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ORIGINAL PAPER

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# The efficacy of the combination of sertraline with buspirone for smoking cessation

## A randomized clinical trial in nondepressed smokers

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**Abstract** In a double-blind placebo-controlled trial, we evaluated the efficacy of the combination of sertraline and buspirone plus cognitive-behavioral treatment to promote tobacco abstinence in individuals referred to a chemical dependency clinic. Ninety eight individuals 18–65 years of age were randomized to placebo or sertraline 25 mg/day for 2 days, followed by 50 mg from day 3 to 90, and buspirone 5 mg three times a day for 7 days, and 10 mg from day 8 to 90. The rate of continuous abstinence at the 26th week of follow-up, informed by the patient, was 43.5% in the active treatment group and 17.3% in the control group ($p = 0.01$). The odds ratio for continuous abstinence for the intervention group was 4.74 (95% CI 1.50–14.55) (adjusted for smoker households and number of cognitive sessions). Nicotine withdrawal symptoms were common in both groups (98.7% vs. 95.5% $p = 0.37$). The combination of sertraline and buspirone with cognitive-behavioral therapy was more effective than placebo and cognitive-behavioral therapy to promote smoking cessation.

**Key words** smoking cessation · sertraline · buspirone · antidepressant · anxiolytic

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## Introduction

Tobacco is among the leading risk factors to global and regional burden of disease [10]. Findings from the 2002 National Youth Tobacco Survey [27] indicate that current use of any tobacco product ranged from 13.3% among middle school students to 28.2% among high school students. The European Community Respiratory Health Survey on the general population of young adults (20–44 years old) reported 36.9% of current smokers [3]. In a population-based survey, we identified that 34.9%, 95% Confidence Interval (CI) from 31.9 to 37.8, of adults living in Porto Alegre, southern Brazil, are smokers [29]. According to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria, about 50–80% of smokers in the United States are dependent on nicotine and approximately 80% of smokers want to quit smoking but less than 5% succeed without external assistance [1]. Nicotine dependence is associated with deficiency of dopamine, serotonin, and norepinephrine in the brain [9]. Nicotine increases neuronal activity related to euphoric effect and when it vanishes depression and anxiety supervene [9, 24].

Nicotine-replacement therapy has been widely used to treat smoking dependence but its efficacy is still unsatisfactory [9, 20]. Anti-depressive drugs such as bupropion [17, 20] and nortriptyline [32] have been effective to promote smoking cessation. Varenicline, a parcial agonist at the $\alpha 4\beta 2$ nicotinic acetylcholine receptor, was more effective than bupropion in one clinical trial [21]. Buspirone, a non-benzodi-

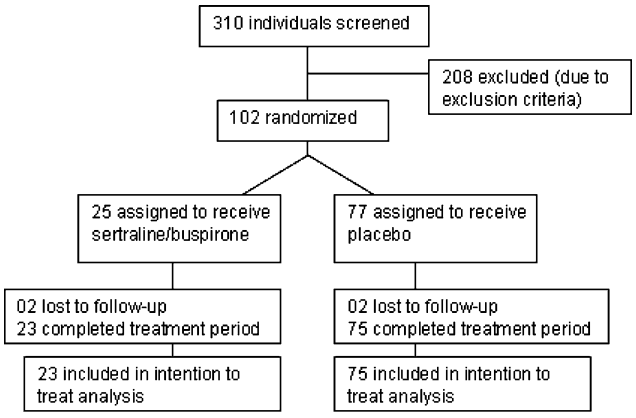


**Fig. 1** Flow chart showing the patients allocated to the treatment groups

azepinic anxiolytic drug acting on serotonergic neurotransmission, showed variable efficacy over abstinence rates and nicotine withdrawal symptoms [3, 16, 18]. Buspirone 30 mg/d and transdermal nicotine were associated with similar efficacy on smoking cessation [16]. In a meta-analysis [18] that included only two small trials comparing buspirone with placebo, the pooled odds ratio was 0.71, with a 95% CI between 0.34 and 1.48, which does not rule out a clinically useful effect. Patients with high levels of anxiety may benefit [4]. Sertraline, an antidepressive that inhibits serotonin re-uptake, showed to reduce craving compared with placebo [31]. It has also pharmacokinetic advantages and low occurrence of adverse reactions. The association of an antidepressant drug with an anxiolytic has not yet been tested to date [16, 17]. Therefore we decided to explore the hypothesis that the combination of these agents could have a synergistic effect, improving the smoking quitting rates.

