Nicotine Gum vs. Placebo Gum:
Comparisons of Withdrawal
Symptoms and Success Rates

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Until recently, the importance of nicotine in smoking and the existence of nicotine-specific withdrawal have been hard to demonstrate empirically. Several investigators succeeded in focusing attention on nicotine and presenting a strong case for nicotine as the critical factor in smoking dependence (Gritz 1980b; Jarvik 1970; Russell 1980; Russell and Feyerabend 1978). However, smoking is a complex dependence in which pharmacological and psychosocial reinforcement systems are confounded. What we have needed is a direct means of testing the relative contributions of these factors to why people smoke, to variations in individual habit patterns, and to why cessation is difficult and relapse rates high.

The introduction of nicotine gum and its placebo counterpart (Ferno et al. 1973) has provided a means of manipulating nicotine intake independent of the behaviors associated with the habit. The idea of varying nicotine levels and studying withdrawal is not new. Manipulation of nicotine was reported as early as 1942 by Johnston using repeated doses of nicotine in injections. Johnston (1942) administered the injections to himself and several volunteers and reported dysphoric reactions upon their abrupt cessation. In laboratory settings, intravenous nicotine studies provide basic information for the role of nicotine in smoking (Henningfield et al. 1983; Feyerabend et al. 1985). For application in cessation studies, the intravenous method is impractical.

Surprisingly, snuff has not been used to vary nicotine levels in the study of withdrawal nor in any formal cessation procedure. Given that there are snuff users and absorption of nicotine is rapid (Russell et al. 1980a), nasal snuff use may approximate the nicotine delivery in a cigarette best while eliminating the habit reinforcers. Gritz et al. (1981) have noted that comparable levels of nicotine can be achieved using chewing tobacco as with cigarettes. In our own laboratory experience, we have found smokers reluctant to switch to snuff in attempting cessation. Similarly, another means of separating nicotine from the other reinforcers of smoke would be in the use of nicotine-free cigarettes. These could be used in a long-term cessation study and would allow alteration in nicotine intake with controls for psychological variables. Unfortunately, nicotine-free cigarettes have also been unacceptable to smokers even for short periods in an experimental context.
Finally, one of the most promising tools for the study of the role of nicotine in withdrawal and cessation may come with a transdermal nicotine patch (Rose et al. 1984). This would allow as does nicotine gum the testing of withdrawal and cessation in a potentially acceptable form and for prolonged periods of time.

For the present, we have access to nicotine gum in several doses. Nicotine gum is both easily self-administered and well received by smokers. It allows for the manipulation of nicotine intake during smoking abstinence while holding psychosocial and sensory factors constant. Russell et al. (1976a); Russell et al. (1977); Russell et al. (1980b); and McNabb et al. (1982) have demonstrated that nicotine in gum can theoretically produce blood levels sufficient to prevent nicotine withdrawal. In addition, the slow buccal absorption does not produce the peak nicotine "boll" delivered in smoke. Controlling nicotine withdrawal and nicotine seeking should enhance success rates if nicotine is important in cessation. In effect, the active and placebo gums allow for systematic testing of the role of nicotine in the appearance and alleviation of withdrawal and in the cessation process.

The specific questions we addressed in testing may be summarized for outcome as follows: 1) Will use of nicotine gum enhance success rates over placebo? 2) Under what conditions (dispensed, clinic-support) will this occur?

The specific questions regarding withdrawal are: 1) Is there nicotine-specific withdrawal? 2) Can nicotine replacement with gum be effective in alleviating or preventing withdrawal? 3) Are certain symptoms or emotional states more responsive to nicotine replacement than others?

While there are many questions concerning selection of smokers (see Jarvik and Schneider 1984) and parameters for proper use, the present article will focus on outcome and withdrawal data. Results are summarized for two studies (clinic and dispensary) in which outcome and withdrawal have been tested. Both published and previously unpublished findings are reported.

