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Adjustment of nicotine replacement therapies according to saliva cotinine concentration: the ADONIS* trial—a randomized study in smokers with medical comorbidities

Ivan Berlin[1], Nelly Jacob[2], Mathieu Coudert[3], Jean Perriot[4], Laurette Schultz[5] & Nicolas Rodon[6]

Département de Pharmacologie, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière-Faculté de médicine, INSERM U894, Paris, France,[1] Département de Biochimie, Hôpital Pitié-Salpêtrière, Paris, France,[2] Département de Biostatistique, Unité de Recherche Clinique, Hôpital Pitié-Salpêtrière, Paris, France,[3] Dispensaire Emile Roux, Clermont Ferrand, France,[4] Centre Hospitalier de Valenciennes, Valenciennes, France[5] and Laboratoire de Santé Publique et Informatique Médicale, Département de Santé Publique, Faculté de Médecine René Descartes, Paris, France[6]

ABSTRACT

Aims To assess the efficacy of nicotine replacement therapies (NRT) when the daily dose was adapted according to saliva cotinine concentrations. **Design** Randomized, multi-centre, single-blind, controlled trial. **Setting** Twenty-one smoking cessation clinics in France. **Participants** A total of 310 smokers with medical comorbidities, motivated to quit, smoking ≥10 cigarettes/day, for whom smoking cessation was mandatory. NRT was administered for 3 months. The standard care group received nicotine patches with monthly dose decreases; buccal absorption NRT could be co-administered at the discretion of the investigator. In the dose adaptation group, the aim was a 100 ± 5% nicotine substitution with respect to smoking state based on the determination of saliva cotinine concentrations. NRT daily doses were prescribed according to the previous week's saliva cotinine concentrations in the dose adaptation group; saliva cotinine concentrations were not provided in the standard care group. **Measurements** Prolonged abstinence rate (weeks 9–12, main outcome measure), point-prevalence and continuous abstinence rate, saliva cotinine concentration, NRT daily dose, craving for cigarettes. **Findings** The median daily prescribed NRT dose was 30 and 31 mg/day in the first study week and 17.25 and 35.5 mg/day during weeks 9–12 in the standard care group and dose adaptation group, respectively. Saliva cotinine remained stable in the dose adaptation group and decreased in the standard care group ($P < 0.01$) by weeks 9–12. The cotinine substitution rate was significantly lower in the standard care group than in the dose adaptation group. Despite differences in NRT doses and cotinine substitution rates, prolonged (standard care group: 26.4%, dose adaptation group: 30.3%), continuous (standard care group: 8%, dose adaptation group: 12%) and point-prevalence abstinence rates were similar. **Conclusions** In smokers with medical comorbidities and highly motivated to quit, adaptation of the nicotine replacement therapy daily dose according to saliva cotinine does not appear to be substantially superior to standard nicotine replacement therapy use.

Keywords NRT, saliva cotinine, smoking cessation.

Correspondence to: Ivan Berlin, Département de Pharmacologie, Hôpital Pitié-Salpêtrière, 47, bd de l'Hôpital, 75013 Paris, France.
E-mail: ivan.berlin@psl.aphp.fr
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INTRODUCTION

Despite a significant reduction in smoking prevalence in developed countries, certain groups of smokers continue to smoke, notably those with smoking-related illness. These smokers need more effective, specific and intensified interventions because they are unable to quit, despite knowledge about the negative health effects of smoking.

The last updated Cochrane Review included 132 trials of nicotine replacement therapies (NRT) and found a

*Adjustment of DOses of NIcotine in Smoking Cessation (ADONIS)

relative risk ratio of 1.58 [95% confidence interval (CI): 1.5–1.66] of abstinence with any form of NRT [1]. Most NRT trials were conducted with smokers without comorbid medical conditions, such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), cancer, diabetes and asthma. The recent Treating Tobacco Use and Dependence 2008 Update states that additional research is required to evaluate the 'impact and effectiveness of specialized assessment and tailored interventions in these populations' [2].

Because smoking cessation is cost-effective and improves health outcomes at any age, in any disease condition and at any stage of disorder, research into new methods aiming to improve abstinence rates with NRT seems warranted. One way to improve the effectiveness of NRT is to optimize nicotine substitution rates.

The aim of this study was to compare NRT efficacy when the NRT daily dose was determined by progressive dose adaptation, based on saliva cotinine concentrations, to obtain 100% substitution and to compare to the standard monthly decreasing dose nicotine patch use which could be completed by buccal absorption NRT. We hypothesized that the dose adaptation regimen would result in better abstinence rates than the NRT regimen without saliva cotinine-based dose adaptation. If this hypothesis is confirmed, saliva cotinine determinations could be used to tailor NRT daily doses individually to smokers who continue to smoke despite knowledge of the deleterious effects of continuing smoking.

METHODS

Study design

This study was a single-blind, randomized, parallel group trial. The trial took place at 21 smoking cessation outpatient clinics in France. The study investigators were physicians, as per French law on biomedical research; all the investigators had a postgraduate diploma specializing in smoking cessation treatment. Smokers attending the smoking cessation clinics were invited to participate. Interested smokers were interviewed individually. Because no centralized recruitment process could be established, we were unable to define the number of smokers interviewed, the number of eligible smokers and how many of the interviewed smokers declined to participate. Participants provided written informed consent during the first visit. The study was conducted between November 2005 and April 2008.

