

Review

Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: A review

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This paper reviews the data on blood nicotine or saliva cotinine concentrations with concomitant smoking and use of nicotine replacement (NR) products. Eleven studies that provided data on blood nicotine concentrations, carbon monoxide in exhaled air, and number of cigarettes smoked were reviewed. At least one day had to be spent on concurrent use of cigarette and NR products. With simultaneous use of smoking and acute NR products (gum and inhaler) the nicotine concentrations were unchanged, whereas they increased (+54%) with nicotine patches. With both types of NR products, the number of cigarettes smoked per day was reduced by approximately 50% and carbon monoxide (CO) by 30%. Where smokers had the intention or received instructions to reduce smoking, a greater reduction in cigarettes smoked and exhaled CO was observed. Despite substantially increased nicotine concentrations (e.g., up to 3 times the approved dose) there were no significant adverse reactions. Concurrent use of NR products and cigarette smoking appears to be safe.

Introduction

When asked about their level of interest in quitting smoking sometime in the future, 54% of European Union smokers express such an interest. Not all of these smokers actually make a serious attempt to quit, however, and only a few percent succeed at each attempt (Hughes, 1992).

Given this scenario, new ways to address the major health threat that smoking causes (e.g., it prematurely shortens the life of 50% of its long term users) are being developed (World Health Organization, 1999). Many believe that smokers who cannot or do not want to quit should at least be encouraged to take steps in the direction of obtaining better control over their smoking, smoking less, reducing risk, and finally, it is hoped, being able to quit (Fagerstrom, Tejding, Westin, & Lunell, 1997). Few if any alternatives to complete and abrupt quitting have

been developed. There is hardly any other medical risk factor with this all-or-none concept. Even illicit-drug-dependence programs do not focus exclusively on abstinence (Reuter, 2000). Typically, if a risk factor cannot be eliminated immediately, it is advisable to work gradually to resolve its negative impact on health. Over the past years there have been increasing data indicating that tobacco smoking may lend itself to harm-minimization procedures. The major rationales for this approach are that, first, the mortality and morbidity from smoking are generally dose related; second, nicotine is what makes smokers smoke; and third, nicotine itself only plays a minor role in the increased risk for death and disease (Balfour, Benowitz, Fagerström, Kunze, & Keil, 2000). Consistent with these rationales, data from a recent prospective study found smokers who reduced their smoking by at least 5 cigarettes per day showed reductions in overall mortality (Nordström, Kinnunen, & Garvey, 2000). Nicotine replacement (NR) products in intervention studies have also been found helpful in reducing smoking in smokers with no interest in quitting (e.g., Bolliger, Zellweger, Danielsson, Biljon, & Robidou, 2000; Fagerstrom et al., 2000).

There has been a concern that reducing smoking could adversely affect the motivation to give up smoking completely. That may not necessarily be the case,

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Table 1. Acute nicotine replacement

Study	N	Duration	Product	Percent Reduction		
				Nic. Conc.	No. of Cigs.	CO
Instruction or intention to reduce						
Carpenter 2000	16	4W	Gum & inhaler	-3% ¹	-51%	-40%
Fagerström 2000	40	2W	Inhaler	-29%	-74%	-38%
Hurt 2000	23	24W	Inhaler	-9% ²	-36%	-13%
Murray 1998	35	260W	Gum	6% ^{1,3}	NA	NA
Fagerstrom 1997	143	4W	Gum, inhaler spray & tablet	-2% ¹	-54%	-35%
Average				-7%	-54%	-29%
Instruction to smoke ad libitum						
Ebert 1984	12	4D	Gum 2 mg	3%	NA	NA
			Gum 4 mg	37%	NA	NA
Russell 1976	43	2D	Gum	-9%	-36%	-25% ⁴
Average				10%	-36%	-25%
Total average				-1%	-50%	-28%

D = Day 1. Cotinine in saliva 3. From 1 to 5 Year follow up
W = Weeks 2. Cotinine in plasma 4. Measured as carboxyhemoglobin

however. One study found that when smokers who were not interested in quitting were offered a smoking reduction program, motivation was significantly increased (Fagerstrom et al., 1997). More importantly, many unmotivated smokers, usually highly dependent, recruited to reduced-smoking studies actually give up smoking eventually (e.g., 9% [Bollinger et al., 2000] and 2–4% [Fagerstrom et al., 1997]).