OUTCOME

In several of the initial gum studies, titration was the focus of study (Brantmark et al. 1973; Russell et al. 1976b; Turner et al. 1977). In the first two studies, active gum reduced tobacco consumption compared to placebo controls. However, the efficacy of nicotine gum is best studied when total smoking abstinence is required. Several efforts to study total cessation with nicotine gum were marred by lack of chemical verification (e.g., Puska et al. 1979). absence of long-term followup (e.g., Malcom et al. 1980) or inadequate controls. Raw et al. (1980) found improved cessation rates with nicotine gum but compared those results to a "psychological" control tested 2 years earlier.

Prior to our study, several investigators reported the advantage of nicotine gum over placebo, depending, in part, upon the support
conditions. Jarvis et al. (1982) implemented a cessation study in which clinic support was provided and cessation was verified with carbon monoxide. Nicotine gum significantly elevated success rates at 1 year compared to a lower dose “placebo” control. The placebo in that study was an unbuffered 1 mg nicotine gum which could produce an active effect if enough was chewed (20 pieces). However, conceptualized as a dose-response study, the results suggest that the more nicotine replacement, the greater the success. Jarvis et al. (1982) also reported that success rates were elevated for nicotine gum when restarts were included. For a detailed description of this study, see Russell and Jarvis, this volume.

Fagerstrom (1982) reported striking success rates in a Swedish clinic for both nicotine and placebo groups with a significantly higher success rate for the active gum subjects at 6 months. This significant effect, however, disappeared at 1 year although the trends still favor the active gum. In this study, as in Jarvis et al. (1982), success is attributed to the interaction between active gum use and clinic support.

In the above studies, the subjects were studied by researchers knowledgeable in the effects and appropriate use of gum. In a study reported by the British Thoracic Society (1983), nicotine gum plus advice and a smoking dangers booklet did not improve success rates over advice alone, advice plus the booklet, or placebo gum plus advice and the booklet. Rates were low (between 8-12%) across groups. The authors attribute their poor findings to the population (chest clinic patients who may have been unmotivated) and to poor instructions but concluded that their study reflects instructed use in the real world. In a critique of that study, Jarvis and Russell (1983) take issue with that conclusion and point out additional flaws in the study. To those criticisms it should be added that nicotine gum in the British Thoracic Society study (1983) was given with “instructions to substitute it for a cigarette when there was an urge to smoke.” From our own pilot work, we have found that allowing any smoking with chewing undermines cessation.

The issue of what conditions of support may be necessary for success with nicotine gum was the focus of our outcome testing (Schneider et al. 1983). Two studies had been designed to test the efficacy of nicotine vs. placebo gum use. In one, clinic support was provided for both groups; in the other, gum was “dispensed” with minimal intervention. The latter was intended to mimic administration of gum by physician prescription where little support and/or followup may be provided. The most recent clinical replications (Hall et al. 1984; Hjalmarson 1984; Killen et al. 1984) and recent physician studies (Jamrozik et al. 1984; Russell et al. 1983) are discussed later.

Method

In both studies, subjects were heavy smokers (30-35 cigarettes a day) in good health who had tried repeatedly to quit smoking. The studies were double-blind, and subjects were allowed to chew the gum ad lib both in terms of daily number of pieces and length of time on gum. The clinic study included measures of withdrawal which are
described in the next section. Baseline questionnaires and repeated measures testing are listed in Table 1. The tests listed under repeated measures were all given at baseline with the exception of the questionnaires on side effects and gum use.

### Table 1

**Materials**

**Baseline Materials - All Subjects**

1. Consent Forms
2. Subject Bill of Rights
3. Health Screening
4. Smoking and Quitting History (includes demographics)
5. Motivation Questionnaire
6. Expectations Questionnaire
7. Why I Smoke
8. Smoking Occasions
9. Why I Want to Quit
10. Fagerstrom Tolerance Questionnaire
11. Weight Questionnaire
12. Gum Instructions
13. Address Sheet
14. Subject Comments and Questions

