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Pharmacotherapy and smoking cessation at a tobacco dependence clinic

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Abstract

Background. Tobacco dependence medications are effective, and combinations may offer advantages. This study evaluates abstinence rates among smokers treated in a tobacco specialist clinic with individual and/or group counseling plus combination pharmacotherapy.

Methods. 790 smokers treated at the Tobacco Dependence Clinic in New Jersey from 2001–2003 and contacted 4 weeks after quit-date were studied. Patients received medications and behavioral interventions. Abstinence over the previous 7 days was evaluated at 4 weeks and 6 months. Patients lost to 6-month follow-up were considered still smoking.

Results. Overall, 36% of patients were abstinent at 6 months (20% who used no medications, 37% using one medication, 37% using 2 medications, 42% using 3 medications, and 42% using 4+ medications) ($P = 0.017$). 27% still used medications at 6 months, and had higher abstinence rates (65%) than those who stopped their medications (27%) ($P < 0.001$). Number of medications predicted abstinence at 4 weeks [adjusted odds ratios = 2.30 (95% CI; 1.27–4.18) for 1 medication, 4.78 (2.72–8.40) for 2 medications, 5.83 (2.98–11.40) for 3 medications, and 11.80 (4.10–33.95) for 4+ medications]. Increasing age, increasing level of education, longer time after waking to first cigarette, more than 7 clinical contacts, and more medications used were related to higher abstinence at 6 months.

Conclusions. Smokers attending a specialist tobacco dependence treatment clinic who used more medications and for longer duration had higher abstinence rates.

Keywords: Tobacco; Smoking; Cessation; Medications; Pharmacotherapy; Tobacco dependence treatment

Introduction

Tobacco remains the leading cause of preventable death in our society (USDHHS, 2004). Over the past 20 years, there have been significant advances in pharmacotherapy for treating tobacco dependence. These therapies have demonstrated effectiveness in numerous trials (Hughes et al., 1999; Fiore et al., 2000; Silagy et al., 2004; Hughes et al., 2004). Some data suggest that combination (Fagerstrom et al., 1993; Kornitzer et al., 1995; Puska et al., 1995; Blondal et al., 1999; Jorenby et al., 1999; Bohadana et al., 2000; Hand et al., 2002; Croghan et al., 2003; Prochazka et al., 2004) and extended duration (Hays et al., 2001; Hurt et al., 2002; Hall et al., 2004) pharmacotherapies may offer some advantages, especially in dependent smokers, but these results have been inconclusive (Croghan et al., 2003; Simon et al., 2004). Using other chronic diseases such as hypertension and diabetes as a model, where combinations of medications are advantageous, there may be a role for combining therapies to treat smokers. For some of these chronic diseases, patients may require 3 or 4 medications for acceptable responses. The optimal combinations of medications for tobacco dependence treatment are not fully understood, and few studies have evaluated the effects of more complex combinations. This study evaluates whether various combinations and extended duration therapies are related to higher abstinence rates at 4 weeks and 6 months after quit-date, and characterizes some combinations that are successful in treating tobacco dependence.

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Methods

Design

This study is a retrospective cohort analysis of 790 smokers treated at the Tobacco Dependence Clinic of the University of Medicine and Dentistry of New Jersey-School of Public Health from 2001–2003. The study was approved by the University's Institutional Review Board.

Treatment

Treatment at the Clinic is evidence-based and addresses management of nicotine withdrawal symptoms and behavioral change in social situations. An initial assessment was conducted lasting approximately 60 min (see Measures). This included an individualized treatment plan with a quit-date, usually within 1–2 weeks. Patients met with the medical director (MS) to develop a medication plan. Each medication was described in detail and the choice of medications and dosing was determined through assessment of dependence, previous experiences with medications, personal preferences, medical contra-indications, and co-morbidities. Patients were encouraged, but not required, to attend group treatment and use medications. The standard group treatment consisted of 6 weekly, 90-min sessions, aimed at maximizing support during the first 4 weeks when withdrawal is most severe. Sessions were designed to enhance motivation, prevent relapse, and encourage group problem solving. All groups were conducted by the clinical social worker (DR) and clinical psychologist (JF), while the medical director (MS) attended sessions 1–2 to assure that medication plans were set.