One method to help unmotivated and highly nicotine-dependent smokers to reduce has been to administer nicotine replacement (NR) products to satisfy their need for nicotine. Theoretically this should lead to fewer cigarettes smoked and to less intake of exhaled carbon monoxide (CO) and other toxins. Nicotine replacement has been used in part due to its good safety profile (Balfour et al., 2000), and because nicotine itself is generally not thought to be involved with cancer and respiratory disease. The role of nicotine in cardiovascular disorders is less clear, although carbon monoxide is thought to play a more important role than nicotine (Balfour et al., 2000). The one possible exception to nicotine's good safety record is that nicotine during pregnancy may be involved in developmental disorders (Slotkin, 1998).

The main purpose of this paper is to review data available on blood nicotine or cotinine concentrations resulting from concomitant cigarette smoking and use of NR, due to concern that a possible increase in concentrations could lead to significant adverse effects. A secondary objective was to review the data included in the studies on number of cigarettes smoked and exhaled CO concentrations. Because acute administration forms of NR (gum and inhaler) produce more detectable effects of nicotine, plus their dose is self administered, we examined their results separately from the slower administration form (patch).

Methods

Studies from any time were searched, and were acquired both from Medline article bibliographies and by asking research colleagues for studies. A requirement for inclusion was that subjects should have spent at least one full day on concurrent use of NR and smoking. Where there were several time points within a treatment, the last point was chosen. Results for nicotine, cotinine, and CO concentrations and for cigarettes per day are presented as mean change from baseline values. Median values were also calculated, but since they were almost identical to the means, only means are shown. Pooling data across studies to conduct a meta-analysis was not possible because the large variability in study designs resulted in heterogeneity of results. Studies are presented in chronological order within each type of product—transdermal or non-transdermal (acute forms) delivery—and summarized in tables.

Results

Acute dosing systems

Russell, Wilson, Feyerabend, and Cole, 1976. Forty-three smokers with an average daily consumption of 36 cigarettes per day participated in a crossover study, with 2 days on placebo and 2 days on 2 mg gum in a randomized order. The smokers were instructed to smoke as they felt inclined and not to make any attempts to cut down, and to chew 10 pieces of 2 mg gum (Nicorette) per day.

The nicotine concentration (measured just after having smoked a cigarette) was reduced from 33 ng/ml at baseline to 24 ng/ml on placebo and to 30 ng/ml on 2 mg gum. Cigarette smoking declined from 33 to 23 and 21 cigarettes per day on placebo gum and 2 mg gum respectively. COHb values were 8% at baseline, 7% on

placebo, and 6% with active gum. For change from baseline in nicotine concentrations, CO, and cigarettes per day for all studies with acute NR, see Table 1. The most common untoward effects were sore mouth/throat and nausea. No serious side effects were observed. The authors concluded about the nicotine concentrations, 'The fact that on the nicotine gum they were not significantly higher than the initial level when smoking . . . supports the view that the individual smoking pattern is modified to regulate nicotine intake.'

Ebert, McNabb, and Snow, 1984. Twelve recovering-alcoholic inpatient smokers were instructed to smoke as they felt the urge for the duration of the 4-day study. The subjects were not interested in either reduction or cessation. On the first day they just smoked, while on the second, third, and fourth days they were instructed to chew 10 pieces per day of placebo, 2 mg, or 4 mg gum (Nicorette). Plasma concentrations of nicotine in the middle of the day were 30 ng/ml with placebo, 31 ng/ml with 2 mg gum, and 41 ng/ml with 4 mg gum. The corresponding numbers of cigarettes per day were 16, 14, and 14, and the respective CO concentrations were 40, 35, and 33 ppm. No baseline smoking and CO data are available. No side effects were reported. The authors concluded that 'subjects appear to have compensated almost completely for the decreased intake from 2 mg gum by decreasing the inhalation of tobacco smoke.'