**Repeated Measures - Clinic Groups**

1. Pulse Rate
2. Weight
3. Daily Abstinence - 2 Scales:
   - Schneider Smoker Complaint Scale (SCS)
   - Shiffman-Jarvik Scale
4. Mood Checklist
5. Carbon Monoxide (as verification in all groups; as feedback in clinic groups)
6. Side Effects
7. Gum Use - Satisfaction and Open-Ended Remarks

**Treatment**

Treatment consisted of either 2 mg nicotine gum or placebo gum. The low dose (2 mg) was chosen to avoid side effects associated with 4 mg gum, although eventually mixed use of both doses may prove advantageous (see Schneider et al., 1977). Subjects were instructed to chew each piece slowly for 20 to 30 minutes to insure the release of nicotine. Buccal absorption was explained. Weaning from nicotine may be said to begin with the switch from cigarettes to gum in terms of both the slower absorption and reduced speed of reinforcement. With 2 mg gum the immediate blood levels are reduced compared to...
4 mg gum or a 1.2 mg cigarette as noted earlier. Three-month prolonged use of 2 mg gum has also recently been shown to produce significantly less nicotine than cigarettes or 4 mg gum (McNabb 1984). The oral-manipulative component of gum use was expected to aid cessation while not disrupting extinction of smoking behaviors.

Procedure

Subjects were given the baseline questionnaires for survey purposes and for assessment of their selective and predictive value. Baseline scores were obtained for all repeated measures and tests (see table 1).

Sixty subjects participated in the clinic study - 30 subjects in the nicotine group and 30 subjects in the placebo group. Total abstinence was required and was verified at all test intervals (including daily the first week) with carbon monoxide expired air analyses. Following baseline testing (always on a Friday), clinic subjects were instructed to quit the next Monday morning and were given pieces of gum to take home. Subjects then came to the laboratory daily for 1 week for testing (withdrawal, CO, pulse rate, gum use, weight) and for individual support sessions with the experimenter. The sessions lasted between 1/2 and 1 hour. Clinic subjects were also asked to fill out withdrawal scales at home in the morning and evening for the first week of abstinence (see withdrawal section). Followup test intervals (including all measures and support) occurred weekly for 4 additional weeks and then at 3 months, 6 months, and 1 year. Not counting baseline, this amounted to a total of 12 visits for subjects completing the study.

The dispensary groups consisted of 13 nicotine gum subjects and 23 placebo gum subjects. Testing at baseline was identical for clinic and dispensary groups. However, subjects in the dispensary groups did not return to the laboratory for first-week testing and support. One appearance was required (on Thursdays) for gum supplies and CO verification of abstinence in the first week. Thereafter, subjects appeared once a week for 4 more weeks and at 3 months, 6 months, and 1 year for verification and supplies. No testing (besides CO) was allowed at any of the followup intervals. Thus, the baseline testing and abstinence checks served as minimal intervention compared to the clinic groups.

Results

Results of the clinic study and dispensary study appear in Schneider et al. (1983). A survival analysis was performed on outcome curves for both groups in the clinic study. The success rates are presented in figure 1. The nicotine group was significantly more successful than the placebo group in abstinence over time (p<.03).
As can be seen from figure 1, the differences between groups are most apparent at 3-4 weeks and at 6 months. The groups are fairly equivalent during first-week treatment and separate by the second week with a peak difference at 6 months (28%). Between 6 months and 1 year, relapse in the nicotine group reduces the difference to 10%.

Success curves for the two dispensary groups are presented in figure 2. The data in figure 2 indicate that neither 2 mg nor placebo gum was effective in cessation when no support or guidance was offered. After 1 week, both groups had dropped to the same level and by 1 year, low rates of 8% for nicotine and 13% for placebo were observed. It should be noted that subjects stopped using gum in the dispensary groups within the first few days to 1 week of the study. The only difference in the clinic and dispensary groups following baseline testing and instructions was the first-week support and testing provided for the clinic groups. It is assumed that the clinic appearances indirectly and directly encouraged the subjects to continue gum use.

