Short-Term Effects of Nicotine Gum

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Pharmacological treatments of drug dependence vary in their approach. Medications may make drug administration aversive (e.g., disulfiram), block the reinforcing effects of the drug (e.g., naltrexone), substitute for the drug (e.g., methadone), or relieve the discomfort of drug withdrawal (e.g., benzodiazepines).

Based on these approaches, several types of medications, such as taste adulterants, stimulants, and tranquilizers have been tested as aids to smoking cessation (Kozlowski, in press; Raw 1978; Grabowski and Hall, this volume). Most of these medications have not been efficacious. Nicotine chewing gum is the exception (Hughes and Miller 1984). The major hypotheses to explain the efficacy of nicotine gum are that the gum substitutes for the reinforcing effects of cigarettes or that the gum relieves tobacco withdrawal symptoms.

This article will review studies of the short-term effects of nicotine gum that test these two hypotheses. Although we will attempt some conclusions, the reader should be aware that, as with most drugs (Thompson and Johanson 1981), the effects of nicotine depend on several conditions. For example, differences in dose, duration and route of administration, drug history, external stimuli, genetics, personality, rate of ongoing behavior, schedule, time since drug ingested and tolerance can produce marked differences in nicotine's actions (Aston and Stepney 1982; Emley and Hutchinson 1984; Gibert 1979; Goldberg et al. 1983; Henningfield 1984; Henningfield and Goldberg 1983; Hughes, in press; Mangan and Golding 1984). For example, differences in external stimuli (Goldberg et al. 1983), instructional set (Hughes et al., in press-a), and schedule (Goldberg et al. 1983) can determine whether nicotine will serve as a reinforcer or a punisher. Thus, when we summarize "the" short-term effects of nicotine gum the reader should realize the results obtained in laboratory studies may not generalize to those obtained in medical practice.

EFFECT ON SMOKING BEHAVIOR

The effects of nicotine on smoking vary widely both between and even within studies (Brammark et al. 1973; Ebert et al. 1984; Kozlowski et al. 1975; McM Turner et al. 1977; Ohlin and Westling 1975; Russell et al. 1976; Westling 1976). Of the 16 comparisons in these studies, 7 showed nicotine gum decreased smoking and 9 did not.
These contradictory results may be due to differences in subjects (those who were vs. were not trying to quit), sample size (8 vs. 92 Ss), design (within- vs. between-group design), dose (1 vs. 2 vs. 4 mg), schedule of dosing (e.g., single vs. ad-lib administrations), duration (30 min vs. 2 wks), and dependent measures (self-report vs. objective measures and frequency vs. topographical vs. biochemical measures). Whether any of these differences do, in fact, control whether nicotine gum influences smoking might be determined by looking for an association between positive results and a methodological procedure (e.g., use of smokers trying to quit) across the studies. Unfortunately, the small number of studies and the fact that the different methods are confounded with each other prohibits such an analysis. About the only conclusion that can be reached is that, at this time, a conclusion cannot be reached.

**EFFECT ON CIGARETTE CRAVING**

Perhaps the major hypothesis to explain the efficacy of nicotine gum is that the gum relieves craving for cigarettes during abstinence. Tests of this hypothesis have thus far been restricted to examining the effects of nicotine gum on subjects' endorsements of descriptions of craving, such as desire to smoke, thoughts about cigarettes, difficulty refraining from smoking, urges to smoke, hunger for a cigarette, and awareness of not having a cigarette. Nicotine gum decreased some of these measures of craving in some subjects in three small studies (Russell et al. 1977; Ryden 1975; Schneider et al. 1977). However, nicotine gum did not decrease these measures of craving in large, placebo-controlled trials of the gum (Hughes et al. 1984; Jarvis et al. 1982; Ohlin and Westling 1975; Schneider et al. 1984; West et al. 1984). Thus, the weight of the evidence does not support the hypothesis that the efficacy of nicotine gum is due to its ability to relieve craving.

