Dossier

Dependence potential and abuse liability
of nicotine replacement therapies *

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Summary — Some abstinent smokers develop withdrawal symptoms when they stop using nicotine gum or when
placebo is substituted; thus, physical dependence on nicotine gum does occur. Some smokers also use nicotine gum
beyond the recommended period; thus, behavioral dependence on the gum occurs. Many (7—41 %) smokers misuse
nicotine gum by smoking cigarettes and chewing the gum concurrently. Among smokers who stop using the gum,
many (35—90 %) do not stop gum use by the recommended 3 months, and a substantial percentage (13—38 %) persist
in gum use for 1 year. Among quitters, long-term use of nicotine gum appears to be greater than that of placebo
gum. If rapidity of onset and frequency of use are determinants of dependence potential, then nasal sprays and
aerosols but not nicotine patches should have dependence potential. There are no reports of misuse of the gum by
non-smokers; thus, the gum appears to have little if any abuse liability.

abuse / dependence / nicotine

Résumé — Responsabilité de l'abus dans la dépendance aux produits nicotinés de substitution. *Certains
ex-fumeurs développent des symptômes de sevrage quand ils cessent d'utiliser un chewing-gum à la nicotine ou quand
un placebo lui est substitué. Ainsi voit-on bien apparaître une dépendance physique au chewing-gum à la nicotine.
Quelques fumeurs aussi se servent de cette gomme au-delà de la durée recommandée. On peut donc également observer
une dépendance comportementale pour la gomme. Beaucoup de fumeurs (7—41 %) se servent de la gomme à la nicotine
d'une manière inappropriée en consommant des cigarettes de façon concomitante. Parmi les fumeurs qui abandonnent
la gomme, beaucoup (35—90 %) ne se conforment pas à la durée d'utilisation recommandée de 3 mois, et une proportion
notable (13—38 %) continue jusqu'à 1 an. Parmi ceux qui arrêtent la gomme, l'utilisation au long cours apparaît plus
fréquente pour celle qui contient de la nicotine que pour le placebo. Si la rapidité d'action et la fréquence d'utilisation
sont des facteurs déterminants pour la dépendance, les sprays par voie nasale et les aérosols devraient comporter un risque
de dépendance, mais non les patches de nicotine. Aucune observation d'usage inapproprié de gomme n'a été rapportée
chez les non-fumeurs. Par conséquent, la gomme elle-même ne semble guère avoir de responsabilité, pour autant qu'elle
en ait, dans l'abus du produit nicotiné de substitution.*

abus / dépendance / nicotine

Introduction

Several terms will be used in the present paper :
physical dependance, behavioral dependence,
drug misuse and drug abuse. Since each term
carries many connotations and has been defined
in several ways, the reader should pay close
attention to the operational definitions for the
terms that will be used.

Many definitions of these terms require that
drug use cause some impairment in functioning,
e.g. in health, family, interpersonal, occupational,
legal or recreational functioning; or some distress
in the individual [1]. Since the harmful effects of
nicotine have been reviewed by Christen and
Benowitz (in Pomerleau *et al.*; see footnote to
present article), this criterion will not be discussed
in the present paper.

This discussion will focus on the dependence potential of nicotine gum, as there is little data on dependence regarding other forms of nicotine replacement. General principles found for nicotine gum may apply to other nicotine replacements.

Nicotine gum : physical dependence

Physical dependence is usually defined as the presence of tolerance or the onset of withdrawal signs or symptoms upon cessation of the drug [17]. Physical dependence has also been referred to as physiological dependence, and more recently as neuroadaptation (DSM-III Revision Work Group, 1986). I know of no studies on whether tolerance develops to nicotine gum; thus, I will restrict my criterion of physical dependence to the onset of withdrawal.

The study of West and Russell [25]
In the first study in this area, the subjects were 6 female ex-smokers who used a mean of 13 pieces of nicotine gum per day for at least 1 yr ($x=20$ months). Subjects were entered into a within-subjects, $A_1 - B - A_2 - C$ design in which $A_1 =$ baseline nicotine gum, B = abstinence or placebo (0.5 mg unbuffered gum) for 24 hr, $A_2 =$ return to baseline for 1–3 weeks, and C = converse of B.

Heart rate decreased 10 bpm in both the abstinence and placebo conditions but skin temperature did not. Subjects had increased withdrawal symptoms during abstinence and placebo substitution. They also reported craving for nicotine gum but not cigarettes. Abstinence and placebo substitution reliably increased irritability and difficulty in concentrating ($P<0.05$) but not tiredness, hunger, depression, anxiety, unsociability, restlessness, inability to cope, dizziness and constipation.