With support, nicotine gum clearly enhanced short-term (6-month) success rates over placebo (Schneider et al. 1983). These clinic results are consistent with the placebo-controlled findings of...
Fagerstrom (1982) and Jarvis et al. (1982), although in the latter success rates between treatments were still significant at 1 year. The differences between the groups in the Jarvis et al. (1982) study were as high as 47% with nicotine gum vs. 21% treated with an unbuffered 1 mg nicotine placebo. When a stricter criterion of outcome was used in which no relapses between the initial assessment and end assessment were allowed, these figures remained significant at 31% in the active group vs. 14% in the placebo group.

In a study comparing nicotine gum to placebo gum (Hjalmarson 1984), success rates were also doubled at 1 year, with 29% abstaining in the active gum group vs. 16% in the placebo group. In Hall et al. (1984) and Killen et al. (1984), the value of clinic support in combination with active gum use was demonstrated in a different format. In Hall et al. (1984), subjects were assigned to either nicotine gum with minimal intervention, intensive behavioral treatment by itself, or to a combination of the intensive behavioral treatment plus nicotine gum. The combination of the nicotine gum plus the intensive treatment produced better success rates than the other two conditions. This was significant at the 3-month and 6-month intervals, but not at 1 year. This was validated with blood cotinine levels and those with the higher levels appear to be helped.
more by nicotine gum than those with lower levels at the start of
the study. Interestingly, and in contrast to the physician studies
to be discussed below, the low contact nicotine gum group did better
than the behavioral only group; however, the low contact group did
meet four times over a 3-week period, which in itself constitutes
some intervention.

In Killen et al. (1984) the subjects were assigned to one of three
conditions: nicotine gum only, skills training only, or a combi-
nation of skills training and nicotine gum. There was some inter-
vention in the nicotine gum only group in that they attended a
clinic weekly for 7 weeks to receive gum and complete assessments.
Abstinence rates at 10-1/2 month followup were 23% for nicotine gum
only, 30% for skills training only, and 50% for a combination of the
skills training plus nicotine gum. Carbon monoxide and thiocyanate
levels verified the subjects' reports of abstinence. In this study
a combined treatment doubled the rates obtained with nicotine gum
alone.

The studies which look at some form of dispensary tactic show mixed
results. In our study, simply dispensing nicotine or placebo gum
resulted in early failure and in no differences between the groups.
Similar findings were observed in the British Thoracic Society
(1983) and Jamrozik et al. (1984) studies. The British study has
been correctly critiqued by Jarvis and Russell (1983) and, in
general, problems with dispensing may be due to inadequate
instruction and training in proper gum use.

While the clinical studies clearly show that support systems are
instrumental in producing successful cessation, we cannot conclude
that dispensing cannot be successful. It may be that variables
involving the carefully instructed use of the active gum may play a
part in its viability as a smoking cessation tool. For example,
Russell et al. (1983) reported a study in which there was a
nonintervention group; a second group receiving advice to stop
smoking, a booklet, and a warning of followup; and a third group
receiving the same as the second group but with the offer of
nicotine chewing gum. The results showed that the overall rate of
cessation is lower than anything observed in clinics. For the
no-advice group there was a 3.9% success rate, for advice only a
4.1% success rate, and for advice plus nicotine gum an 8.8% success
rate. However, when the data were analyzed by the amount of gum
used, those subjects who used more than one box of gum had a
long-term success rate of 24% after validation. This is a
surprisingly high success rate considering the very minimal
intervention in this study. It suggests that if we can identify the
use variables which enhance success, we can increase success rates
with the dispensing of gum. This is particularly important in that
physicians can prescribe this preparation and have the opportunity
to help in the treatment of cigarette smoking.

In a variation of the low contact physician studies, Fagerstrom
(1985) looked at short- vs. long-term followup with nicotine gum vs.
no gum. He found significant differences between nicotine gum and
no gum groups at 1 year with validation. Again, the rates were lower than in any of the clinical studies, but differences were still observed. At 12 months the following was reported for four groups: a group given advice, long-term followup, and nicotine gum showed a 27% success rate. Advice, short-term followup, and nicotine gum yielded a 22% success rate. Advice, long-term followup, and no gum reduced success to 15%. Finally advice, short-term followup, and no gum produced a low 3% success rate.