There are several reasons why nicotine gum might not reduce cigarette craving. First, the route of administration (oral vs. inhalation) might be crucial. Oral nicotine produces low levels of nicotine (Hughes and Miller 1984) that might be insufficient to reduce craving. However, previous studies have shown that nicotine via other routes of administration, e.g., capsules (Jarvik et al. 1970) or intramuscular (Johnston 1942) and intravenous (Henningfield et al. 1983; Lucchessi et al. 1967) injections decrease smoking and cigarette craving. Unfortunately, none of these studies reported examining self-reported craving during abstinence. Oral nicotine also does not reproduce the "bolus" injection of nicotine from smoking. Bolus injections may be essential to replicate the effects of smoking (Russell and Feyerabend 1978). However, Kumar et al. (1977) found that intravenous bolt of nicotine did not decrease smoking frequency. Second, other ingredients in tobacco may control the desire for a cigarette. Although there are several reasons to believe nicotine is the major psychoactive ingredient in tobacco, the psychopharmacological properties of several thousand other compounds in tobacco have not been tested (Jarvik 1977). Third, craving may be controlled by environmental factors. Smoking occurs many times per day, in a variety of situations, and produces a psychoactive effect quite rapidly (i.e., within 7 seconds); thus, the opportunities for environmental conditioning are great. Recent studies with
amphetamines suggest that once a conditioned drug response is established, the response may no longer be influenced by agonists or antagonists of the drug (Benninger and Hahn 1983). If this is true, then once tobacco craving is conditioned to environmental cues, nicotine alone may no longer reduce craving.

A fourth possibility is that nicotine reduces craving only in the more "dependent" smoker (Hughes, in press-b). The results of Russell's study (1977) are consistent with this hypothesis in that they suggest the reduction in cigarette craving by nicotine gum varies widely across smokers. To test this hypothesis we divided smokers in our study into a dependent and nondependent group according to their scores on the Tolerance Questionnaire (Fagerstrom 1978). We then compared the reduction in cigarette craving from nicotine and placebo gum between the two groups. The reduction in craving was the same for dependent and nondependent smokers; thus, the hypothesis that nicotine reduces craving only in the more dependent smoker was not supported.

Finally, there is the possibility that self-reported craving is a poor measure. Perhaps better measures would be direct, objective tests of nicotine self-administration during abstinence such as concurrent access (Hughes et al., in press) to tobacco and non-tobacco cigarettes or the amount of work to obtain nicotine or tobacco (Griffiths et al. 1982).

The inability to document that nicotine gum reduces craving during abstinence may have clinical implications. At present, when smokers are prescribed nicotine gum they are told the gum will reduce cigarette craving. Perhaps instead smokers should be told not to rely on the gum to relieve all craving and be encouraged to develop a plan to deal with craving that does not respond to the gum (e.g., engaging in alternative behaviors or avoidance of cues). When smokers are prescribed nicotine gum they are also told to use the gum whenever craving for a cigarette occurs. If nicotine gum does not reduce craving, perhaps they could be told to use the gum on a fixed time schedule instead of a PRN schedule. Fixed time schedules might be preferable to PRN schedules as the former schedule helps extinguish conditioned craving responses and decreases the probability that use of nicotine gum itself will become conditioned to craving cues. Another alternative is that smokers should be told to use the gum not when cigarette craving occurs, but rather when withdrawal symptoms occur (see below).

EFFECT ON TOBACCO WITHDRAWAL

Abstinence from smoking induces a variety of withdrawal symptoms (Hatsukami, this volume; Shiffman 1979). Several double-blind, placebo-controlled studies have tested the effect of nicotine gum on tobacco withdrawal. Some studies correlated withdrawal symptom ratings into a total withdrawal discomfort score. These withdrawal scores consisted of a single global self-report rating (Russell et al. 1976; Véstling 1976), number of symptoms reported (Puska et al. 1979), or a cumulative score based on the sum of intensity ratings for individual symptoms (Fagerstrom 1982; Hughes et al. 1984; Killen et al. 1984; Schneider et al. 1984). In all but one of these
studies (Puska et al. 1979). Nicotine gum reduced total withdrawal discomfort (see figure for an example).