Patients were encouraged to use combinations of one or more "long-acting" medications (patch/bupropion) with one or more "short-acting" medications (spray/inhaler/gum/lozenge), use enough medications to feel comfortable, and not discontinue medications too soon. Patients were educated that the medications are safe and use will not cause an "overdose" of nicotine. Patch, gum, and lozenges were subsidized by the Department of Health and Senior Services and available at a discount; the lozenges became readily available in 2003. Additionally, inhaler samples were available for patients to try before filling the prescription.

Patients were advised not to reduce medications until going 14 consecutive days without significant cravings, withdrawal symptoms, or brief relapses (smoking on an isolated occasion). This timeframe was designed to address the problem of ceasing medications too early in treatment and corresponded to the standard 2-week supply of medications that we typically dispensed. If patients went 14 consecutive days feeling comfortable, they generally did well with a medication reduction.

The general protocol for weaning medications was to wean off the patch first (7 mg dose reduction every 2 weeks if comfortable), then wean bupropion SR (300 mg reduced to 150 mg for 1 week, then discontinued), and finally wean the short-acting medications as tolerated. The short-acting medications were often utilized for extended periods of time, even at minimal doses.

Sample

1025 patients were seen and had set a quit-date between 1/1/01 and 12/31/03. Of those, 790 patients (77%) entered treatment and were contacted 4 weeks after their quit-date. Medication data were systematically collected at this 4-week point. Since, the purpose of the study was to evaluate what medications the patients *actually used*, instead of what they were initially advised to use, those who were not contacted at 4 weeks were excluded from the analysis. Nearly all of the excluded patients (90%) were only seen for one or two encounters, so no further data were available on them.

Of those who initiated treatment and were contacted 4 weeks after the quit-date, 626 patients (79%) were contacted at 6 months for follow-up. All initial assessment data were collected in-person, while the 4-week follow-up was collected either in-person (39% of the responses), or by mail or telephone (61% of the responses). At least 4 telephone attempts were made, after which written questionnaire and self-addressed stamped envelope were mailed. Six-month follow-up was generally collected by telephone or mail. For the purpose of analyses, patients who were not reached at 6 months were assumed to be smoking.

Measures

Data collected during the initial assessment included demographics, tobacco use history, triggers, previous quit attempts with medications used, measures of dependence, medical assessment, psychiatric and substance use history, motivation/importance in quitting, and treatment preferences for the current quit attempt. Data collected at the 4-week and 6-month follow-up included smoking over the past 7 days, amount smoked in the past 7 days, days since last cigarette, number of contacts with the Clinic, and type and duration of cessation medications used. The primary outcome was 7-day point abstinence rates (no smoking during the previous 7 days). Continual abstinence from quit-date (no smoking since quit-date) was also recorded. Abstinence rates were confirmed by expired carbon monoxide (CO) levels of less than 10 parts-per-million (ppm), when possible. At the 4-week follow-up, 307 of 790 (39%) patients were seen in-person. Among those who were seen in-person, 255 claimed to be abstinent, and of those, 253 (99.2%) had an expired CO less than 10 ppm.

Statistical analysis

Data were analyzed using SPSS Software (Version 11.5). Frequencies of demographic variables are reported. Chi square analyses were used to determine differences between categorical variables, Student's t tests were used to determine differences between continuous variables, and logistic regression was used to calculate adjusted odds ratios with 95% confidence intervals for the primary outcome of tobacco abstinence. All variables that were significant in the bivariate analysis were included in the regression model. Significance was defined as P value < 0.05.

Results

Patient characteristics

Characteristics of the patients seen in the Clinic during the study period are described in Table 1. The mean age of patients was 44 years, with a range of 15–80. Patients were predominantly female, Caucasian, and had at least a high school education. More than half of the patients had previously received treatment for mental health or behavioral problems and more than a quarter reported receiving help with a substance abuse problem.

In terms of tobacco related characteristics (Table 1), patients reported significant tobacco use history and markers of dependence. They smoke on average 27 min after waking, with many (44%) smoking within 5 min, and smoke an average of 22 cigarettes per day, with most (68%) smoking a pack or more per day. Patients were asked about the importance of their quitting now, with 65% reporting "extremely important" (maximum on a 1–10 scale).