The study of Hughes et al. [9]
Subjects were 6 female and 2 male ex-smokers who used a median of 9.5 pieces of nicotine gum for at least 1 month (median = 5 months). Subjects were entered into a double-blind, within-subjects, A–B–C–A design in which A = nicotine gum, B = placebo or nicotine gum and C = converse of B. Order of nicotine or placebo gum for conditions B and C was randomized and counterbalanced. Subjects were told that there was a 50/50 chance that placebo would be substituted

during one of the conditions. Conditions lasted 1 week. Withdrawal effects were measured 3 times per week by observer ratings (spouse or friend).

Placebo substitution did not alter heart rate or weight. It did increase observed irritability, anxiety, restlessness and impatience but not drowsiness. It also increased self-reported symptoms consistent with observed behavior and self-reported craving for tobacco, difficulty in concentrating and hunger. Observer ratings of withdrawal symptoms increased in 7 of the 8 subjects. The 2 subjects with the highest observer ratings relapsed back to nicotine gum or smoking during placebo substitution.

These two studies clearly document physical dependence on nicotine gum, which is important as it could be hypothesized that the low level of nicotine in the gum is insufficient to produce physical dependence. It is also important because it supports the clinical recommendation that gum users gradually reduce their intake prior to stopping.

The degree to which physical dependence contributes to behavioral dependence on nicotine gum, *i.e.* whether gum withdrawal symptoms are a major cause of prolonging gum use beyond the recommended period, is unknown. One could hypothesize that all those who are physically dependent are also behaviorally dependent. However, several lines of evidence indicate that physical and behavioral dependence can occur independently [5]. For example, several prescription drugs (*e.g.* anti-cholinergics, antidepressants and antipsychotics) produce physical but not behavioral dependence. In addition, benzodiazepines and narcotic analgesics can produce physical but not behavioral dependence (in patients without a history of drug abuse).

The prevalence of physical dependence cannot be estimated from the studies reported above, as the samples were small. Furthermore, drug dose, dosage (dose and frequency) of drug and duration of use usually influence the development of physical dependence [17]. Whether this applies to physical dependence on nicotine gum has not been studied; neither has the question of whether the onset of withdrawal after cessation of nicotine gum prompts relapse to smoking.

Nicotine gum : behavioral dependence

Behavioral dependence has been defined in several ways, but all definitions include persistent use

of the drug. Behavioral dependence has been referred to as psychic or psychological dependence. A clinical definition applicable to prescription drugs will be used in this paper; *i.e.*, persistent use despite a clear recommendation to stop the drug. This definition does not include other indices of dependence used with illicit drugs, *e.g.* preoccupation with use and intoxication [27]. However, the definition clearly includes those subjects who are unable or unwilling to stop gum use.

Methodological issues
The standard method to determine the prevalence of behavioral dependence on nicotine gum is to calculate the percentage of subjects who are still using the gum at 1 yr follow-up. This procedure has several aspects that might overestimate or underestimate the true prevalence of behavioral dependence.

First, this cross-sectional definition does not assess whether an individual reports unsuccessful attempts to stop or has been advised to stop. Thus, an ex-smoker who uses nicotine gum long after cessation of smoking because his doctor recommends he do so will be defined as behaviorally dependent. Unfortunately, many studies on nicotine gum do not report which instructions smokers were given about when, if ever, to stop using the gum.

A second problem is produced by requiring only use at follow-up, and not persistent use since cessation of smoking. For example, Jarvis *et al.* [14] found that of the 7 subjects using nicotine gum at 1 yr follow-up, only 4 had used it continously throughout the year. Thus, using only cross-sectional data may falsely inflate the reported incidence of behavioral dependence.

A third problem is variability in ease of access to the gum. For example, all but 2 of the nicotine gum trials gave out free gum. This is significant, because a recent experimental study we carried out showed that having to pay for nicotine gum significantly decreases use of the substance [24]. Thus, the use of free gum may increase the incidence of dependence. On the other hand, one can easily discourage dependence on nicotine gum by requiring subjects see a physician each time they need a refill, etc.