In terms of individual withdrawal symptoms, the only effect of nicotine that was consistent across studies was a reduction in irritability, anger, and frustration (Table 1). Depression was also reduced by nicotine gum in two of the four studies.

Abstinence from cigarettes produces behavioral as well as self-report changes (Hatsukami et al. this volume). Our study examined the effects of nicotine gum on such behavioral changes by collecting observer ratings of abstinent smokers. Observers (e.g., spouse or employer) rated subjects who received nicotine gum less irritable, anxious, restless, and impatient than subjects who received placebo gum (Table 2). Thus, nicotine gum produced behavioral changes that occurred in the natural environment and were apparent to persons near the smoker.

Abstinence often produces weight gain. Post cessation weight gain may be due to several factors, e.g., increased hunger, increased consumption of sweets, decreased resting metabolic rate, or decreased motor activity (Grunberg, in press; Hatsukami et al. this volume; Hughes et al. 1982; Wack and Rodin 1981). Nicotine decreases appetite, increases resting metabolic rate, and increases physical activity (Grunberg, in press); thus, nicotine gum could be expected to counteract the weight gain associated with smoking cessation. Two double-blind placebo-controlled trials reported that subjects who received nicotine gum reported less hunger (Jarvis 1982) and gained less weight (Bantmark et al. 1973) at 6-month followup than subjects who received placebo gum. In contrast, similar trials by Puska et al. (1979), Hall et al. (in press) and Hjalmarson (1984) found no difference in weight gain or hunger between those on nicotine gum and those on placebo. Also, both West et al. (1984) and we (Hughes et al. 1984) found that nicotine did not reduce hunger during the first few days of abstinence.

Although this evidence suggests nicotine gum does not decrease post cessation weight gain, clinical trials of nicotine gum may not be fair tests. This is because some subjects in a clinical trial will relapse to smoking. Since nicotine gum keeps people from smoking and since abstinence increases weight, then nicotine gum will appear to increase weight gain due to its therapeutic efficacy. To truly test the effect of nicotine gum on post cessation weight gain, a study must prevent attrition—back to smoking and study the effect of nicotine gum on weight gain only in abstinent smokers.

Another less well-documented effect of abstinence from smoking is analgesia. Milgrom-Friedman et al. (1983) examined whether nicotine gum would influence abstinence-induced analgesia. They studied non-smokers, smokers smoking ad lib, abstinent smokers who chewed nicotine gum and abstinent smokers who did not chew nicotine gum. Each group had a tourniquet applied to one arm and then reported the time to onset of pain and the time until the pain was intolerable. Abstinent smokers who chewed nicotine gum reported pain onset similar to that of abstinent smokers who did not chew gum. Both these groups had a pain onset longer than that of smokers smoking and
Figure. Mean and standard error of daily discomfort score by experimental condition and drug group for our nicotine gum study (Hughes et al. in press). Open circles = placebo, closed circles = nicotine.
Table 1. Effects of nicotine gum on the commonly reported symptoms of tobacco withdrawal

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability/Anger/Frustration</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
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<tr>
<td>Anxiety/Tension</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>None</td>
</tr>
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<td>Difficulty Concentrating</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>Reduced</td>
<td>None</td>
</tr>
<tr>
<td>Restlessness/Impatience</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>Reduced</td>
<td>None</td>
</tr>
<tr>
<td>Headache</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Drowsiness/Alertness</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Gastrointestinal Problems</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Other Criteria</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Depression</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>Reduced</td>
<td>None</td>
</tr>
<tr>
<td>Fatigue</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hunger</td>
<td>None</td>
<td>None</td>
<td>Reduced</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Insomnia</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Behavioral effects of nicotine gum

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Baseline</th>
<th>Abstinence</th>
<th>F value for Nicotine &lt; Placebo&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>Placebo</td>
<td>0.4</td>
<td>0.9</td>
<td>10.7**</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>0.5</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>Placebo</td>
<td>0.6</td>
<td>1.1</td>
<td>4.7*</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>0.6</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>Placebo</td>
<td>0.4</td>
<td>0.9</td>
<td>7.5*</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>0.6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Impatience</td>
<td>Placebo</td>
<td>0.5</td>
<td>1.0</td>
<td>10.5**</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>0.7</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> All ratings based on scale of 0=not present, 1=mild, 2=moderate, and 3=severe. All standard errors <0.15.