The clinic and physician studies taken together show that success rates can be enhanced 1) with active gum compared to no gum or placebo, and 2) with support vs. minimal or no behavioral intervention. It should be noted that in the present study it is not necessarily known which aspects of the support system contributed to success. On the one hand, individual attention and problem solving were offered by the experimenters. Lowered carbon monoxide levels served as positive feedback. Test taking, in itself, may have helped by allowing the subject an outlet for dysphoria and the difficulty of quitting. Thus, strong psychological support was provided in the first week and ensuing followup visits. On the other hand, by coming to the laboratory daily, the subject was encouraged to continue using the gum. Side effects and fears associated with use could be allayed and increased use tested in a "safe" setting. It may be this initial monitoring of use per se that accounts for success.

One final issue that also has not been systematically tested is that of length of use. Several investigators have observed post hoc that longer use (3 to 4 months) may be a significant factor in outcome (Russell et al. 1980b, 1983; Wilhelmsen and Hjalmarson 1980) and that by extending use past at least one box, success rates can be elevated.

In summary, initial use and prolonged use of nicotine gum may both figure prominently in outcome. We cannot conclude from the present work that the enhancement of success with clinical support is due to psychological factors alone. Use variables (dose, number of pieces, length of time on gum instructions) must be defined through controlled evaluation. We suggest that appropriate dose and carefully instructed use are critical and that intervention should focus on long-term relapse prevention. Ultimately, a combination consisting of physicians advising patients to stop, treatment of pharmacological dependence, and long-term behavioral training and support could provide the most valuable smoking cessation intervention to date.

WITHDRAWAL

Underlying the development of nicotine gum and its use in cessation are the assumptions that nicotine withdrawal occurs and that its alleviation through a replacement procedure will improve success rates. The questions are 1) Can nicotine-specific withdrawal be demonstrated? and 2) If so, will replacement other than in bolus smoke delivery be effective? If nicotine gum alleviates or prevents
symptoms compared to placebo, then it is effective. By inference, withdrawal symptoms (to the degree they are relieved) can be attributed to the removal of nicotine per se. Ultimately, symptom relief should correlate with short-term and/or long-term success in cessation.

In the early studies using nicotine gum titration effects, by combining gum and smoking and continued partial reinforcement with smoking, precluded the assessment of withdrawal. Brantmark et al. (1973) acknowledged that their attempts to measure withdrawal were rendered "meaningless" because of the simultaneous use of gum and smoking. In Puska et al. (1979) the same problem is encountered. In a recent and interesting study by West et al. (1984), smokers' baseline blood levels were taken and compared in one group with a switch to an ultra-low nicotine cigarette. It was observed that plasma nicotine concentrations dropped 60% when they were switched to the ultra-low cigarette. A slight drop in heart rate and an increase in hunger were observed with the lowered levels. However, it was not paralleled by typical withdrawal symptoms such as irritability. Ironically, this is consistent with the concept of a lesser replacement of nicotine with nicotine gum. That is, in both instances the partial amount of nicotine obtained provides enough nicotine to alleviate irritability. Although some physiological changes were observed in this study, nicotine-specific withdrawal will probably be best demonstrated by comparing nicotine replacement to no replacement.

In Jarvis et al. (1982), withdrawal symptoms were measured in nicotine and placebo groups during total abstinence from smoking. Ratings of withdrawal were taken once a week and averaged across 6 weeks. Unfortunately, abstinence was confirmed with carbon monoxide breath analyses only at 1 year and not at earlier intervals. It should also be noted that not all subjects attended all sessions, although this probably occurred for both groups. The authors used an unbuffered 1 mg nicotine gum as their placebo which, as they point out, can produce a pharmacological effect when enough is chewed (20 pieces). In this sense, the study is a dose-response comparison. Given these qualifications, this remains one of the few early tests of withdrawal during total abstinence. Jarvis et al. (1982) reported significantly "less irritability" and "less hunger" for the 2 mg group compared to the 1 mg unbuffered controls. Several other symptoms were reduced in the 2 mg group but these differences were not significant.