Fagerström et al., 1997. One hundred and forty-three relatively heavy smokers who were not interested in quitting were recruited. The study duration was 5 weeks with the first week being a sampling week when the smokers were encouraged to test and use all of the 5 NR products available to them: 15 mg patch over 16 hours, gum (2 or 4 mg), spray (1 mg/dose), sublingual tablet (2 mg), and inhaler (all Nicorette products). After the sampling week, half of the subjects could choose what product to use during the remaining 2 weeks while the other half was randomized to product. The smokers were instructed to smoke less and use as much NR as they wished but at all occasions to smoke enough to feel comfortable. After 2 weeks there was a crossover of these conditions for another 2 weeks. Subjects were told from the beginning to use as much NR as they wished and smoke enough to feel comfortable.

At baseline, the saliva cotinine concentrations were 360 ng/ml, and at the end of each 2 week testing period they were 350 and 349 ng/ml respectively. No significant differences were found over time. Choice vs. no choice of product had no effect on the cotinine levels. Number of cigarettes smoked decreased from 22 per day at baseline to 10 cigarettes per day at the end of the study. Carbon monoxide concentrations also decreased significantly from 23 ppm to 15 ppm. Adverse effects indicative of overdose were not seen.

Murray, Nides, Istvan, and Daniels, 1998. Patients with mild to moderate chronic obstructive pulmonary disease

entered this smoking cessation study. Use of 2 mg nicotine chewing gum was encouraged and it was provided liberally even to those who had not quit or had relapsed. At 1-year follow-up, 497 subjects were both smoking and chewing nicotine gum, while 1,625 exclusively smoked. At 3 years the numbers were 103 and 439 respectively, and at 5 years the numbers were 35 and 482 respectively. The saliva cotinine for concurrent smokers and chewers was 290 ng/ml at 1 year, 324 ng/ml at 3 years, and 309 ng/ml at 5 years. For continuous smokers, the corresponding concentrations were 302 ng/ml, 307 ng/ml, and 311 ng/ml. There was no evidence of change in cotinine concentrations over the years. The 5-year values were similar to those of abstinent ex-smokers (N = 176) using gum (316 ng/ml).

Hurt et al., 2000. Extremely dependent smokers (FTND score = 8.4) with a high average cigarette consumption of 42 per day and who were interested not in quitting but in reducing smoking were recruited. In order to reduce smoking (the objective was by 50%) and harm, subjects were encouraged to use the oral inhaler. At 24 weeks follow-up, while still using NR with smoking, the cotinine concentration was reduced from 355 ng/ml at baseline to 322 ng/ml, cigarettes per day from 42 to 27, and CO from 30 to 26 ppm. Curiously, there was no correlation between inhaler use and cotinine concentration. No side effects of the inhaler were reported.

Fagerstrom et al., 2000. This study recruited smokers who were not interested in quitting smoking but were interested in smoking less and reducing their risk from smoking. The smokers participated in a crossover study, two weeks each on the nicotine inhaler and a new cigarette-like substitute, Eclipse, that heats rather than burns tobacco. The smokers were instructed to use as much as possible of the inhaler and Eclipse and smoke as few cigarettes as possible.

Using Eclipse, there was no change in nicotine concentration in plasma from baseline 17 ng/ml to 18 ng/ml. Using the inhaler, there was a decline from 17 ng/ml to 12 ng/ml. Average number of cigarettes smoked per day at baseline was 19, and at 4 weeks 5 cigarettes per day were smoked with the inhaler and 2 with Eclipse. On the inhaler the exhaled carbon monoxide decreased from 21 ppm to 13 ppm, but with Eclipse it increased from 21 ppm to 33 ppm. No adverse systemic events that could be related to increased nicotine intake were observed.