<sup>b</sup> F value for the interaction that the increase in the behavioral rating would be less for the nicotine group than for the placebo group, df=(1,79).

* p<.05
** p<.01
nonsmokers. Thus, nicotine gum did not reverse abstinence-induced analgesia.

In summary, nicotine gum decreases both self-reported and observed symptoms of tobacco withdrawal. The most consistent effect of nicotine gum is to decrease irritability/anger/frustration. Whether the gum reduces other withdrawal phenomena, such as weight gain, is unclear.

BIOCHEMICAL/PHYSIOLOGICAL EFFECTS

One hypothesis to explain the ability of nicotine gum to decrease withdrawal symptoms is that the gum dampens the arousal associated with tobacco withdrawal. The only biochemical effects of nicotine gum that have been tested are its effects on serum glucose and excreted catecholamines. Gennser et al. (1975) and Manning and Feyerabend (1976) reported that neither the 2 mg nor the 4 mg gum changed the blood glucose of pregnant women. West et al. (1984) reported that the fall in excreted catecholamines during abstinence was similar in nicotine (2 mg) and placebo groups.

The physiological effects of nicotine gum that have been examined are its effects on cardiovascular function, tremor, and, in one study, evoked potentials. Most studies of the cardiovascular effects of nicotine gum on nonsmokers and nonabstinent smokers report that the 4 mg gum but not the 2 mg gum increases heart rate (Fredholm and Sjorgen 1979; Gennser et al. 1975; Jarvik 1982; Manning and Feyerabend 1976; Nyberg et al. 1982). Neither dose of gum influenced EKG measures or blood pressure (Fredholm and Sjorgen 1979; Nyberg et al. 1982). A report that the 4 mg gum decreases skin temperature (Fredholm and Sjorgen 1979) was not replicated (Nyberg et al. 1982). Among the studies of the effect of nicotine gum on the cardiovascular response of abstinent smokers, two reported that nicotine gum 2 mg dampened the fall in heart rate during abstinence (Schneider et al. 1984; West et al. 1984); however, our study (Hughes et al. 1984) failed to replicate this finding. In addition, our study (Hughes et al. 1984) found that nicotine gum tended to reduce the increase in orthostatic response (i.e., the increase in heart rate upon standing) after abstinence.

The two other physiological responses that have been studied are tremor and evoked potentials. The 4 mg, but not the 2 mg, dose of gum increased hand tremor in nonabstinent smokers (Shiffman et al. 1983). The 2 mg dose also failed to counteract the decrease in tremor after abstinence in our study. Finally, nicotine gum has been reported to have the same effect as smoking on visual evoked potentials (Milgrom-Friedman et al. 1981).

In summary, the effects of the gum on biochemical and physiological indices of arousal appear to be dose-dependent; i.e., the 4 mg gum does cause some changes, but the 2 mg gum does not appear to have any significant effects.
TIME COURSE OF NICOTINE EFFECTS

The time course of a drug's effects may be crucial to its ability to produce therapeutic effects. The onset of nicotine gum's effects appears quite rapidly (see figure). In two studies, the gum reduced total withdrawal discomfort within 24 hours (Hughes et al. 1984, West et al. 1984) and in a third study within 48 hours (Schneider et al. 1984).

The duration of the effects of nicotine gum has not been well studied. In our study, the effect of the gum tended to decrease over four days (see figure) and a similar effect appeared to occur in the study of Schneider et al. (1984). Unfortunately, no studies have tracked gum effects over longer periods.

Schneider and Jarvik (1984) also demonstrated an interaction between time of day and the effect of the gum such that the nicotine gum reduced withdrawal symptoms later in the day more than it reduced withdrawal symptoms earlier in the day. Whether this interaction was due to diurnal variation in the intensity of withdrawal symptoms or in the intensity of nicotine effects is unclear.

