting with 4 mg than with 2 mg gum (33% *vs* 19%, respectively).

It can be concluded [50] that none of the placebo controlled double-blind studies are adequate in the sense that their findings cannot be generalized to the whole smoking population. Furthermore, in many trials, the follow-up begins from the initiation of Nicorette treatment and not from the time the gum is no longer provided. Since a sizeable number of people are still using the gum after several months, the effective duration of the follow-up has to be greatly reduced [51].

Mode of action of nicotine chewing-gum. According to the producer, with the aid of nicotine chewing-gum, the smoker is supposed to break the dependence on tobacco in two stages:

1) the habit of smoking, without experiencing withdrawal symptoms after cigarette cessation;

2) the nicotine dependence, by gradual reduction of the gum-consumption.

Nicotine chewing-gum also provides a substitute oral activity during cigarette withdrawal [52]. The symptoms of the withdrawal syndrome show large variations from

smoker to smoker in type, intensity and duration; they are relatively mild in comparison with those of ethanol or barbiturate withdrawals. They return to normal upon resumption of smoking [53].

The following symptoms have been described, besides decreased heart rate:
1) affective symptoms: irritability, anxiety, inability to concentrate, total mood disturbance;
2) hunger;
3) craving for cigarettes (defined as an extreme desire for a cigarette), increasing as the day progresses; craving is the earliest, the most consistent and the most severe symptom of cigarette withdrawal [54], playing an important role in maintaining the habituation;
4) impaired psychomotor performance;
5) insomnia.

Most symptoms of the withdrawal syndrome reach maximal intensity 24–48 h after cessation and gradually diminish in intensity over a period of 2 weeks [55]. Symptoms 2 and 5 are not substantially relieved by nicotine gum [34, 56–59]. Craving for cigarettes drops more sharply over time in totally abstinent than in partially abstinent smokers during a two week period of observation [60].

Nicotine chewing-gum increases nicotine plasma levels to values at about a third (with 2 mg) and two thirds (with 4 mg) of the levels found after smoking and remain unchanged during 3 months [61–63]. No wonder in these conditions that, in controlled and validated trials, the desire to smoke (craving) is only reduced (and not eliminated) and that the abstinence-associated discomfort is only lessened [58] during the first week of abstinence. After 4 weeks of treatment with nicotine gum, the urge to smoke initially present in 58% of the subjects, declines to 35%. Increased hunger remains a problem, even at the fourth week [64].

Weight gain is very common among those who stop smoking, for one or more of the following reasons:
1) nicotine is considered as an appetite suppressant, so that an improved appetite after cessation may increase calorie intake [34];
2) metabolic changes can occur after cessation [65, 66], short-term observation demonstrating that 24 h smoking increases energy expenditure during 24 h, by approximately 10% [67];
3) withdrawal from nicotine may also cause an exsmoker to crave high calorie sweet tasting foods [68].

A high dependence index for nicotine is a predictor for a higher weight gain after giving up and, at least among those who were heavy smokers, a strong negative correlation exists between weight gain and number of pieces of nicotine chewed daily [69, 70]. Weight gain among quitters (at 6 months) is higher (3.1 kg) among infrequent users of nicotine gum than among frequent users (2.2 kg) [71]. The level of blood nicotine obtained with the 2 mg nicotine gum is not sufficient to alleviate hunger and eating [56] so that use of 4 mg strength nicotine gum can be considered in order to achieve a better control of weight gain. Furthermore, it is possible that use of nicotine gum simply delays weight gain, the weaning from nicotine chewing gum being followed by a new increase in weight. Dietary restraints are in any case, imperative. Finally, nicotine gum does not seem effective in reducing the level of smoking in smokers who are not trying to stop smoking [55].

Side-effects of nicotine gum. The immediate adverse effects of the gum are the following: hiccups, nausea, belching and even vomiting, together with burning throat and mouth (pH 8), aphthous ulcers, gastritis and jaw muscle ache. The stiffness of the gum can cause problems in subjects with dentures (gum sticking).

As many as 40% of the users undergo these effects, which abate over time and also by chewing more slowly. The bad taste of the gum is frequently mentioned by smokers, but seems to be a factor favouring the progressive weaning and avoiding dependence on gum! The long-term risks of nicotine gum remain to be established. The gum shares the potential adverse effects of nicotine, a contributor to the cardiovascular effects of smoking, to peptic ulcer disease (since a substantial amount of nicotine is swallowed), and to low birth weight and increased perinatal morbidity and mortality in women smoking during pregnancy.