Medications used

Nearly 87% of patients who were followed-up at 4 weeks reported use of medications as part of their treatment plan. The nicotine patch was the most common medication, used by 64% of patients; 56% used the nicotine inhaler, 32% used bupropion SR, 16% used nicotine gum, 5% used nicotine lozenges (which only became available halfway through the study period), and 3% used nicotine nasal spray. More than three-quarters of the

Table 1
Demographic and tobacco use characteristics of patients (n = 790 unless specified) 2001–2003; Tobacco Dependence Clinic-New Jersey

Characteristic	n (%) or mean (SD)
Gender	
Male	308 (39%)
Female	482 (61%)
Race (n = 787)	
Caucasian	562 (71%)
African–American	154 (20%)
Hispanic	49 (6%)
Other	22 (3%)
Education	
Less than high school degree	76 (10%)
High school graduate	191 (24%)
Some college	291 (37%)
College graduate	145 (18%)
Graduate degree	87 (11%)
Marital status (n = 789)	
Married or living with someone	351 (44%)
Divorced, separated, or widowed	202 (26%)
Never married	236 (30%)
Number of patients who had received previous treatment for a mental health, emotional, or behavioral problem (n = 789)	406 (51%)
Number of patients who had received previous treatment for an alcohol or other drug problem	201 (26%)
Number of patients reporting symptoms or disease that they believe are caused by or made worse by smoking	469 (59%)
Cigarettes per day (n = 780)	
Less than 10	65 (8%)
10–19	185 (24%)
20–39	410 (53%)
40 or more	120 (15%)
Time to smoking first cigarette of the day (n = 776)	
Less than 5 min	340 (44%)
5–30 min	306 (39%)
More than 30 min	130 (17%)
Mean age of first tobacco use (n = 786)	15.2 ± 4.5
Mean age of regular tobacco use (n = 784)	17.4 ± 4.5
Mean number of years using tobacco (n = 788)	24.6 ± 13.5
Mean number of previous quit attempts (n = 775)	7.4 ± 14.7
Mean rating of importance of quitting (n = 781) (1–10 scale; 1 = not important; 10 = extremely important)	9.3 ± 1.2
Mean rating of confidence in ability to quit (n = 779) (1–10 scale; 1 = not confident; 10 = extremely confident)	7.1 ± 2.3

patches initially used were 21 mg dose, and similar proportions of gum and lozenges used were the higher (4 mg) dose. Perceived novelty and availability of samples may have increased inhaler use.

Combinations of medications were commonly used among patients with 23% using one medication, 42% using 2 medications, 17% using 3 medications, 4% using 4 medications, and less than 1% using 5 medications. Some of the most commonly used medication treatments were patch + inhaler (23%), patch alone (11%), and patch + bupropion SR + inhaler (10%).

Abstinence rates

Overall, 59.4% of patients reported previous 7-day abstinence at 4 weeks. Also, 48% of patients had not used tobacco at all since their quit-date (continuous abstinence) at 4 weeks. At 6-month follow-up, 36% of patients had a self-reported, 7-day point abstinence, and 21.4% reported continuous abstinence since their quit-date. For the remainder of the analyses, 7-day point abstinence rates are used.

Bivariate analyses of abstinence rates at 6 months by selected characteristics are reported in Table 2. Abstinence rates were higher with increasing age, varied by race/ethnicity, and were generally higher with increasing education level and longer time to first cigarette of the day. Patients with previous treatment for mental health or substance abuse problems had lower abstinence rates. Those patients who had more than 7 face-to-face contacts had higher rates of abstinence at 6 months (57%) than those who attended up to 7 sessions (34%). This cut-point represents the initial assessment plus the standard 6-session group treatment. Those patients who had more than 7 contacts had more than the Clinic's "standard" intensity of treatment.

The mean number of previous quit attempts did not differ between those smokers who were abstinent at 6 months (7.6 ± 15.6) and those who were not abstinent (7.3 ± 14.2). Data were not available for the length of previous quit attempts.

Combination medications

The number of medications used was related to abstinence rates, with higher number of medications generally resulting in higher abstinence rates (Fig. 1).

The number of medications used was also related to clinical markers of dependence. Those patients with higher markers of dependence were more likely to receive combination medications (Table 3). Those patients who declined to use medications had, on average, moderate levels of dependence.

Extended duration of medications

A significant proportion of patients who started medications (n = 686) continued to use medications for an extended duration with 72% of patients still using medications at 4 weeks, and 27% continuing to use medications at 6 months. Those patients who were still using medications at 6 months (n = 183) were more likely to remain abstinent from tobacco (65 vs. 27% abstinent) ($P < 0.001$) compared with those who had stopped their medications prior to 6 months (n = 607). This assumes that those patients not reached for follow-up were still smoking and not using medications.