NICOTINIC VS. EXPECTANCY EFFECTS

Subjects in "double-blind" studies of psychoactive drugs can often tell if they are receiving active drug (e.g., Brownell and Stunkard 1982, Johnson and Hughes 1976). There is anecdotal evidence that smokers (Schneider et al. 1977) and their therapists (Fagerstrom 1982; Westling 1976) are able to discriminate nicotine from placebo gum. Such knowledge of drug receipt may produce expectancies that will influence tobacco withdrawal symptoms (Gritz 1980) and the efficacy of nicotine gum (Fagerstrom and Strom 1981); thus, it is particularly important to verify that any effects of nicotine gum are not actually expectancy effects.

In our study we directly tested whether the reduction in withdrawal symptoms by nicotine gum could have been due to subjects' identification of whether they received nicotine or placebo gum (Hughes and Krahn, in press). Although many subjects in our study could identify their drug assignment, the effect of nicotine gum on withdrawal discomfort was present independent of identification of drug assignment (table 3).

SIGNIFICANCE

The studies reviewed indicate that nicotine gum does relieve withdrawal discomfort. This fact might be interpreted to support the hypothesis that tobacco withdrawal is due to nicotine deprivation (e.g., Schachter 1978); however, the logic of this interpretation can be questioned. Demonstration that a drug relieves a syndrome is consistent with, but not equivalent to, a demonstration that the syndrome is due to deprivation of the drug or class of drugs. Morphine relieves congestive heart failure but congestive
Table 3. Analysis of variance of withdrawal discomfort score by drug group and belief of drug assignment

<table>
<thead>
<tr>
<th>Identification of Drug Assignment</th>
<th>Correct</th>
<th>Incorrect</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5.34 (n=19)</td>
<td>2.14 (n=15)</td>
<td>3.03 (n=16)</td>
</tr>
<tr>
<td>Nicotine</td>
<td>1.10 (n=34)</td>
<td>0.03 (n=6)</td>
<td>0.74 (n=9)</td>
</tr>
</tbody>
</table>

\[ F \text{ for main effect of drug group (1,90) = 14.8, } p < 0.001 \]
\[ F \text{ for interaction between drug group and belief (2,89) < 1.0, } p > 0.10 \]

\[ t \text{ for nicotine < placebo within correct identification group (14) = 14.4, } p < 0.001 \]
\[ t \text{ for nicotine < placebo within incorrect identification group (16) = 1.7, } p = 0.06 \]
\[ t \text{ for nicotine < placebo within uncertain (24) = 2.1, } p = 0.04 \]
heart failure is not due to morphine deprivation. Several alternative explanations are available. Perhaps nicotine relieves irritability, etc., regardless of its source.

Another interpretation of the finding that nicotine reduces withdrawal discomfort is that this indicates the efficacy of nicotine gum is due to its ability to relieve withdrawal. However, none of the previous studies have directly related reduction in withdrawal discomfort by nicotine to improved long-term cessation success.

In summary, many of the short-term effects of nicotine gum are consistent with theories that nicotine dependence plays a role in maintaining smoking. However, other results directly contradict this hypothesis and crucial tests of the hypothesis (e.g., does nicotine gum relieve withdrawal which then improves cessation?) have not been reported.

FUTURE RESEARCH

In the introduction we mentioned that several nonpharmacologic factors can control nicotine's actions (e.g., instructional set). Thus, one explanation for the many inconsistent results of studies of nicotine gum is that nonpharmacologic factors that control nicotine's actions varied across the studies. If this is true, then empirical studies are needed to determine those factors that are necessary and sufficient for nicotine gum to have beneficial effects. For example, studies that contrast different doses (1 vs. 2 vs. 4 mg), durations of administration (1 vs. 3 vs. 6 months), schedules (fixed time vs. ad-lib) or subjects ("dependent" vs. "nondependent" smokers) must be more useful than simple outcome studies pitting nicotine gum vs. a standard treatment.

REFERENCES


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