Contra-indications. Nicotine gum should be avoided or at least used with caution in persons with peptic ulcers, oesophagitis, cardiovascular disease (recent myocardial infarction, serious arrythmias, severe angina pectoris, hypertension), pregnancy and breast feeding, temporal-mandibular joint disease, insulin-dependent diabetes and hyperthyroidism [11].

Modalities of treatment. The rationale and expected results of chewing-gum therapy should be discussed with the patient. Each gum must be chewed gently, slowly, with pauses as soon as they experience a taste or tingling, without swallowing, for 20–30 min, a technique which allows the release of 91% of the nicotine content of the chewing-gum [31]. Smokers should practice chewing 2–3 gums a day for a few days to get used to it before the target day for giving up smoking. On their target day, they should stop smoking abruptly [52].

Nicotine chewing-gum is useful in nicotine dependent smokers, who can be detected through the FAGERSTRÖM [72] or the HORN-RUSSEL questionnaires [73]. The more dependent the smoker, the more useful is the chewing-gum [39]. In highly dependent smokers, the 4 mg dose is more adequate while the 2 mg dose is useful in moderately dependent smokers. Smokers with high cotinine blood levels are also more likely to be helped by nicotine gum [74].

Nicotine chewing-gum is intended to *replace* the nicotine of cigarette smoke: its concomitant use with cigarettes should be avoided. As many as 30 gums per day can be used, as soon as the craving for smoking develops; most people do not chew more than 10–15 pieces a day. Since most relapses of smoking occur during the first 3 months after quitting [75], some chewing-gum use should be maintained at least during this period. Frequent office, telephone or letter follow-ups should be planned to provide the necessary support. The low risk of permanent addiction to nicotine chewing-gum (3–7%) has been confirmed in several clinical trials [34, 70, 76],

although TONNESSEN *et al.* [37] recently referred to 15% of their smoking abstainers still using the gum after 2 yrs.

In a randomized, double-blind, placebo-substitution trial, HUGHES *et al.* [77] demonstrated in eight exsmokers who had stopped smoking with the aid of nicotine gum and had used the gum for longer than the recommended three months, that withdrawal symptoms appear during the week of placebo-gum administration. Subjects using nicotine gum can thus develop a physical dependence on it: in 2 cases, smoking relapse was observed. Similar data were obtained by WEST and RUSSEL [78]. The best way to avoid withdrawal discomfort seems to be the gradual reduction of nicotine gum.

Conclusions. When used correctly, nicotine gum is evidently a useful pharmacological adjunct in nicotine dependent inhaler smokers [51], seeking help for quitting, either in specialized smoking cessation clinics, or in other medical facilities, in so far as its prescription is included in a minimal smoking cessation programme. The use of the gum in general medical practice, without the necessary psychological help remains questionable.

However, its acceptability to smokers remains limited, and at best, its long-term success rates obstinately remain at 30–40% [79]. Once the gum is discontinued, many return to smoking, at least after short treatment periods.

A more individualized approach and possibly better results would be possible if a range of other nicotine substitutes suited to the different clinical problems were accessible, for use separately or in combination.

Alternative routes of nicotine delivery

Transdermal nicotine. The transdermal route might have three significant advantages over chewing-gum:
1) it would avoid the bad taste and gastrointestinal symptoms associated with nicotine gum;
2) it would facilitate compliance to treatment by use of a long-acting patch, minimizing the effort required from the patient;
3) it would be used in some patients for whom the gum is contra-indicated (peptic ulcers, dentures, etc).

Preliminary results [80, 81] suggest that transdermal nicotine may help smokers resist the increase in cigarette craving after deprivation, and that further investigation is desirable.

Nicotine nasal solution. Preliminary results [80, 82–85] show that nasal nicotine solution is rapidly absorbed, but that a wide range of blood concentrations, varying from one individual to the other, is observed: the overall mean with the 2 mg nasal nicotine solution is between cigarette level and gum level. Nasal administration, probably in a spray, has considerable potential as a treatment aid complementary to nicotine gum.

Nicotine aerosols. BURCH *et al.* [86] suggest that aerosolized nicotine may be useful in smoking cessation since it provides rapid peak levels analogous to smoking.