Carpenter, Hughes, & Keely, 2000. Smokers not interested in quitting but interested in reducing their smoking were given the option to use either the nicotine patch (Nicoderm), gum, or oral inhaler to aid reduction, in combination with behavioral advice. At least a 50% reduction in number of cigarettes was expected of the subjects within a few weeks. Among those who chose gum or inhaler (N = 16), the cotinine concentration in urine was virtually the same from baseline to 4 weeks follow-up, from 1,529 ng/l to 1,481 ng/l. Cigarette con-

Table 2. Transdermal nicotine replacement

	N	Duration	Product	Percent Change		
				Nic. conc.	No. of Cigs.	CO
Instruction or intention to reduce						
Carpenter 2001	12	4W	Nicoderm 14, 21 mg	5% ¹	-55%	-36%
Mahmarian 1997	40	3D	Nicoderm 14 mg	50%	-65%	-39%
		3D	21 mg	88%	-74%	-48%
Average				48%	-65%	-41%
Instruction to smoke ad libitum						
Zevin 1998	12	20D	Nicoderm 21 mg	55%	NA	NA
			42 mg	140%	NA	NA
			63 mg	200%	NA	NA
Pickwort 1994	10	24D	Prostep 22 mg	105%	-16%	-18%
			44 mg	231%	-28%	-27%
Foulds 1992	30	2W	Nicorette 15 mg	19%	-20%	-15%
			Average			
			<23 mg	60%	-21%	-20%
			>22 mg	190%		
Total Average			<23 mg	54%	-43%	-31%
			>22 mg	190%		

D = Days W = Weeks 1. Cotinine in saliva

sumption decreased from 22.6 to 11.0 per day and CO from 23.6 to 14.2 ppm.

An interesting feature in this study was that there was a group of smokers (N = 12) who had chosen not to use any NR. Their cotinine level was basically unchanged (+6%), while they had reduced smoking by 16% and CO by 19%, which is less than those using NR. No adverse reactions were reported in the study.

Over all studies, the average nicotine concentration with acute NR is virtually identical (-1%) to that with baseline smoking. The number of cigarettes is reduced by 50% and CO by 28% (see Table 1).

Transdermal administration

Foulds et al., 1992. Thirty smokers who smoked at least 10 cigarettes per day participated in a crossover study, with one week smoking plus wearing a placebo patch, and another week smoking plus using a nicotine patch (15 mg over 16 hours, Nicorette). The smokers were instructed to not consciously alter their smoking behavior. The nicotine concentrations (blood drawn directly after a cigarette was smoked) were 37 ng/ml at baseline, 36 ng/ml with placebo, and 44 ng/ml with active patch. Carbon monoxide levels were lower with the active patch (28 ppm) than with the other conditions (33 ppm). Numbers of cigarettes smoked per day were 20 at baseline and 16 with the nicotine patch. For change from baseline values in nicotine concentration, CO, and cigarettes smoked per day for all studies with transdermal NR, see Table 2. A number of subjective effects were assessed, but the authors conclude that 'subjects experienced almost no toxic effects from their cigarette smoking while wearing the patches.'

Pickworth, Bunker, and Henningfield, 1994. Ten inpatient heavily-dependent smokers smoking at least 20 cigarettes per day participated. Five had a history of extensive illicit drug use and the other five had a history of occasional illicit drug use. None of the subjects were interested in quitting or reducing smoking. After a 3-day ad libitum smoking baseline was established, the smokers were given transdermal nicotine of 0, 22 mg, and 44 mg per day over 24 hours (Prostep). They served one week on each dose, in total 24 days, and the order of doses was randomized. Subjects were instructed to smoke ad libitum.

Nicotine concentrations were 30 ng/ml at baseline, 19 ng/ml for placebo, 39 ng/ml for 22 mg, and 63 ng/ml for 44 mg. Number of cigarettes smoked was 18 at baseline, and for the placebo, 22 mg, and 44 mg patches it was 17, 15, and 13 cigarettes per day respectively. The CO values were 22 ppm, 18 ppm, 18 ppm, and 16 ppm on baseline, placebo, 22 mg, and 44 mg respectively.