Continuance of treatment from 4 weeks to 6 months was examined. Among smokers who were abstinent at 4 weeks

Table 2
Abstinence rates at 6 months by selected characteristics 2001–2003; Tobacco Dependence Clinic-New Jersey

Characteristic	Abstinence rate at 6 months *n* (%)	*P* value
Age		
Under 25 years	18/70 (26%)	<0.001
25–44	104/342 (30%)	
45–64	130/325 (40%)	
65 years and older	29/53 (55%)	
Gender		
Male	108/308 (35%)	NS
Female	173/482 (36%)	
Race		
Caucasian	215/562 (38%)	0.013
African–American	41/154 (27%)	
Hispanic	12/49 (24%)	
Other	10/22 (45%)	
Education		
Less than high school degree	15/76 (20%)	0.001
High school graduate	57/191 (30%)	
Some college	107/291 (37%)	
College graduate	67/145 (46%)	
Graduate degree	35/87 (40%)	
Cigarettes per day		
Less than 20	87/250 (35%)	NS
20 or more	189/530 (36%)	
Time to first cigarette of the day		
Less than 5 min	105/340 (31%)	0.044
5–30 min	117/306 (38%)	
More than 30 min	54/130 (42%)	
Previous treatment for mental health, emotional, or behavioral problem		
Yes	130/406 (32%)	0.032
No	151/384 (39%)	
Previous treatment for alcohol or other drug problem		
Yes	53/201 (26%)	0.002
No	228/588 (39%)	
Number of self-reported face-to-face contacts during first 4 weeks after quit-date		
Up to 7	231/673 (34%)	<0.001
More than 7	44/77 (57%)	
Used patch as part of treatment		
Yes	194/508 (38%)	0.039
No	87/282 (31%)	
Used inhaler as part of treatment		
Yes	175/442 (40%)	0.008
No	106/348 (30%)	
Used bupropion SR as part of treatment		
Yes	115/249 (46%)	<0.001
No	166/541 (31%)	

(*n* = 469), those who were still using medications at 6 months had higher abstinence rates (82%) than those who discontinued medications prior to 6 months (52%) ($P < 0.01$).

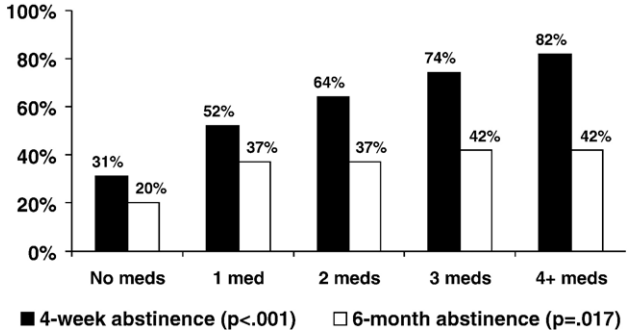

Fig. 1. Abstinence rates by number of medications used (*n* = 790) 2001–2003; Tobacco Dependence Clinic-New Jersey.

Multivariate predictors of abstinence

Using logistic regression, factors that are predictive of increased adjusted odds ratio for 4-week and 6-month abstinence are described in Table 4. Gender, race, importance in quitting, and number of cigarettes were included in the model, but were not significant predictors of abstinence. After adjusting for other variables, patients with increasing age and higher levels of education had higher odds of abstinence. Smokers who had their first cigarette more than 30 min after waking were twice as likely to be successful compared to those who smoked within 5 min. Finally, increasing number of medications predicted higher abstinence rates at 4 weeks, and those patients who used medications maintained a 2- to 3-fold increased chance of success at 6 months compared with those who did not use medications. The differences between one or more medication combinations were not significant at 6 months.

Discussion

Results from our study show that use of combinations of medications was associated with higher odds of remaining abstinent. At 4 weeks, increasing number of medications was the strongest predictor of abstinence. Despite this trend flattening at 6 months, there remain higher rates of abstinence with medications. It is important to consider that, in this cohort study, the patients receiving more medications were more dependent as indicated by higher cigarettes per day and shorter time to first cigarette of the day (Table 3). Despite this, they

Table 3
Markers of dependence by number of medications used 2001–2003; Tobacco Dependence Clinic-New Jersey

Number of medications used	Minutes to first cigarette mean, (SD)	Cigarettes per day, mean (SD)
0[a]	34.7 (75.0)	22.3 (12.1)
1	39.5 (80.2)	19.1 (10.5)
2	21.2 (37.9)	22.4 (11.7)
3	20.3 (28.8)	25.2 (13.2)
4	14.9 (24.8)	27.2 (14.1)
P value	0.001	<0.001

[a] Patients not using medications had generally chosen to do so against clinical advice.