Tobaccoless smoke-free cigarette. JACOBSON *et al.* [87] described briefly in 1979 a tobaccoless smoke-free cigarette (Favor) allowing inhalation of nicotine vapour, and obtaining serum nicotine levels approximating those measured following cigarette smoking. There is a lack of adequate data on this product, already on sale in the US without medical prescription. A real pulmonary resorption seems unlikely since a whole inspiration cannot be sucked through the device [79].

Behavioural substitutes for nicotine. Nicotine stimulates catecholamines and beta-endorphin release in circulating plasma. Now, these endogenous substances have been shown to influence behaviour and subjective state (namely in provoking pain reduction and alleviation of anxiety, and even giving a rewarding effect). Since physical exercise also has powerful effects on neuroregulators, including catecholamines and endogenous opioïds, it can be expected that deep breathing, muscle relaxation or aerobic exercise, or even intake of dietary precursors of neuroregulators might help exsmokers to cope with the demands of daily living without using nicotine [88].

Sustaining nicotine blood levels. Prescribing sodium bicarbonate or other alkalizing agents results in an increased urine alkalinity which could sustain nicotine plasma levels. This effect seems somewhat trivial [89] so that this strategy has only a few proponents. On the other hand, acid loading which results in a large increase in renal excretion of nicotine, results in an 18% compensatory increase in the intake of nicotine from cigarette smoking [90].

Blockade therapy: nicotine antagonists

Drugs blocking the rewarding effects of nicotine could theoretically be used as agents of extinction. Unlikely to aid initial cessation, they may have a role in helping to prevent relapse, by suppressing the reinforcements obtained by smoking. Since the main behavioural effects of nicotine are mediated centrally, through cholinoceptive sites resembling those in autonomic ganglia, ganglion blocking drugs were experimented with in this setting.

Hexamethonium and chlorisondamine administered systemically, block the peripheral nicotine receptors but fail to block the behavioural effects of nicotine because they do not penetrate well into the central nervous system [27]. The same is true for metoprolol (2×80 mg), a cardioselective β-blocking agent (Lopressor®) and for oxprenolol (2×100 mg: Trasicor®), a non-selective one, which were of no specific value in assisting smoking withdrawal [91]. Propranolol, another β-blocking agent, appeared ineffective in a large double-blind study [92].

Another approach of the ganglion blockade is a topical application of anaesthetics over the sphenopalatine ganglion which could decrease the physical discomfort of nicotine withdrawal [93]. Of 27 heavy smokers, initially included in the trial, 17 had a minimum of 6 treatment days (nasal introduction of bupivacaïne, cocaïne, or saline with a cotton-tipped applicator). The symptom score (withdrawal symptoms) was significantly lower and diminished more rapidly in the experimental treatment

group than in the control group. A four week success rate of 91% was obtained in those patients able to complete the treatment phase.

Mecamylamine, a centrally and peripherally acting blocker of the C_6 nicotine receptors, which are most relevant to the action of nicotine derived from tobacco [55], acts at doses which have no untoward effects [94] and reduces the satisfaction and other effects of cigarette smoking [95]. Used in acute trials on heavy smokers, it induces an increase in the number of cigarettes smoked [27, 96, 97]. In an open, uncontrolled study [98] mecamylamine seemed to block the effects of nicotine and to reduce craving. After a few days without smoking, most of the subjects nevertheless relapsed. Further controlled double-blind studies are evidently needed on the chronic effects of mecamylamine, in smokers highly motivated to give up or for whom nicotine is contra-indicated. Pempidine would probably have the same advantages and disadvantages as mecamylamine [27].

In fact, smokers frequently select other options rather than antagonist treatments, which have no reinforcing properties [94]. Blockade therapy may thus have a role in preventing relapse rather than in helping initial cessation [27]. In any case the potential complications of ganglionic blockade (orthostatic hypotension, ileus, urinary retention) could interfere with the generalized use of this treatment.

Symptomatic treatment of withdrawal symptoms

Clonidine. Central noradrenergic activity, the cell bodies for which are principally located in the locus caeruleus of the brain stem, seems to be increased during withdrawal from opiates, alcohol and cigarettes, this being a common feature of their pathophysiology. Clonidine (Catapressan®, Paracefan®), an alpha$_2$-noradrenergic agonist of the presynaptic autoreceptors which acts as a brake on the production of the presynaptic transmitter and thus provokes a decrease of noradrenergic activity in the locus cearuleus, could decrease the withdrawal symptoms.