Randomization

A computer-generated list containing 400 numbers was created independently of the coordination centre and investigators. The non-stratified treatment arms were balanced in blocks of four without replacement. The randomization list was incorporated into the study's electronic case report form (eCRF) and activated at the randomization visit (V1). Participants were assigned randomly to one of the study groups: standard care or dose adaptation.

Power calculation

We considered that a 15% difference in prolonged abstinence rate (main outcome measure) between the standard care group and dose adaptation group would be clinically meaningful in order to change standard care. According to the most recent meta-analyses, compared to a control (or placebo) the abstinence rate with NRT provided a risk ratio ranging from 1.43 to 2.02 [1] and with bupropion of 1.69 [3]. Because the change from standard to dose adaptation care would result in increased costs (saliva cotinine determination), the benefit of dose adaptation should be greater than the benefit of existing pharmacological interventions. Thus, an odds ratio of 3 was accepted as clinically meaningful to justify increased costs. We hypothesized a 10% abstinence rate in the standard care group and a 25% abstinence rate in the dose adaptation group, respectively. At an alpha = 5% and a 1-beta = 90%, this necessitated randomization of 146 smokers by group, allowing for a non-compliance rate of 5–10% in each group.

Participants

Smokers aged 18 years and over and reporting smoking $\geq$10 cigarettes per day for at least 5 years were included. All had either a known smoking-related disorder or an underlying disease with increased risk for smoking-related illnesses. In addition, participants had been unable to quit previously, despite knowledge about the risk to their health of continued smoking. Smokers were included if at least one of these medically verified conditions were present: coronary heart disease (previous history of myocardial infarction, unstable or stable angina, angioplasty with or without stent or coronary bypass surgery); peripheral arterial disease (including neck and head arteries); hypertension; previous history of a cerebrovascular event; COPD; type 1 or type 2 diabetes; and previous history of a malignant disease where a relationship with smoking has been demonstrated. Smokers were included if (i) they intended to stop smoking in the coming weeks and had a score $\geq$5 on a Likert scale of motivation to quit (range 0–10), and (ii) they signed the consent form, by which they also stated that they would comply with the study's requirements. Exclusion criteria were as follows: breast feeding and pregnant women, enrolment of another household member, smokers treated with bupropion during the

previous 2 months; smokers on NRT, neuroleptics, opioid substitution medication or on anticoagulant medication with unstable international normalization ratio (INR) or prothrombin time. The participants were informed that only study medications were allowed. Use of any out-of-study smoking cessation medication led to the participant's exclusion from the study.

Ethics

The study protocol was approved by the Ethics Committee of the Pitié-Salpêtrière Hospital, Paris, France on 23 March 2005.

Study outline

Once a smoker was included, a saliva sample was collected between 11:00 and 20:00 hours 2–3 weeks before randomization, when the participant still smoked his/her usual number of cigarettes. This was considered to be the baseline saliva cotinine concentration, reflecting the participant's level of nicotine substitution by cigarettes at 100%. Participants were asked specifically not to reduce their consumption before the first saliva sampling. At the next randomization visit the standard care group received a nicotine patch and potentially buccal absorption NRT products; the dose adaptation group received a nicotine dose (either by patch or buccal absorption NRT or both) according to the saliva cotinine concentration based on a saliva cotinine/daily NRT dose conversion factor of 0.1. For example, if the saliva cotinine concentration was 200 μg/l, the daily NRT dose was 20 mg/day. The nicotine to plasma cotinine conversion factor has been estimated to be 0.08 (95% CI: 0.047–0.102) after intravenous nicotine administration or after having smoked a cigarette [4], meaning that 1 mg of nicotine leads to an increase of 12.5 μg/l in the plasma cotinine concentration. The systemic nicotine intake per cigarette, independent of nicotine yields from machine-smoked cigarettes, has been estimated to be 1.17–1.31 mg [5] and 0.26–1.47 mg [6]. For practical reasons, we considered that the nicotine intake from a cigarette is 1 mg. The suggested modification of the daily dose of nicotine for dose adaptation was calculated according to the following formula: (baseline saliva cotinine concentration – current saliva cotinine concentration)/10 (mg of nicotine) + mean number of cigarette smoked during the last 7 days × 1 mg of nicotine. For example, if the baseline saliva cotinine was 250 μg/l and the current saliva cotinine is 200 μg/l (80% substitution), and the participant reports having smoked on average five cigarettes per day (= 5 mg of nicotine), the current daily NRT dose should be increased by 10 mg to obtain 100% substitution. Compared to simply keeping the first NRT dose based on baseline cotinine, this formula takes into account the difference between current and baseline nicotine exposure (approached by saliva cotinine concentration), which is the sum of nicotine intake from NRT and cigarettes.

Saliva cotinine was collected 1, 3, 5 and 7 weeks after the target quit day in both groups. Dose adaptation occurred at the next visit 1 week later, i.e. at weeks 2, 4, 6 and 8. NRT doses could not be changed during weeks 9–12. In the dose adaptation group, *but not in the standard care group*, saliva cotinine results were posted on the eCRF before the next NRT prescription visit, which thus followed the saliva cotinine sampling visits by 1 week. Target quit day was defined at the randomization visit. NRT was started on target quit day and was administered for 3 months, with a follow-up at 6 months. Relapsers were encouraged to remain in the study, and relapse to smoking was not considered as a dropout.