In our clinic study, withdrawal measures were obtained daily for 5 days for 50 subjects remaining abstinent. Twenty-six subjects formed the nicotine group and 24 formed the placebo group. To insure completion of scales, the scales were given in the laboratory (in-lab) each day. Carbon monoxide tests were also taken daily to confirm self-reported abstinence.

Pulse rate was taken as a physiological measure of withdrawal. Subjective responses were obtained using a Smoker Complaint Scale (SCS), the Shiffman-Jarvik (1976) Scale, and a mood checklist.
Ratings were obtained for four physical symptoms associated with withdrawal from smoking (Shiffman 1979). Because of item wording and scaling problems in the Shiffman-Jarvik Scale, the study focus was on the SCS. This scale was derived from smokers' reports on the nature of withdrawal symptoms experienced in previous cessation attempts. These reports were obtained from pilot subjects and subjects in a "cold turkey" study. Responses were scaled so that 1 represented "very definitely not" and 7 represented "very definitely." The SCS consisted of the following 14 items: anxiety, irritability, fluctuations in mood, craving for cigarettes, concern about weight, trouble sleeping, disorientation, impaired concentration, depression, feeling left out, restlessness, hostility, annoyance, and frustration. Where items overlapped with the Shiffman-Jarvik Scale (e.g., irritability), responses were checked for consistency between the scales. The mood checklist is described in the following section along with those results. The four physical items included: nausea, constipation, diarrhea, and headache.

Results

Pulse rate and SCS total scores appear in Schneider et al. (1984). Pulse rates decreased significantly for placebo subjects (15 bpm over 5 days) compared to a slight reduction in those using active gum (4 bpm over 5 days). For SCS totals a repeated measures ANOVA with trends was performed on the data. A significant effect of treatment was observed (p<.03) as well as a significant quadratic treatment x time interaction (p<.01). The pattern was as follows: baselines did not differ between groups (separate ANOVA); for both groups there was a rise from baseline to Day 1; thereafter, withdrawal in the placebo group continued to increase in severity while symptom reduction occurred in the nicotine group. Differences between groups were significant for Days 2, 3, and 4. By Day 5, the group scores tended to merge. When baselines were covaried, the results were the same except that the quadratic component became linear. Figures for the pulse rate and withdrawal findings by treatment are presented in Schneider et al. (1984).

We also attempted to look at which items were more sensitive to nicotine replacement than others (previously unreported data, Table 2). As can be seen from Table 2, almost every symptom on the SCS scale except for weight concern and craving showed a significant increase from baseline smoking levels to abstinence days. In addition, annoyed, hostile, irritable, and fluctuations in mood showed significant changes between groups with frustration and depression showing borderline effects.

Craving and weight concern showed no effects on the SCS. From the Shiffman-Jarvik Scale, craving was assessed by asking the question differently in two ways: Do you have an urge to smoke right now? and do you miss a cigarette? On that questionnaire those two items showed significant quadratic treatment effects at the p<.05 level. Given that craving is one of the most important issues, these three items taken together suggest that semantics are going to be a key
TABLE 2

Item Analyses for the SCS Scale*

<table>
<thead>
<tr>
<th>Withdrawal Symptom</th>
<th>Main Effect Time</th>
<th>Main Effect Treatment</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annoyed</td>
<td>p&lt;0.001**</td>
<td>p&lt;0.008</td>
<td></td>
</tr>
<tr>
<td>Hostile</td>
<td>p&lt;0.001**</td>
<td>p&lt;0.03</td>
<td>p&lt;0.05**</td>
</tr>
<tr>
<td>Irritable</td>
<td>p&lt;0.01</td>
<td>p&lt;0.05</td>
<td>p&lt;0.03</td>
</tr>
<tr>
<td>Fluctuations in Mood</td>
<td>p&lt;0.01</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Frustration</td>
<td>p&lt;0.001**</td>
<td>p&lt;0.06</td>
<td>ns</td>
</tr>
<tr>
<td>Depression</td>
<td>p&lt;0.002**</td>
<td>p&lt;0.07</td>
<td>ns</td>
</tr>
<tr>
<td>Left Out</td>
<td>p&lt;0.02**</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Anxiety</td>
<td>p&lt;0.01</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Concentration</td>
<td>p&lt;0.001</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Disorientation</td>
<td>p&lt;0.01</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Restlessness</td>
<td>p&lt;0.01</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Trouble Sleeping</td>
<td>ns</td>
<td>ns</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Concern About Weight</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Craving</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Analyses of Variances were performed on each item and included baseline and 5 days of abstinence.