A fourth problem is the method for calculating the incidence of dependence. The problem here is 2-fold. First, the standard 1-yr follow-up is arbitrary and may underestimate the true incidence. If an ex-smoker is told to stop using gum

at 3 months, but is unable to do so until 10 months, he/she is estimated to be non-dependent by the 1-yr criterion, despite persistent use well beyond the recommended period. Second, the denominator in the standard calculation is inflated by smokers who have not quit, or who have relapsed back to smoking and thus do not use gum. For example, if 100 smokers receive a prescription for nicotine gum and 10 use it a year later, then by the standard definition the incidence of behavioral dependence would be 10%. Prior reports indicate that of every 100 persons prescribed the gum, about 30 stop using the gum [11]. Reports also indicate that of the 10 who still use the gum at long-term follow-up, only 9 are abstainers [8]. So, among the quitters, the incidence of dependence is ≈ 30% (compared with 10% among all those prescribed the gum).

Dependence on nicotine gum vs *other prescription drugs*
With the standard criteria, several studies report the prevalence of use after 6 months to be 9—50% [2, 12]. With similiar criteria, the rate is < 1% for narcotic analgesics [21] and 21—27% for benzodiazepines [18, 20].

Behavioral dependence on nicotine gum among quitters
To calculate the incidence of behavioral dependence, I have tried to avoid the methodological problems described above by using 3 criteria for determining the prevalence of behavioral dependence on nicotine gum : 1) the study reported statistics such that the prevalence of chronic gum use could be calculated among quitters; 2) the investigators advised cessation of gum by a certain date; and 3) the study made gum available thereafter. Although these criteria seem straightforward, they eliminated all but 4 of the studies. One other criterion, *i.e.* reporting whether use at follow-up represents persistent use was considered, but was not utilized as our study was only one that documented persistent use [9].

Incidence of behavioral dependence on nicotine gum
Incidence figures from the 4 studies that meet the criteria indicate that many abstinent smokers are unable to stop after recommended cessation (35—90%), and that a substantial proportion (13—38%) persist for up to a year.

Dosage of nicotine gum among dependent users
Among those who persist in gum use, the total daily dosage of gum is moderate after recommen-

Table I. Prevalence of behavioral dependence on nicotine gum among abstinent smokers.

	Use at 6 months	Use at 1 yr
Withdrawal clinic studies		
Axellson & Brantmark, 1977	47	
Harackiewicz *et al.* (in press)	50	13
Gust *et al.*, 1985	90	
Medical practice studies		
Hughes *et al.*, 1986	35	38

ded cessation, *i.e.* 10—20 mg/day at 6 months ([2], and Harackiewicz *et al.*, in press), and decreases to a minimal dose by long-term follow-up, *i.e.* 3—11 mg/day at 1 yr (Harackiewicz *et al.*, in press; [13]).

Determinants of physical and behavioral dependence on and abuse of nicotine gum

Pharmacological actions of nicotine

Several studies using the standard criteria have reported that the incidence of long-term use is higher for those who received nicotine gum than for those who received placebo gum [13]. These figures, however, are based on gum prescriptions. This distinction is significant as increased incidence in nicotine gum use over placebo gum may not be because nicotine produces behavioral dependence in abstinent smokers, but rather that more smokers quit with nicotine gum; and therefore more smokers are at risk of using the gum longer. To test this hypothesis, we calculated the incidence of nicotine gum use among quitters only. At 6 months follow-up, the incidence of continuous use of nicotine and placebo gums among abstinent smokers was identical (35 %). At 9 months follow-up, the incidence of continued use was 28 % for the nicotine group and 11 % for the placebo group (*P*<0.10).

Other studies did not report giving concrete advice to stop chewing gum by a certain date. In their second trial, Hall *et al.* [7] reported no difference in the incidence of use of nicotine and placebo gums at any assessment. On the other hand, the data of Hjalmarson [8] indicate that 54 % of quitters with nicotine gum were using the gum at 6 months follow-up compared to 0 % of those who stopped using placebo. In summary, the results of our trial and that of Hjalmanson

suggest that long-term use of nicotine gum is due to the reinforcing effects of nicotine in ex-smokers; but the results of Hall *et al.* do not agree with this conclusion. As mentioned before, among prescription drugs, physical dependence does not necessarily lead to behavioral dependence. In addition, it is possible that behavioral dependence on nicotine gum occurs during tobacco withdrawal, but not thereafter. After tobacco withdrawal has subsided, persistent use of nicotine gum may be due not to the pharmacological effects of the gum, but rather to the success attributed to the gum being chewed.