Interventions

The standard care group followed French marketing authorization of the nicotine patch used in this study (Nicopatch®, Laboratoire Pierre Fabre Santé, Boulogne, France). The initial dose was determined according to the Fagerström Test for Nicotine Dependence (FTND) [7] and number of cigarettes smoked per day. If the FTND was ≥5 or the subject smoked ≥20 cigarettes/day, Nicopatch® 21 mg/24 hours was started followed by a monthly decrease to 14 mg/24 hours and then to 7 mg/24 hours patch. If the FTND was <5 or the subject smoked <20 cigarettes/day, Nicopatch® 14 mg/24 hours was administered during the first 2 months and 7 mg/24 hours during the third month. Based on clinical assessment, buccal absorption NRT, either nicotine gum (Nicogum® 2 mg, Laboratoire Pierre Fabre Santé) or lozenges (Nicopass® 1.5 mg, Laboratoire Pierre Fabre Santé), could be co-administered at the investigator's discretion. Co-administration of a second nicotine patch was not allowed in the standard care group. Saliva cotinine results were not available for prescription in the standard care group.

In the dose adaptation group the aim was a 100 ± 5% substitution rate with respect to the smoking state based on determination of saliva cotinine concentrations. NRT daily doses were prescribed (increases or decreases) according to the previous week's saliva cotinine results. Any form of NRT could be used to obtain the 100% substitution. The last NRT daily dose was prescribed at visit 9, and did not change for the remainder of the study.

Participants received counselling for at least 10 minutes at each visit, starting at the pre-quit inclusion visit. The type and content of counselling was left to the investigator's discretion.

Outcome measures

Abstinence

Abstinence was defined as self-reported abstinence: no cigarette, not even a puff, confirmed by expired air carbon monoxide (CO) concentration ≤8 parts per million (p.p.m.) (Smokeanalyzer®, Bedfont Scientific Ltd, Rochester, Kent, UK).

The main outcome measure was prolonged abstinence (defined as self-reported abstinence: no cigarette, not even a puff, confirmed by expired air CO concentration ≤8 p.p.m.) during weeks 9–12 of the treatment period. Secondary outcome measures were complete and continuous abstinence since target quit day (abstinence at each visit) and point-prevalence abstinence: self-report of 7 days of abstinence, confirmed with expired air CO ≤8 p.p.m. [1,8].

Saliva cotinine concentration

A saliva sample was collected for the same participant at approximately the same hour of the day. A cotton roll was placed in the gingival cleft for 1 minute and placed immediately into the Salivette® tube (Sarstedt, Nümbrecht, Germany), kept at 4°C and sent in less than 24 hours to the central biochemistry laboratory (Hôpital Pitié-Salpêtrière, Laboratoire de Biochimie, N. Jacob) for determination. The quantification limit for cotinine was 7.5 μg/l and the between-run coefficient of variation 5–8% [9].

Results of saliva cotinine concentration were posted on the eCRF in the dose adaptation group and were not provided in the standard care group.

Other measures

Craving for cigarettes was assessed by the 12-item version (FTCQ-12) [10] of the French Tobacco Craving Questionnaire (FTCQ) and withdrawal symptoms by the Minnesota Nicotine Withdrawal Scale (MNWS) [11]. Items were summed yielding a total craving and withdrawal score.

Adverse effects recording was based on spontaneous reporting when asked: 'Did you have any signs or symptoms since the last visit?'. Compliance was assessed by counting the content of dispensed and returned blisters of both patches and buccal absorption NRT.

Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND) [7] and alcohol-related problems by the cut-down, annoyed, guilt, eye-opener (CAGE) questionnaire [12].

Data analysis

Efficacy and safety analyses were performed on the intent-to-treat population, which comprised all randomized subjects. Data are presented as means (95% CI) and medians for continuous variables and as frequency (percentage) (95% CI) for categorical variables. Prolonged abstinence was compared across groups using a χ^2 test. All participants who were lost to follow-up were considered smoking and missing abstinence data were counted as smoking, which is the standard and conservative procedure for intent-to-treat analyses. A sensitivity analysis was also performed to confirm the results by counting missing data as non-smokers. For each outcome measure, a mixed-effect logistic regression was performed allowing for the adjustment on covariates such as gender, baseline saliva cotinine concentration, FTND and cigarettes per day. The centre was considered as a random effect in all analyses. Because no centre effect was detected for any variable, the centre effect is not reported further.

A mixed-effect Cox regression model was used to compare time to the eventual resumption of smoking. Point-prevalence abstinence was compared using a mixed-effect logistic model for longitudinal binary data using a pattern-mixture analysis. Characteristics of completers (defined as completing the last treatment visit) and dropouts were similar and are not reported further. Daily NRT dose, saliva cotinine concentration, level of nicotine substitution, FTCQ-12, MNWS and body weight were compared using mixed linear models for repeated measure data. NRT dose, cotinine concentration and nicotine substitution were log-transformed because of residual heteroscedasticity.

The incidence of adverse events was compared using Fisher's exact tests and χ^2 tests.

RESULTS

Participants' characteristics

Three hundred and fifteen smokers provided written informed consent and 310 were randomized and included in the intent-to-treat population analyses (Fig. 1).

The participants' characteristics were similar in the two groups (Table 1). The most frequent primary diagnoses were COPD, coronary artery disease and peripheral atherosclerosis.