**These differences disappeared when baseline was used as a covariate. Thus, there was an initial rise from baseline (still smoking) to abstinence days but no additional differences in temporal course beyond that rise.

It should be kept in mind that with ad lib use we are not certain to what degree differences in amount of chewing accounted for the results. For example, where there are no differences between groups, it may be that more pieces of 2 mg gum or a higher dose is indicated, particularly in the first week. In a current uncontrolled clinical trial it has been observed that lethargy, spaciness, and disorientation respond to the 4 mg dose of gum whereas the 2 mg dose is less effective. Also, consistent and minimal use of 2 mg gum (10 to 15 pieces daily) helped reduce symptoms such as anxiety, irritability, and restlessness better than low level (5 to 6 pieces daily). A dose-response study should define the extent to
which symptoms can be alleviated with nicotine gum (Schneider, unpublished data; manuscript in preparation).

An ANCOVA was also performed on the withdrawal data described above for treatment x sex. Thus, these results are the same as the SCS totals described above except that conditions are subdivided into male and female. The treatment x sex findings are graphed in figure 3. The number of subjects within each category were as follows: nicotine gum female (12); nicotine gum male (14); placebo gum female (14); placebo gum male (10).

The main effect of treatment was significant \( (p < 0.05) \), and there is little overlap between treatments (both placebo groups vs. both nicotine groups in figure 3). The pattern (with baselines covaried) showed a significant quadratic component \( (p < 0.01) \) with all groups reporting withdrawal at Day 1, separating during the middle 3 days, and merging at Day 5. No main effect of sex was observed and there were no interactions between treatment and sex over time. This may have been a consequence of the small sample size when groups are divided in this manner. It is tempting to explore possible gender effects further in a larger sample. As Gritz (1980a) has noted, male/female differences have received little attention.

The pattern of responding suggests that nicotine gum may not be effective in first-day withdrawal. This could be a consequence of anticipation factors, of inadequate dose (including the initial

![Graph of SCS Withdrawal Responses by Treatment and Gender](image)
change from inhalation bolus to gum. Improper gum use (subjects may have waited for first clinic visit) or may be attributable to changes with cessation (e.g., loss of ritual behaviors). The effectiveness of the gum becomes apparent as cessation progresses. A dose-response study should clarify whether symptoms can be alleviated entirely with replacement.

In addition to totals, specific items, and sex differences, we looked at a time-of-day effect in compliant subjects. Subjects were asked to fill out the withdrawal scales at home in the morning and evening. Of the 50 abstinent subjects providing the in-lab data, 3.2 cooperated in filling out the home scales. These results have been reported in Schneider and Jarvik (1984). The basic finding was a treatment x time-of-day effect. For placebo subjects, the severity of withdrawal symptoms was significantly higher than nicotine subject responses and increased in the evenings compared to a more stable withdrawal level in the nicotine group. The results indicate that withdrawal varies within a given day as well as across days and that nicotine is implicated in these fluctuations.