Among 15 heavy smokers experiencing withdrawal symptoms in the morning, forcing them to smoke before they had breakfast, clonidine (0.2 mg) as well as aprazolam (1.0 mg) (a benzodiazepine-like substance) did better than a placebo in reducing anxiety, irritability, tension and lack of concentration during 7 h after drug intake [54, 99]. Clonidine appeared better than aprazolam and much better than a placebo in inhibiting the craving for cigarettes, and appeared to increase its activity during the day, whilst craving usually increases as the day progresses.

Reducing the withdrawal symptoms does not necessarily imply a facilitation of smoking cessation, since the smoker may continue to smoke because he derives rewarding effects from smoking, and not because he experiences withdrawal symptoms after stopping!

A double-blind, randomized trial was designed among 71 heavy (mostly highly dependent) smokers who still wished to stop smoking after unsuccessful former cessation, and who followed a behavioural smoking cessation programme [100]. The clonidine group received 50 µg on the first day, and escalating doses every day to 200 µg on the quit day. Clonidine was given daily during 4 weeks, and later gradually withdrawn by 50 µg every 3 days. Those included in the survey were subjects who had succeeded in reducing their smoking intake to at least 50% of baseline level (otherwise, clonidine could not work since it is supposed to alleviate withdrawal symptoms). The success rate, verified by serum cotinine determination, attained 61% in the clonidine group *versus* 26% in the placebo group. The superiority of the clonidine effect was limited to women (72% *vs* 15%), while among the male smokers, drug treatment did not significantly affect the outcome (47% *vs* 50%). Six months after discontinuing medication, the smokers' own reports (without cotinine validation) indicated that 27% of the clonidine treated were still not smoking *versus* 5% of the placebo treated. An unexpectedly high frequency (60%) of previous major depression was observed in the whole sample, and had a consistent influence on the cessation rate (33% with a history of depression, 57% with no history).

A beneficial trend of 0.2 mg clonidine peroral administration without any behavioural support was also observed in a double-blind study in 186 "quitting" smokers, but without persistent statistical significance [101] (validated abstinence in 11.8% of the placebo group *vs* 20.4% of the clonidine group at three months). Reported side-effects were frequent, especially dry mouth (77%) and drowsiness (65%) in the clonidine group.

In a short, double-blind, randomized, placebo controlled but non-biologically validated trial in 40 cigarette smokers, volunteers in an out-patient mental health clinic, 20 of each sex, one week administration of transdermal clonidine (Catapres TTS$_2$®), delivering ±0.2 mg clonidine per day during a week, appears to ameliorate some of the short-term withdrawal symptoms, especially craving [102]. The side-effects of transdermal clonidine were generally mild.

Further clinical trials including larger numbers of smokers are evidently needed before definitive conclusions can be drawn on the efficacy of clonidine in smoking cessation programmes.

Naloxone. A relatively short acting opioid antagonist, naloxone, which reduces the intake of food and alcohol, was administered subcutaneously at the dose of 10 mg in an acute, double-blind drug-placebo crossover design. It reduced smoking and the desire to smoke in 7 experimental subjects [103], and also the pleasure of smoking [104]. It blocks the nicotine-induced increased pain threshold (antinociception). Aversive effects of naloxone (feelings of lethargy, inactivity and less well-being) could limit its acceptance by smokers [105].

Fluoxetine. A serotonin reuptake inhibitor, fluoxetine, may decrease craving and is undergoing multicentre trials in the USA. It also decreases carbohydrate food intake [79].

ACTH. In response to stimulation by nicotine, the anterior pituitary gland is supposed to secrete corticotrophin which induces a (proven) increased output of

glucocorticoids by the adrenal cortex [106], resulting in a temporary rise in blood sugar [107] which coincides with the smokers "lift". Corticotrophin has been used in order to correct the syndrome appearing after suppression of the nicotinic stimulation of endogenous ACTH secretion. Out of 10 smokers given 180 I.U. of corticotrophin *i.m.*, 9 stopped smoking, while the tenth could stop after a second injection of 80 I.U. [108]. After 7 months, none of the patients had resumed smoking. The results of this uncontrolled study were not validated by CO determinations. Further observations are necessary before definitive conclusions can be drawn.