NRT dose, saliva concentration and substitution rate

The mean saliva concentration when participants were still smoking before quit day was 307 μg/l (95% CI: 282–332, median: 278) in the standard care and 319 μg/l (95% CI: 297–342, median: 296) in the dose adaptation groups, respectively ($P = 0.31$). The lowest saliva cotinine concentration was 35 μg/l and the highest 1054 μg/l. In the standard care group, as expected, the mean daily NRT

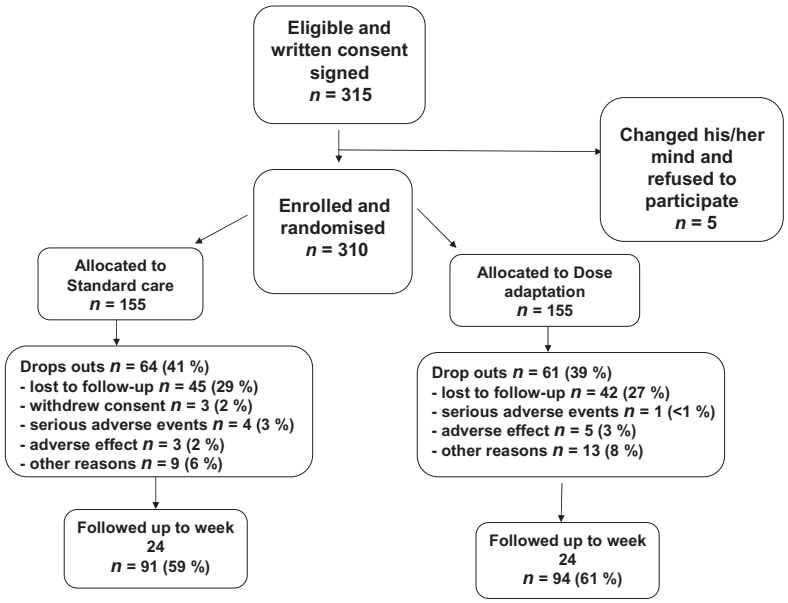

Figure 1 Flow of participants through the trial

dose decreased from 30.82 mg/day (median: 30 mg) in the first study week to 17.86 (median: 17.25) mg/day during month 3; in the dose adaptation group the respective values were 32.14 (median: 31) and 39.97 (median: 35.5) mg/day [time × group interaction, estimate 0.086, standard error (SE) 0.00799, $P < 0.0001$] (Fig. 2a). The highest NRT dose was 162 and 63.5 mg/day in the dose adaptation and standard care groups, respectively.

The mean saliva cotinine concentration (Fig. 2b) remained stable in the dose adaptation group and decreased in the standard care group (time × group interaction, estimate 0.018, SE 0.008, $P = 0.04$). The mean saliva cotinine concentration at the last determination (visit 8) was 337 μg/l (95% CI: 294–380, median: 260) in the dose adaptation and 249 μg/l (95% CI: 220–278, median 204) in the standard care group ($P < 0.01$). More participants had a dose increase at week 2 in the standard care than in the dose adaptation group (69%, 95/138 versus 56%, 78/140, $P = 0.024$). At the last dose adaptation visit, 88% of the participants in the standard care and 82% in the dose adaptation group used short-acting (buccal absorption) NRT. The cotinine substitution rate was lower in the standard care than in the dose adaptation group (time × group interaction, estimate 0.027, SE 0.012, $P = 0.023$).

Abstinence outcomes

Despite differences in daily nicotine dose and saliva cotinine concentrations, prolonged abstinence (complete abstinence during weeks 9–12 after quit day) was similar: standard care: 41/155 (26.4%); dose adaptation: 47/155 (30.3%) ($\chi^2 = 0.57$, $P = 0.45$). This result did not change when only completers were considered: standard care, 41/96 (42.7%); dose adaptation, 47/106 (44.3%) ($\chi^2 = 0.05$, $P = 0.81$).

There were 12/155 (8%) and 19/155 (12%) continuously abstinent smokers in the standard care and dose adaptation groups, respectively ($P = 0.18$). This lack of difference was not modified by the covariates gender, baseline saliva cotinine and daily NRT dose.

The hazard ratio (HR) to relapse was similar between the standard care and dose adaptation groups (HR = 0.09, 95% CI: 0.72–1.21, $P = 0.58$) (Fig. 3a).

Point-prevalence abstinence increased progressively in both groups (Fig. 3b). There was no difference between the standard care and dose adaptation groups. A pattern-mixture mixed-effects logistic regression model was conducted to test whether or not the treatment group effect on point-prevalence abstinence was similar among completers, dropouts and non-completers. This analysis showed that dropout and completion rates did not influence the results.

At the 6-month follow-up visit, 33/155 (21%) in the standard care and 34/155 (22%) in the dose adaptation group were abstinent ($\chi^2 = 0.02$, $P = 0.89$).

The prolonged abstinence rate was similar among males and females: 15 (27.8%) women and 26 (25.7%) men in the standard care and 18 (29.03%) women and 29 (31.18%) men in the dose adaptation group had prolonged abstinence, and there was no gender × intervention group interaction.

Outcomes by cotinine substitution rate

Mean saliva cotinine at the last cotinine measure (visit 8) was 276 μg/l (95% CI: 225–328, median 253) and 350 μg/l (95% CI: 283–416, median 269) in non-

Table 1 Baseline characteristics of participants allocated to the standard care and the dose adaptation groups. Values are means or numbers (*n*) (percentages) and 95% confidence intervals (CI).