Dose

For most drugs, increased dose increases the likelihood of physical or behavioral dependence. Two studies have experimentally varied dose and examined gum use [6, 16]. In both studies, the incidence of use was similiar for 2 and 4 mg groups at 3 months follow-up. Our study found that at 9 months follow-up, the prevalence of gum use was greater in the 2 mg group than in the 4 mg group [6]. In the study of Kornitzer *et al.* [16], subjects were allowed to switch gum at 3 months. Of those using gum at 3 months, 72 % of those taking 4 mg gum switched to 2 mg gum, but only 3 % of those taking 2 mg gum switched to 4 mg gum. Thus, both studies suggest the 2 mg gum is more likely to produce behavioral dependence than the 4 mg dose.

Dosage

Clinicians and patients often believe that the degree of initial use of a drug (*e.g.* frequency of use in the first week) predicts behavioral dependence. This has not been tested for nicotine gum. In fact, the scientific basis for this opinion among other drugs (*e.g.* benzodiazepines) is quite scanty.

Duration of use

For most drugs, longer-term use increases the incidence of behavioral and physical dependence. No studies have experimentally examined the effect of duration of use on physical or behavioral dependence.

Schedule

Ad lib (PRN) schedules are thought to promote both behavioral and physical dependence. Several studies comparing the PRN *vs* fixed-time schedules of nicotine gum are under way (Fortman, personal communication; Goldstein, personal communication).

Cost

Increased response requirement to obtain drug decreases behavioral dependence; thus, one could hypothesize that having to pay for nicotine gum would decrease the incidence of behavioral dependence. We are presently running a clinical trial in which subjects are randomly assigned to one of 3 groups : 1) free gum; 2) pay $ 6/box; or 3) $ 20/box. Preliminary results indicate that cost decreases initial use [24].

Reduction rate

At present smokers are counseled to gradually decrease use of gum on the assumption that as with most drugs, abrupt cessation produces more relapse than gradual cessation. Westling [26] compared rapid and gradual tapering off with *ad lib* use. Although data on smoking has been reported, unfortunately, data on long-term use of gum between rapid and gradual tapering off has not been provided.

Adjunct therapy

If behavioral dependence on the gum is due to fear of relapse to smoking, then one could hypothesize that subjects who received a behavioral treatment for smoking in addition to nicotine gum should be less likely to become dependent on nicotine gum than those who did not receive a behavioral treatment. Four trials have studied gum use with and without behavior therapy. The only one that reported gum use found no difference in gum use between the high and low intensity behavior therapy groups.

Sample characteristics

Rates of behavioral dependence at 6 months follow-up appear to be higher in smokers seen in clinics than in medical practice, although the data are sketchy (Table I). The increased rate of dependence in clinics certainly contradicts the hypothesis that behavior therapy decreases dependence on nicotine gum. However, the increased use of nicotine gum in clinics could be due to the fact that clinical samples are more dependent on nicotine than the general population of smokers [22]. This raises the interesting possibility that it is those smokers whom nicotine gum helps most that are most likely to become dependent on the gum.

Summary

Behavioral dependence on nicotine gum appears to be due to the ability of nicotine to serve as a reinforcer in abstinent smokers; however, the data on this are contradictory. The role of factors such as dose, schedule, duration, cost, rate of decrease, adjunct therapy and sample characteristic is also unclear due to the small number of experimental tests.

As with all drugs of abuse, simple exposure is a very weak cause of dependence [5]. We have only begun to look for the factors that might account for dependence on nicotine replacement therapies.

Cessation of nicotine gum and smoking relapse

A major deterrent to stopping nicotine gum among ex-smokers may be the fear of relapse to smoking. In fact, retrospective evidence indicates that longer use of the gum is associated with success at cessation [4]. However, the single prospective experimental study failed to confirm these retrospective associations [4].

If stopping gum increases relapse to smoking, then the rate of relapse after ex-smokers are forced to stop nicotine gum should be greater than the relapse rate among ex-smokers permitted to continue gum use. A present there is no such experimental trial. One non-experimental test of this notion is to compare the rate of relapse to smoking after nicotine gum is made unavailable with the relapse rate for the corresponding time period among smokers in a non-drug group.

Smoking relapse after recommended termination of gum

Two studies provide data to examine the rate of relapse after recommending gum cessation at 3 months. The 6-month follow-up data of Harackiewitz *et al.* (in press) indicated slightly more relapse to smoking after recommended cessation of nicotine gum than during the same time period in a self-help group (24 % *vs* 17 %). Similar data from our study [9] found relapse rates to be similar in the nicotine and placebo groups (55 % *vs* 47 %).