No adverse subjective experiences were reported. Heart rate and systolic blood pressure were slightly elevated with the 22 mg but not with the 44 mg dose.

Mahmarian et al., 1997. In this study, 40 patients interested in giving up smoking and who had coronary artery disease participated. They had to smoke > 19 cigarettes per day and have a >4% exercise-induced reversible perfusion defect of the heart. Patients started at the quit day by wearing a 14 mg patch for 24 hours (Nicoderm). After a minimum of 3 days (mean 8 days) exercise, single-photon emission computed tomography was performed. Nicotine patch dose was thereafter increased to 21 mg over 24 hours. Smoking was reduced from 31 cigarettes per day at baseline to 11 and 8

Table 3. Nicotine concentrations in Zevin et al., 1998

TP Dose in mg	Nicotine concentrations in ng/ml	
	TP plus smoking	TP only
0	20	5
21	31	21
42	48	40
63	60	52

TP=Transdermal patch

cigarettes per day on the 14 and 21 mg patches respectively. Nicotine blood levels rose from baseline 16 ng/ml to 24 ng/ml with the 14 mg patch and to 30 ng/ml with the 21 mg dose. The exhaled CO levels decreased from baseline 23 ppm to 14 ppm on the 14 mg patch and to 12 ppm on the 21 mg patch dose.

A significant reduction in the total exercise-induced perfusion defect size was observed from baseline to treatment with the 21 mg patch. The reduction in perfusion defect size was associated with a significant reduction in cigarettes smoked per day and carbon monoxide level.

This study demonstrates that nicotine patches, when used to promote smoking cessation, significantly reduce the extent of exercise-induced myocardial ischemia despite higher nicotine concentrations. The authors conclude that 'CO and possibly other components of cigarette smoke, rather than nicotine, may actually be more critical for the development of myocardial ischemia.' The adverse reactions noted were 2 patients who had nausea and vomiting.

Zevin, Jacob, and Benowitz, 1998. In this study, 12 heavy smokers with no intent to quit or reduce smoking, who smoked more than 19 cigarettes per day, and who had cotinine levels higher than 150 ng/ml in plasma were treated as inpatients for 21 days. The subjects served 5 days in each of the 4 conditions: placebo transdermal patch (TP), 21 mg TP, 42 mg TP, and 63 mg TP. The latter two conditions are 2 and 3 times the normal doses of TP. In all conditions, smoking was ad libitum during days 1-4 and subjects abstained on day 5. Total nicotine exposure was substantially higher with active TP (Nicoderm) plus smoking compared with smoking alone and placebo TP (see Table 3). For example, smoking plus a placebo patch produced a nicotine level of 20 ng/ml, whereas smoking plus a 63 mg patch produced a nicotine level of 60 ng/ml. No statistical differences in cigarettes per day between conditions were seen. Actual data for cigarettes per day is not available in the report.

Despite these high nicotine levels, there were no haemodynamic effects of additional nicotine from TP on heart rate, blood pressure, noradrenalin, white blood cell count, fibrinogen, hematocrit, cortisol, or lipids compared with smoking alone. Carboxyhaemoglobin levels

became progressively lower as TP dose increased, most likely due to less smoking with higher TP doses.

When patches were applied at 8-hour intervals, no adverse reactions were seen.

The authors concluded that 'treatment of heavy smokers with high dose transdermal nicotine appears to be safe.'

Carpenter et al., 2000. As described earlier, smokers not interested in quitting but interested in reducing their smoking were given the option to use either the nicotine patch (Nicoderm), gum, or an oral inhaler (Nicorette) to aid reduction, in combination with behavioral advice. Subjects were expected to reduce smoking by at least 50% within a few weeks. After 4 weeks, patch users (N = 12) had increased their urine cotinine levels from 1,710 ng/l to 1,799 ng/l, and decreased their cigarette consumption from 23 to 11 per day and CO intake from 23 to 15 ppm.