	Standard care, n = 155		*Dose adaptation, n = 155*	
	Mean	*95% CI*	*Mean*	*95% CI*
Age (years)	50	48–51	50	48–51
BMI (kg/m^2)	25.99	25.2–26.8	25.06	24.5–26
Education (years)	10.5	10–11.1	10.72	10.1–11.3
Cigarettes per day	25.8	23.9–27.7	25	23.4–26.6
Age of first cigarette smoked (years)	15.6	15.1–16.2	15.7	15–16.3
Age started regular smoking (years)	17.7	17.2–18.2	18.1	17.4–19.9
Previous quit attempts	2.03	1.7–2.4	1.85	1.6–2.1
FTND	6.6	6.3–6.9	6.6	6.3–6.9
Number of alcoholic drinks per day	1.45	1–1.9	1.27	0.9–1.6
Motivation to quit score (0–10)	8.2	7.9–8.5	8.2	7.9–8.5
	n (%)		*n (%)*	
Gender				
Male	101 (65)	58–73	93 (60)	52–68
Female	54 (35)	27–42	62 (40)	32–48
Professional status				
Working	75 (480	41–56	73 (47)	39–55
Retired	30 (19)	13–26	31 (20)	14–26
Housewife/house-husband	12 (8)	4–12	15 (10)	5–14
Unemployed	37 (24)	17–31	35 (23)	16–29
Student	1 (1)	0.02[a]–3.54[a]	1 (1)	0.02[a]–3.54[a]
Marital status				
Married	94 (61)	53–68	105 (68)	60–75
Single	16 (10)	6–15	21 (14)	8–19
Widowed	4 (3)	0.71[a]–6.48[a]	5 (3)	1.06[a]–7.37[a]
Separated	34 (22)	15–28	20 (13)	8–18
Divorced	7 (5)	1.83[a]–9.08[a]	4 (3)	0.71[a]–6.48[a]
Household income (€)				
<12 000	71 (46)	38–54	65 (42)	34–50
12 000–30 000	60 (39)	31–46	69 (44)	37–52
>30 000	24 (15)	10–21	21 (14)	8–19
Ethnic origin				
European	150 (97)	92.63[a]–98.94[a]	151 (98)	93.52[a]–99.29[a]
African	3 (2)	0.4[a]–5.55[a]	4 (2)	0.71[a]–6.48[a]
Other	2 (1)	0.16[a]–4.58[a]	0 (0)	0[a]–2.35[a]
Disease condition				
Myocardial infarction	29 (19)	12–25	23 (15)	9–20
Unstable angina pectoris	2 (1)	0.16[a]–4.58[a]	2 (1)	0.16[a]–4.58[a]
Stable angina pectoris	18 (12)	7–17	9 (6)	2.69[a]–10.74[a]
Lower limb atherosclerosis	38 (25)	18–31	25 (16)	10–22
Carotid artery stenosis	7 (5)	1.83[a]–9.08[a]	10 (6)	3–10
Hypertension	59 (38)	30–46	50 (32)	25–40
Stroke	9 (6)	2.69[a]–10.74[a]	9 (6)	2.69[a]–10.74[a]
COPD	84 (54)	46–62	94 (61)	53–68
Diabetes	27 (17)	11–23	27 (17)	11–23
Cancer (related to smoking)	6 (4)	1.43[a]–8.23[a]	6 (4)	1.43[a]–8.23[a]
CAGE questionnaire				
Have you ever				
Felt the need to cut down your drinking?	57 (37)	29–44	52 (34)	26–41
Felt annoyed by criticism of your drinking	44 (28)	21–35	45 (29)	22–36
Had guilty feelings about drinking	53 (34)	27–42	50 (32)	25–40
Taken a morning eye opener	16 (10)	6–15	10 (6)	3–10

BMI: body mass index; CAGE: cut-down, annoyed, guilt, eye-opener; COPD: chronic obstructive pulmonary disease; FTND: Fagerström Test for Nicotine Dependence. Confidence intervals are Z approximated except [a]exact CI.

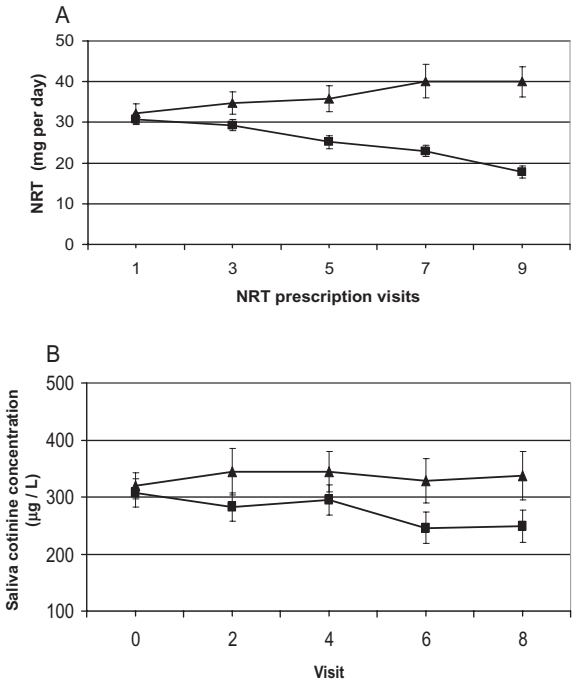

Figure 2 Daily dose of nicotine replacement therapies (NRT) (a) and saliva cotinine concentration (b) in the standard care (squares) and dose adaptation (triangles) groups. Visit 0 indicates saliva cotinine concentration when still smoking. Data are means ± 95% confidence intervals