Smoking relapse after forced termination of gum

Three studies gave data on relapse after forced cessation of the gum. The data of Killen *et al.* [15] suggest the rates of relapse to smoking after early forced cessation (between 7—15 wk) of gum were similiar for nicotine gum alone, nicotine gum plus behavior therapy, and no gum (behavior therapy alone) groups (16 %, 21 % and 18 %). Two studies

made gum unavailable after 6 months and reported quit rates at 12 months follow-up. In the first study [7], rates of relapse to smoking were 20 % among those on gum alone, 29 % of those on gum plus behavior therapy, and 10 % of those in the no-gum (behavior therapy alone) group. The second study [26] consisted of 3 groups of smokers : 1) rapid tapering off of gum use; 2) slow tapering off; or 3) gum use *ad lib*. Relapse rates in this non-randomized comparison were 30 % and 35 % in the tapering off groups and 26 % in the *ad lib* group.

Summary
The absence of an experimental trial forces us to use indirect tests of whether advising or forcing cessation of gum increases relapse to smoking. Data from 4 of the 6 studies indicate relapse rates are not increased after recommended or forced cessation of nicotine gum. Data from the one placebo controlled study also did not indicate more relapse to smoking after recommended cessation of nicotine gum than of placebo gum [9]. Finally, the studies of Killen *et al.* [7] and Hall *et al.* [15] do not indicate that adding behavior therapy to nicotine gum treatment decreases relapse rates after cessation of gum chewing.

Misuse of nicotine gum by smokers
The prevalence of concurrent use of nicotine gum and tobacco decreases from 41 % at 6 weeks (Harackiewicz *et al.*, in press) to 26 % at 3 mo [3] to 16 % at 6 mo [2] to 7 % at 1 yr (Harackiewicz *et al.*, in press). A consumer survey found that 26 % of those who received nicotine gum never stop but rather use the gum to temporarily refrain from using tobacco in certain situations [19]. Generalizing from these results depends on a knowledge of the instructions given to subjects about chewing gum and smoking, which unfortunately is lacking.

Abuse of nicotine gum by nonsmokers
After 10 years of its being on the market in Europe and the United States, I cannot find a report of misuse of the gum by non-smokers. The only experimental trial of use of nicotine by non-smokers found that neither never-smokers nor long-time ex-smokers reported stimulant, sedative or euphoric effects with nicotine gum, but did report dysphoria with the gum [23]. In addition, when given a choice, both groups preferred to chew placebo gum to nicotine gum.

Dependence potential and abuse liability of other nicotine replacement therapies

Possible replacement therapies other than nicotine gum can be classified by one of 4 routes (Table II) : oral (lozenges or tablets), aerosols (non-combustible cigarette rods), nasal sprays, patches and subcutaneous injections. Intravenous injections are a possible treatment but are impractical. Only the nasal spray has been tested for abuse or dependence potential.

Table II. Factors that might control the dependence potential of nicotine replacement therapies.

	Rapidity of onset	Blood levels	Side-effects	Frequency of use
Present routes				
Cigarettes	Fast	High	Few	Frequent
Gum	Slow	Low	Few	Moderate
New routes				
Aerosols	Fast	Debatable	Few (?)	Often
Nasal sprays	Fast	Moderate	Several	Moderate
Transdermal patches	Slow	Low (?)	Few	Infrequent

Nicotine nasal spray
Jarvis [13] reported that smokers rated a nicotine nasal spray as only slightly less satisfying than a cigarette. In the initial 11 days after cessation, 50—70 % of the smokers stated the nasal spray produced a calming effect and 13—24 % stated that it produced euphoria. Twenty-five subjects were given *ad lib* use of the spray; 9 stopped smoking, but 3 used the spray throughout the year. Although these lines of evidence suggest the spray has dependence potential, the spray has unpleasant side-effects (*e.g.*, nasal irritation, watery eyes) and may be embarassing to use in public.

Factors that might control whether a replacement therapy has potential for physical or behavioral dependence
Pharmacological factors might that increase the likelihood of abuse liability and dependence potential are : 1) rapid onset of action; 2) attainment of high blood levels; 3) few side-effects; and 4) high frequency of use (Table II). Using these criteria, aerosols should have substantial dependence potential as they have a rapid onset, few side-effects and are used frequently. Nicotine patches should have little dependence potential as they have a slow onset of action and are used infrequently.

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