Mood Effects

A mood checklist (items were taken from the POMS mood scale) included 27 items reflective of positive and negative states. Thirteen items were positive: active, alert, carefree, cheerful, clear-headed, considerate, efficient, friendly, full-of-pep, lively, optimistic, proud, and relaxed. Thirteen items were negative: angry, bad-tempered, confused, hopeless, miserable, muddled, nervous, sad, shaky, spiteful, tense, unworthy, and worn-out. One item was dropped (ready-to-fight) because some subjects perceived this as positive and others as negative. In responding, the subject checked as many of the adjectives as applied at the moment. There was no mandatory responding on a scale as required with the SCS items. Responses were recorded as total number checked for the 13 positive items and total checked for the 13 negative items. These totals were obtained for baseline scores and for each of the 5 days of abstinence. For the positive items, the results (previously unreported) are presented in figure 4.

A repeated measures ANOVA with trends was performed on the positive item totals for all days. The results showed a significant effect of treatment (p<.01) as well as a significant quadratic treatment x time effect (p<.02). Subjects on nicotine gum showed only a slight decrease in positive responses checked. For placebo subjects, the drop from baseline to Day 1 is fairly sharp and stays lowered through the first few days. Note that for the SCS scores, the effects are also quadratic but the separation between groups does not occur until Day 2.

The results for negative items (also previously unreported) are consistent with the positive affect pattern by treatment. Placebo gum subjects showed a greater increase in negative responses than nicotine subjects. The repeated measures ANOVA with trends showed no significant main effects or overall interactions, so a
significant quadratic treatment x time effect was ignored. The problem with the negative item testing was that a floor effect occurred. Out of the 13 possible responses, mean responding ranged from 0.50 to 1.70 for the placebo group and 0.53 to 1.11 for the nicotine group. A review of the items suggests that a social desirability effect may have been operating. The items are very strongly negative and tend to go against feelings of self-worth that a smoker trying to quit may be seeking. Because the items are checked, there is no qualifying of the response. By contrast, we were able to assess negative changes in state with the SCS through use of scaled responding and through use of specific complaints associated with smoking cessation.

The withdrawal findings for 5 days of first-week abstinence provide support for the proposed mechanism of action with gum use during cessation. Nicotine replacement alleviated or prevented symptoms compared to nonreplacement with placebo. These findings have been supported by recent reports in the literature of nicotine-alleviated withdrawal (Hughes et al. 1984; West et al. 1984).

In the Hughes et al. (1984) study, symptoms of withdrawal were measured in 100 smokers. After baseline measurement subjects received either nicotine or placebo gum in a double-blind study and were tested in the first, second, and fourth evenings of abstinence. Hughes et al. (1984) report reductions in irritability, anxiety, difficulty concentrating, restlessness, and impatience between groups with nicotine gum alleviating the symptoms. The
nicotine replacement did not reduce increases in craving, hunger, eating, insomnia, tremulousness, or supine heart rate after cessation.

In West et al. (1984) 48 smokers were either given 2 mg nicotine gum or a .5 mg unbuffered nicotine gum "placebo" for 24 hours of cigarette deprivation. In that study, the 2 mg gum alleviated irritability, depression, and difficulties with social interaction, but not hunger or ability to concentrate. As in our study, the drop in heart rate was reduced with active gum. In West et al. (1984) and Hughes et al. (1984) the authors conclude that nicotine replacement reduces symptoms of withdrawal and that nicotine deprivation plays a significant role in producing these effects.

In a recent paper, West (1984) has summarized the four studies representing tests of withdrawal during total abstinence. In conclusion, we suggest that with proper dosage we may reduce most, if not all, symptoms of withdrawal. Maintenance of higher blood levels will be important while the person is already reducing levels of nicotine from cigarettes. As the person adjusts to changing levels, relief should require less and less replacement with gum. However, we cannot view nicotine dependence and withdrawal as operating only in the short term. Urges to smoke long after cessation may represent conditioned nicotine-seeking and coping behavior.

SUMMARY

Our data and that of researchers in the area clearly provide evidence for nicotine-specific withdrawal and its relief with nicotine gum. In addition, outcome efficacy is enhanced when nicotine gum is combined with behavioral treatment.

Nicotine gum appears to be valuable both as a systematic tool and as a means of combating short- and long-term nicotine seeking that contribute to maintenance of smoking and the inability to quit.

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