abstainers during weeks 9–12 in the standard care and dose adaptation groups, respectively. The corresponding values in abstainers were 203 µg/l (95% CI: 161–245, median 164) and 301 µg/l (95% CI: 232–369, median 227). The mean cotinine substitution rate during weeks 9–12 was significantly ($P = 0.003$) higher among those who were non-abstinent than among those who were abstinent, and there was a non-significantly higher ($P = 0.08$) substitution rate among abstainers in the dose adaptation group compared with the standard care group (standard care group: non-abstainers 98%, 95% CI: 83–114%, abstainers 77%, 95% CI: 62–92%; dose adaptation group: non-abstainers 113%, 95% CI: 97–129%, abstainers 89%, 95% CI: 75–102%). The analysis of point-prevalence abstinence following the previous week's cotinine substitution showed that non-abstainers had a non-significantly higher substitution rate ($P = 0.054$). These findings are not surprising, because non-abstainers smoked while having taken NRT. There was an intervention group × point-prevalence interaction ($P = 0.002$), such that among abstainers the cotinine substitution rate was higher in the dose adaptation than in the standard care group. These results are consistent with the expected higher substitution rate in the dose adaptation group.

Craving for cigarettes

Abstinent smokers had significantly lower craving scores than non-abstinent smokers (effect of abstinence: estimate −9.09, SE 0.85, $P < 0.0001$; time × abstinence interaction: estimate 0.48, SE 0.12, $P < 0.0001$) and this was independent of whether the smokers were randomized to the standard care or dose adaptation groups (time × group interaction: estimate −0.11, SE 0.14, $P = 0.43$) (Fig. 4).

Withdrawal symptoms

The MNWS total score decreased in abstainers and did not change in non-abstainers (time × abstinence interaction: estimate −0.10, SE 0.04, $P = 0.01$) and these changes were independent of whether the participants were randomized into the standard care or dose adaptation groups (time × group interaction: estimate 0.022, SE 0.046, $P = 0.63$).

Weight

There was no statistically significant difference in weight. Prolonged abstinent smokers weighed somewhat more than non-abstinent smokers (time × abstinence interaction: estimate 0.065, SE 0.035, $P = 0.061$).

Compliance

Compliance could be assessed among 282 participants. The participants' compliance with the prescribed NRT dose was 94.6% in the dose adaptation group and 96.7% in the standard care group (difference not statistically significant).

Adverse effects

No death occurred during the study. The number of participants with serious adverse events and the number of participants with an adverse effect were similar (Table 2). More adverse effects occurred in the dose adaptation than in the standard care groups (168 versus 210, $P = 0.006$). More participants reported insomnia, nausea and less heartburn in the dose adaptation than in the standard care group (Table 2).

DISCUSSION

We hypothesized that a 100% substitution of the daily NRT dose based on determination of saliva cotinine concentrations compared to standard care would provide better abstinence outcomes in smokers at high risk of smoking-related morbidity and mortality in primary or secondary prevention conditions. If this hypothesis was confirmed, saliva cotinine determinations can be

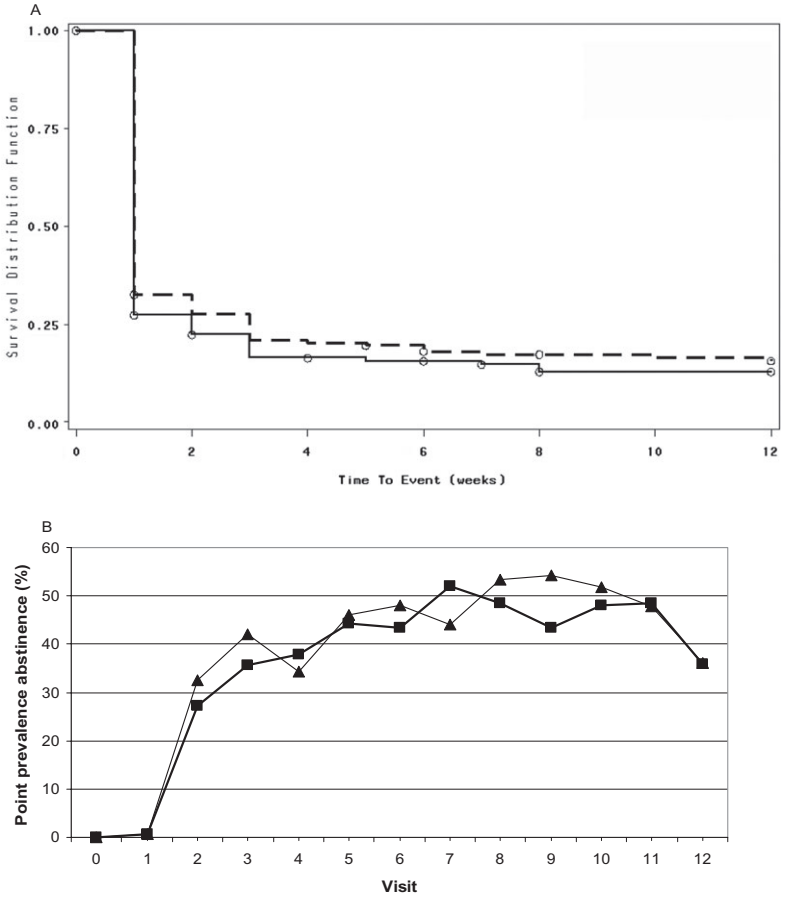

Figure 3 (a) Kaplan–Meier curve of complete and continuous abstinence from target quit day (standard care: dotted line, dose adaptation: full line). (b) Point-prevalence abstinence in the standard care (squares) and dose adaptation group (triangles)