"Nicofree"®. A mixed capsule containing 200 mg of xanthan (a natural fibre swelling in the stomach), 50 mg of glucose and guarana extract, Nicofree®, is supposed to help smokers to stop and to limit weight gain after giving up. Its efficacy has not yet been demonstrated in valid clinical trials.

Anabazin. This product (alpha-piperidyl-beta-pyridine-HCl) was used in a multicentre non-controlled cessation programme with success rates of 36.2% after 4 weeks and 22.5% after one year [109].

Substances mimicking the sensory effects of smoking

Refined cigarette smoke. Since nicotine replacement is only partially successful, an alternative approach to reducing cigarette smoking is to supply smokers with a substitute that delivers many of the familiar sensory cues in smoking, while greatly reducing the delivery of nicotine, tar and CO.

Refining cigarette smoke is a complicated two-step process. Cigarettes are first smoked by a machine, and the particulate fraction of smoke (condensate) is collected by inertial impaction in a small glass collection vial, while harmful gases such as CO, formaldehyde, nitric oxide, ammonia and hydrogen cyanide flow to the vacuum pump.

In a second step, the vial with condensate, sometimes mixed with tobacco powder, is placed in a hollow cylindrical plastic tube, approximately the size of a cigarette, and heat is applied with an alcohol burner to the vial for 4–5 s before each puff; the smoker takes puffs through the vial. This device reproduces many of the sensory characteristics of cigarette smoke, while eliminating most of the nicotine, tar and CO.

The preliminary results [110] suggest that it could be used as an aid to smoking cessation (eventually together with a transdermal nicotine patch) and even, maybe, as a long-term replacement for cigarettes, if the long-term adverse effects of refined smoke appear to be more limited that those of normal smoke.

Citric acid aerosols. Tracheal stimulation by smoke seems critical in mediating immediate smoking satisfaction, since a temporary anaesthesia of smokers' airways causes a dramatic decline in satisfaction [111] and since, on the other hand, nicotine administered in gum, nasally or intravenously, does not satisfy smokers as much as comparable amounts of nicotine delivered by inhaled smoke.

In a blind controlled study, an ultrasonic aerosol of a non-toxic aqueous solution of 15% citric acid appeared to simulate the tracheal sensations of smoking, and even to reproduce some of the subjective pleasure stimulated by smoking the subjects' own cigarette brand [112]. Research examining this type of extinction of chemosensorial reinforcing stimuli could help design improved smoking cessation approaches, for instance by the use of citric acid aerosols together with components which simulate the full flavour of tobacco smoke.

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Approche pharmacologique que du sevrage tabagique. J. Prignot.

RÉSUMÉ: A l'heure actuelle, les possibilités d'intervention pharmacologique dans le processus de sevrage tabagique restent limitées. Certains produits semblent définitivement abandonnés: ce sont les produits dissuasifs, la lobeline, les amphétamines et les sédatifs. L'efficacité d'autres produits visant à traiter le syndrome de privation (par ex. la clonidine), ou cherchant à obtenir l'extinction de l'habitude tabagique en supprimant les effets agréables (par ex. la mécamylamine), devrait encore être vérifiée par des essais contrôlés portant sur de grands nombres de sujets. Il en est de même pour les substituts à la cigarette, récemment préconisés. Pour l'instant, le seul traitement substitutif disponible est la nicotine, sous forme de chewing gum. D'autres modalités d'administration de la nicotine sont en cours d'élaboration. La gomme à la nicotine n'a pas répondu à toutes les attentes de se promoteurs ni des fumeurs qui en attendaient une vraie panacée. Elle permet toutefois d'augmenter modérément le taux de sevrage, ainsi que le taux d'abstinence à long terme pour autant qu'elle soit administrée à des fumeurs fortement dépendants à la nicotine, qui veulent arrêter de fumer, et que ce traitement soit accompagné d'un soutien psychologique indispensable prodigué par le médecin dans le cadre de sa consultation, ou encore par d'autres professionnels de la santé dans les Centres d'aide aux fumeurs ou dans des programmes réalisés dans la collectivité ou dans le milieu industriel. La dépendance à l'égard de la nicotine, substance psychoactive, n'est qu'un des aspects de l'habitude tabagique chez le fumeur chronique. Celui-ci doit être aidé à faire face aux composants comportementaux de son tabagisme. Une aide psychologique individualisée doit compléter la prescription du chewing gum si l'on veut obtenir des taux satisfaisants d' abstention tabagique à long terme.
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