When nicotine is delivered more like a slow infusion from patches, the titration of blood nicotine concentrations is not as good as with gum or inhaler. With ad libitum smoking and use of currently approved patch doses up to 22 mg, the increase was 54%, and for doses above 22 mg the concentration rose by 190%. The number of cigarettes was reduced by 43% and CO by 31% compared with baseline (see Table 2).

Discussion

First, these results show that smokers titrate their nicotine levels quite well with acute NR forms but not as well with nicotine patches.

Second, all NR systems equally and consistently decrease cigarette consumption and, to a somewhat lesser degree, CO intake.

Third, very few and mild adverse reactions were reported with concurrent smoking and use of NR, even when nicotine concentrations were elevated 2 or 3 times with use of very high doses of nicotine from patches.

When considering the mechanisms for tolerance to nicotine, it may not be so unexpected that titration was less precise with patches. The infusion-like delivery from patches does not give a nicotine boost that can be felt subjectively and naturally replace the subjective effect of a cigarette. If nicotine is delivered slowly, the body has

time to adapt and therefore the increase in tolerance may parallel the increase in nicotine concentrations (Porchet, Benowitz, & Sheiner, 1988). One other factor that could contribute to higher nicotine concentrations with patches is that there appeared to be less intervention to reduce or stop smoking in the transdermal studies compared with studies using gum and inhaler. Another possibility is that the use of acute systems may directly interfere with the smoking behavior; e.g., concurrently chewing gum and smoking is not common, and this placebo effect itself may have decreased nicotine concentrations. It should also be realized that, particularly with the acute systems, the actual dose delivered is not known.

There seemed to be no difference in reduction of cigarettes between the acute systems (-50%) and patches (-43%). For CO the figures were also almost identical (-28 vs -31%). Within the patch studies there was some evidence that higher doses produced more reduction. Unfortunately, CO, which can be an indicator of reduced harm, was not reduced as much as the number of cigarettes. For the acute systems, a 50% reduction in the number of cigarettes smoked resulted in a 28% reduction in CO intake. For patches, the corresponding figures were 43% and 31%. It thus seems, as assessment of CO is a necessity in harm/smoking reduction studies in order to secure reduction in harm, a sizable reduction in cigarettes smoked of, for example, 20% may produce little or no reduced harm if CO intake is a valid indicator.

It is no surprise that there were few adverse reactions with acute administration forms, since they just replaced the lost nicotine from cigarettes. It may, however, be more surprising that nicotine concentrations up to 3 times higher than normal, given with patch doses also 3 times higher than currently approved, did not result in substantive subjective or physiological effects. In order to experience subjective effects rapid fluctuations in drug concentrations would be needed. Although it is unclear how systematic the studies were in recording adverse effects, we believe it is a reasonable assumption that the authors would have reported any significant effects, as this requirement is included in most publishing and ethics standards. Another adverse event of concern would be whether dependence on nicotine is increased when NR is used together with smoking. Little research has addressed this issue. Two studies found an insignificant trend towards a reduction in dependence (Fagerstrom & Hughes, this issue; Kralikova, Kozak, Rasmussen, & Cort, 2001). We are not aware of any empirical data that show an increase in dependence with concurrent use, nor do we have any clinical experience of such a problem. Generally dependence is less when a drug is given through a slow infusion compared with rapid delivery, or when the half-life is prolonged. Nicotine delivered via NR products should thus be less dependence-producing than that delivered through cigarettes. If this is true, then replacing nicotine from cigarettes with nicotine from NR products should decrease, not increase, dependence.

In summary, the evidence reviewed here clearly indicates that safety should not be a concern with concomitant use of NR and smoking. With acute administration forms there is normally no increase in blood nicotine or cotinine concentrations, while transdermal NR systems may elevate nicotine concentrations, but, as far as is known, such increases do not produce substantive adverse events.

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