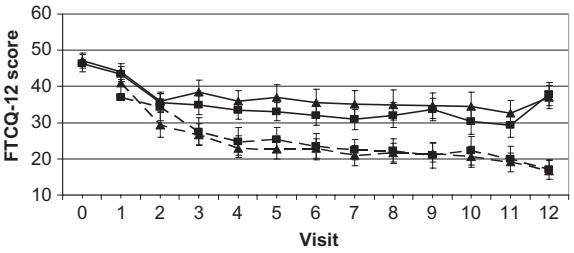

Figure 4 Twelve-item French Tobacco Craving Questionnaire (FTCQ-12) scores (means, 95% confidence intervals). Visit 0 corresponds to the pre-quit smoking state (standard care: squares, dose adaptation: triangles; abstinent smokers: dotted lines, non-abstinent smokers: full lines)

proposed to tailor individually and thus optimize the NRT daily dose in treating smokers who continue to smoke despite knowledge of risk to their health of continuing smoking. The results showed that abstinence rates were not improved by saliva cotinine-based dose adaptation compared to standard care based on clinical assessment.

NRT is well tolerated in smokers with cardiac disease [13] as well as in patients with COPD [14] but, surprisingly, very few studies have examined the efficacy of NRT in smokers with these types of medical comorbidities. Smokers included in the Cochrane Review on the efficacy of NRT [1] were community volunteers, primary care or cessation clinic patients; only two studies with lung clinic referrals were included [15,16]. This contrasts with studies of recently developed smoking cessation medications such as bupropion or varenicline, whose efficacy has also been assessed specifically in COPD patients [17,18] or in patients with cardiovascular diseases [19,20]. Because smokers with medical comorbidities must quit, optimization of NRT use seems to be warranted.

Potential causes of the modest efficacy of NRT include insufficient daily doses, lack of flexible dosing [21] or too-short duration of use [22,23]. In the Collaborative European Anti-Smoking Evaluation (CEASE) trial [24], nicotine patch doses higher than standard were associated with an increase in abstinence rates, but continuation of treatment beyond 8–12 weeks did not increase success rates; this latter finding was not supported in a very recent study of extended-duration nicotine patch use [25]. In other studies, however, fixed high-dose nicotine patches did not increase cessation rates [26,27].

A potential strength of this study is that it was implemented in a clinical practice situation, which allows generalizability of the results for smokers attending smoking

Table 2 Adverse effects in the standard care and the dose adaptation groups. *P*-values shown in bold type mean significant difference at $P < 0.05$ with Fisher's exact or χ^2 test.

	Standard care n = 155 (%)	*Dose adaptation n = 155 (%)*	*P-value*
Number of participants with serious adverse events[a]	12 (7.7)	9 (5.8)	0.498
Number of participants with an adverse effect	83 (53.5)	92 (59.4)	0.303
Adverse effects[b]			
Insomnia	7 (4)	17 (11)	**0.034**
Sleep difficulties	11 (7)	16 (10)	0.314
Rash, patch-related	9 (6)	14 (9)	0.279
Nausea	3 (2)	10 (6)	**0.047**
Depression	8 (5)	6 (4)	0.584
Chest pain	7 (4)	5 (3)	0.556
Irritability	4 (3)	7 (4)	0.357
Constipation	2 (1)	7 (4)	0.173
Headache	6 (4)	6 (4)	1.000
Anxiety	5 (3)	6 (4)	0.759
Fatigue	6 (4)	3 (2)	0.501
Rash	6 (4)	3 (2)	0.501
Stomach/bowel symptoms	1 (1)	6 (4)	0.121
Heartburn	6 (4)	0	**0.030**
Palpitations	2 (1)	5 (3)	0.448
Cough	5 (3)	0	0.061
Dyspnoea, asthmatiform	4 (3)	0	0.123
Diarrhoea	4 (3)	2 (1)	0.684
Pharyngitis	4 (3)	3 (2)	1.000
Stomach ache	3 (2)	3 (2)	1.000
Lower back pain	4 (3)	2 (1)	0.684
Vivid/bad dreams	3 (2)	3 (2)	1.000
Bronchitis	2 (1)	4 (3)	0.684
Itching	1 (1)	4 (3)	0.371
Flu-like symptoms	2 (1)	3 (2)	1.000
Dizziness	2 (1)	3 (2)	1.000
Bloating	1 (1)	3 (2)	0.623
Vomiting	0	3 (2)	0.248

[a]Defined as resulting in death, jeopardizing health prognostics, necessitating hospitalization, resulting in a handicap or long-term incapacity, or qualified by the reporting physician as serious. [b]Number of participants.

cessation clinics. The high compliance rate was due probably to the weekly visits and the subjects' high motivation to participate, and was thus unlikely to jeopardize the results.

The power of the study was sufficient to show a significant difference at $\alpha = 5\%$ and $1\text{-}\beta = 90\%$. In order to become significant, the observed difference of 3.9% in the prolonged abstinence rate would have required randomization of 2800 subjects per group. Such a small difference is clinically highly doubtful. Thus, it can be concluded that the power of the study was sufficient to reject the hypothesis of a type II error.