Table 4
Adjusted odds ratios for 4-week and 6-month abstinence rates[a] 2001–2003; Tobacco Dependence Clinic–New Jersey

	n	4-week abstinence				6-month abstinence			
		Adjusted odds ratio	95.0% CI for OR		*P* value	Adjusted odds ratio	95% CI for OR		*P* value
Age									
Under 25	70	1	Referent			1	Referent		
25–44	342	2.04	1.14	3.64	0.02	1.16	0.62	2.15	0.64
45–64	325	2.61	1.45	4.71	<0.01	1.88	1.01	3.50	0.05
65+	53	3.43	1.49	7.90	<0.01	3.86	1.69	8.81	<0.01
Education									
No high school degree	76	1	Referent			1	Referent		
High school graduate	191	1.07	0.58	1.98	0.83	2.00	0.99	4.04	0.05
Some college	291	1.31	0.73	2.36	0.37	2.42	1.24	4.71	0.01
College graduate	145	2.05	1.06	3.98	0.03	3.32	1.63	6.78	<0.01
Graduate degree	87	1.95	0.93	4.11	0.08	3.00	1.38	6.53	<0.01
Time to 1st cigarette									
<5 min	340	1	Referent			1	Referent		
5–30 min	306	1.96	1.36	2.80	<0.01	1.48	1.04	2.11	0.03
>30 min	130	2.31	1.42	3.78	<0.01	2.07	1.30	3.30	<0.01
Confidence in ability to quit[b]	779	1.11	1.03	1.20	0.01	1.02	0.95	1.09	0.65
Number of face-to-face contacts									
Up to 7	231	1	Referent			1	Referent		
More than 7	44	2.61	1.39	4.88	<0.01	2.48	1.48	4.17	<0.01
Number of medications									
0	104	1	Referent			1	Referent		
1	186	2.30	1.27	4.18	<0.01	1.92	1.00	3.68	0.05
2	335	4.78	2.72	8.40	<0.01	2.32	1.26	4.27	<0.01
3	132	5.83	2.98	11.40	<0.01	2.03	1.02	4.03	0.04
4+	33	11.80	4.10	33.95	<0.01	2.92	1.14	7.46	0.02

[a] Gender, race, importance in quitting, and number of cigarettes were included in the model. These were not significant predictors of abstinence and are not displayed.
[b] Confidence in ability to quit is a *continuous* variable on a 1–10 scale.

still do as well as less dependent smokers at both 4 weeks and 6 month's abstinence. It appears in this sample that more medications overcome higher dependence.

The use of combination therapy has been shown in other studies to possibly offer some advantage compared with single or no medications (Fagerstrom et al., 1993; Kornitzer et al., 1995; Puska et al., 1995; Blondal et al., 1999; Jorenby et al., 1999; Bohadana et al., 2000; Hand et al., 2002; Croghan et al., 2003; Prochazka et al., 2004). However, there remain many misperceptions among smokers about this practice, with many smokers feeling that it is dangerous to combine these medications. This is due in part to the package labeling advising smokers not to combine these medications. It is important to discuss with patients the concept of combining medications. Many patients in this study reported that they would have tried this earlier if they had not been previously dissuaded by the packaging or advice from other healthcare providers.

Another advantage of utilizing multiple medications is the flexibility in delivery options. Those using 4 and 5 medications generally used the patch and bupropion SR with multiple short acting medications. In practice, these smokers are able to use different medications ad lib in various settings (e.g. lozenge during work, inhaler while driving, nasal spray early in the morning). It appears that the liberal availability of these multiple forms may increase success. The real-world limitations of this practice include access to prescribers and the costs for each additional form.

Longer duration of medications also seems to convey some benefit for abstinence (Hays et al., 2001; Hurt et al., 2002; Hall et al., 2004). In this study, those continuing to use medications have better abstinence rates at 6 months (65% vs. 27%). More than one-quarter of patients were still using medications at 6 months after their quit-date. Although data regarding the specific quantity of medications used at this point were not collected, patients were encouraged to continue using short acting medications (gum/lozenge/inhaler/spray) as needed, usually at low doses, and may have continued to use bupropion SR for relapse prevention. Very few continued to use the patch at this stage.