The NRT dose was higher in the dose adaptation group and correspondingly more participants reported non-serious adverse effects with this intervention; however, this did not lead to an increased risk of serious adverse events, confirming the excellent safety profile of NRT even in this population of smokers with medical comorbidities.

No gender differences occurred in the present study. Two meta-analyses addressed gender-related differences in response to nicotine patch treatment. The first meta-analysis did not show lower abstinence rates in women [28] and the second did show [29] lower abstinence rates in women. However, the current study differs from most of the NRT studies in that that it included only smokers with known medical comorbidities.

Limitations

This was a single-blind study, and investigators were trained not to communicate their group affiliation to participants. Implementation of a double-blind design would have protected against a potential leak of group membership.

Although compliance was high, overcompliance in the Standard Care group cannot be excluded. As NRT is accessible over-the-counter, participants could have used

NRT not provided by the study investigators. The inability of the study to control over-the-counter NRT use is a limitation. However, potential overcompliance also shows that symptom-based dose adaptation is effective and does not jeopardize the findings.

No specific training was provided to harmonize counselling. All investigators were experienced smoking cessation treatment specialists and highly familiar with counselling methods. Because of the single-blind design, however, counselling may have been more intense in the standard care group than in the dose adaptation group, reducing the expected difference. Moreover, the study protocol, as in many other similar studies, did not foresee an assessment of counselling intensity, and consequently no adjustment could be made for counselling intensity.

A probable limitation of our dose adaptation procedure is that the first dose titration happened only 2 weeks after the quit date, when many people may have already relapsed, and a more immediate dose adjustment may have resulted in a better outcome. However, the background premise of our procedure was that smokers had 2 months to become abstinent through a trial-and-error-type progressive dose adaptation during this dose-finding period. This is in line with research showing that some smokers unable to quit on quit day are able to quit later [30,31]. Thus, our procedure allowed both early and late abstainers to become abstinent by the end of the trial.

The results of the present study cannot be generalized to populations of smokers who do not have similar medical characteristics to our participants.

CONCLUSION

This study shows that in a sample of smokers with medical comorbidities for whom smoking cessation represents a vital issue, adaptation of NRT according to saliva cotinine concentrations did not perform better in terms of smoking abstinence than usual NRT use based on clinical assessment.

Trial registration

Clinicaltrials.gov Identifier: NCT00235313.

Declarations of interest

I. Berlin reports having received occasional honoraria for participation on the advisory boards of Sanofi-Aventis, Pfizer Ltd; he is an employee of Assistance publique-Hôpitaux de Paris—Université P and M.Curie-Faculté de médecine. N. Jacob reports no conflict of interest; she is an employee of Assistance publique-Hôpitaux de Paris. M. Coudert reports no conflict of interest; he is an employee of the Clinical Research Unit, Assistance publique-Hôpitaux de Paris. J. Perriot reports having received honoraria from Institut National du Cancer (France) and from the following pharmaceutical companies: Pierre Fabre, Pfizer Ltd, Glaxo-Smith-Kline, Astra-Zeneca, Novartis Santé Familiale, Mc Neil, and Sanofi-Aventis; he is an employee of Conseil Général du Puy-de-Dôme, Centre Hospitalier Universitaire Clermont-Ferrand and Facultés de Médecine et de Pharmacie, Clermont-Ferrand. L. Schultz reports no conflict of interest; she is an employee of Centre Hospitalier de Valenciennes. N. Rodon reports no conflict of interest; he is an employee of Assistance publique-Hôpitaux de Paris. None of the authors has connections with tobacco, alcohol and gaming industries.

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List of centres and contributors

Dispensaire E. Roux, Clermont Ferrand (Dr J. Perriot), Centre Hospitalier de Valenciennes (Dr L. Schultz), Centre Hospitalier Universitaire, Reims (Dr B. Picavet), Hôpital A. de Villeneuve (Dr X. Quantin), Hôpital Saint Jean, Perpignan (Dr A. Bour), Centre Hospitalier Régional Metz-Thionville, Hôpital Notre Dame de Bonsecours, Metz (Dr G. Peiffer), Hôpital Beaujon, Paris (Dr D. Alibert), Centre Hospitalier Universitaire, Hôpital du Bocage, Dijon (Dr D. Alibert), Centre Hospitalier de Versailles, Le Chesnay (Dr C. Camus-Cartaud), Centre Hospitalier d'Evreux (Dr C. Wiart), Centre Hospitalier d'Auch (Dr P. Napkane), Centre Hospitalier Universitaire de Nancy (Dr C. Gillet), Centre Hospitalier de Montluçon (Dr N. Djilali), Centre Hospitalier de Maubreuil, Carquefou

(Dr C. Borgat), Hôpital Saint Antoine, Paris (Dr AM. Lepetitcorps), Hôpital P. Brousse, Villejuif (Dr P. Dupont), Hôpital Jean Verdier, Bondy (Dr A. Borgne), Hôpital Bretonneau, Tours (Dr G. Lalande-Errard), Hôpital Trousseau, Tours (Dr S. Balland-Deprez), Centre Hospitalier W. Morey, Chalon-sur-Saône (Dr I. Cusey-Sagnol), Centre Hospitalier Saint-Esprit, Agen (Dr P. Chollet) and Hôpital de A Chenevier, Créteil (Dr S. Franc).

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