This study has some limitations. This was not a randomized, controlled trial, but rather a cohort study. This design limits the conclusions that can be causally attributed to the findings. There are several possible unmeasured or uncontrolled variables that could influence the outcomes. However, this study does give a "real-world" perspective of the treatment of dependent smokers, including those with medical and mental illness who are usually excluded from clinical trials. Additionally, abstinence rates were largely obtained via self-report, and thus rely on patient accuracy. This has the potential to bias the findings. Another limitation is loss to follow-up at 6 months. Since all patients lost to follow-up were considered as continuing to smoke, it is unlikely that our abstinence rates were over-estimated. If anything, with better follow-up, we could see higher abstinence rates, as not all those unable to be

reached are definitely smoking. However, it is unclear how these results would impact on the predictors of abstinence. Another limitation is that the actual quantity of medications used by smokers was unknown, only that they used a particular medication.

From this cohort of tobacco dependent smokers, it appears that patients who used more medications and used them for longer duration had higher abstinence rates. This study's data support these "off-label" uses. More research is needed into the optimal use of pharmacotherapy for treating tobacco dependence.

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References

Blondal, T., Gudmundsson, L.J., Olafsdottir, I., Gustavsson, G., Westin, A., 1999. Nicotine nasal spray with nicotine patch for smoking cessation: a randomized trial with six year follow-up. BMJ 318, 285–289.

Bohadana, A., Nilsson, F., Rasmussen, T., Martinet, Y., 2000. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation. Arch. Intern. Med. 160 (20), 3128–3134.

Croghan, G.A., Sloan, J.A., Croghan, I.T., et al., 2003. Comparison of nicotine patch alone versus nicotine nasal spray alone versus a combination for treating smokers: a minimal intervention, randomized, multicenter trial in a nonspecialized setting. Nicotine Tob. Res. 5 (2), 181–187.

Fagerstrom, K.O., Schneider, N.G., Lunell, E., 1993. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. Psychopharmacology 111 (3), 271–277.

Fiore, M.C., Bailey, W.C., Cohen, S.J., et al., 2000. Treating tobacco use and dependence: clinical practice guideline. US Department of Health and Human Services. Public Health Service, Rockville, MD.

Hall, S.M., Humfleet, G.L., Reus, V.I., Munoz, R.F., Cullen, J., 2004. Extended nortriptyline and psychological treatment for cigarette smoking. Am. J. Psychiatry 161 (11), 2100–2107.

Hand, S., Edwards, S., Campbell, I.A., Cannings, R., 2002. Controlled trial of three weeks nicotine replacement treatment in hospital patients also given advice and support. Thorax 57 (8), 715–718.

Hays, J.T., Hurt, R.D., Rigotti, N.A., et al., 2001. Sustained release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. Ann. Int. Med. 135 (6), 423–433.

Hughes, J.R., Goldstein, M.G., Hurt, R.D., Shiffman, S., 1999. Recent advances in pharmacotherapy of smoking. JAMA 281 (1), 72–76.

Hughes, J., Stead, L., Lancaster, T., 2004. Antidepressants for smoking cessation. Cochrane Database Syst. Rev. 4 [CD000031].

Hurt, R.D., Wolter, T.D., Rigotti, N., et al., 2002. Bupropion for pharmacologic relapse prevention to smoking: predictors of outcome. Addict. Behav. 27, 493–507.

Jorenby, D.E., Leischow, S.J., Nides, M.A., et al., 1999. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. NEJM 340 (9), 685–691.

Kornitzer, M., Boutsen, M., Dramaix, M., Thijs, J., Gustavsson, G., 1995. Combined use of nicotine patch and gum in smoking cessation. Prev. Med. 24 (1), 41–47.

Prochazka, A.V., Kick, S., Steinbrunn, C., Miyoshi, T., Freyer, G.E., 2004. A randomized trial of nortriptyline combined with transdermal nicotine for smoking cessation. Arch. Int. Med. 164 (20), 2229–2233.

Puska, P., Korhonen, H.J., Vartiainen, E., Urjanheimo, E.L., Gustavsson, G., Westin, A., 1995. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. Tob. Control. 4, 231–235.

Silagy, C., Lancaster, T., Stead, L., Mant, D., Fowler, G., 2004. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst. Rev. 3 [CD000146].

Simon, J.A., Duncan, C., Carmody, T.P., Hudes, E.S., 2004. Bupropion for smoking cessation: a randomized trial. Arch. Int. Med. 164 (16), 1797–1803.

US Department of Health and Human Services, 2004. The consequences of smoking: a report of the surgeon general. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.