In this report, we present the results of a randomized, double-blind, placebo-controlled trial testing the efficacy of the association of sertraline with buspirone on the rate of smoking cessation.

## Materials and methods

### Patients selection and randomization

Participants were recruited in a chemical dependency outpatient's clinic of the Brazilian public health system. In the total, 102 out of 310 screened patients fulfilled the selection criteria and were enrolled in the trial (Fig. 1). Seventy-seven were allocated to the placebo group and 25 to the active treatment group in accordance with a computer generated randomization, in blocks of four and in a 3:1 proportion.

To be included in the study patients were required to be between 18 and 65 years old; to have smoked at least 15 cigarettes per day during the last 3 years; and to have nicotine dependence based on the DSM-IV criteria [1]: presence of a cluster of three or more of the seven symptoms listed in DSM-IV occurring at any time in the same 12-month period. We additionally applied the Fagerström Test for Nicotine Dependence (FTND) [15]. Patients should be motivated to quit smoking in 30 days after the initial evaluation (the Prochaskás action stage, stages of change in smoking cessation) [31]. A negative test for pregnancy (human corionic gonadotrophin) was required for women on reproductive age. Exclusion criteria were the use of other psychoactive substances; major depression or distymic disorders in the last 2 years; bipolar disorder, intolerance to the study drugs; two positive answers to CAGE questionnaire [28]; presence of other psychiatric illnesses that could affect the capacity of the patient to follow the medical prescriptions; serious organic illness and a weight lower than 45 kg. A psychiatrist administered the questionnaires and evaluated the presence of clinical and psychiatric co-morbidities.

The study was approved by the Ethics Committee of our Institution, and all patients gave their informed consent to participate.

Patients attended to weekly sessions of cognitive-behavioral therapy (CBT) aiming behavior modification throughout the study. Sessions were conducted by three psychotherapists, who were unaware of the treatment allocation. The topics included motivation, identification of the trigger points for smoking, study of means of resistance, weight control and support for the use of the study medications. When they stopped smoking, the therapy was oriented to the prevention of relapse. Participants who did not show up in a session were contacted by telephone.

### Intervention

The intervention lasted 90 days. Patients randomized to active treatment received a capsule with 25 mg of sertraline on days one and two of the treatment, after breakfast, followed by a capsule with 50 mg from day 3 to 90. Buspirone was given three times a day before meals, in the doses of 5 mg between days 1 and 7, and 10 mg capsules from day 8 to 90. Both drugs were used in lower doses to prevent addictive toxicity (serotonin syndrome). The control group received placebo capsules well-matched in terms of taste and appearance to the sertraline and buspirone, in the same dosage schedule.

In the second week following the starting of treatment (15th day), patients were instructed to attempt to quit smoking. Follow-up visits were scheduled for the first week after the attempt, generally on the third day, and thereafter on the 4, 8, 12, 16, 24 and 26th week after randomization.

### Outcomes

The efficacy of the treatment was assessed by the rate of continuous abstinence 6 months after smoking cessation, the post-quit date. No cigarettes smoking after the quitting date characterized continuous abstinence. Secondary endpoints were the rate of compliance with the use of medication, which corresponded to the utilization of at least 80% of the capsules [30] of sertraline and of buspirone or of the respective placebos, and the incidence of adverse events.

At each visit, the patient was asked by a blinded investigator if he/she had smoked since the last consultation, and if so, how many cigarettes he/she had smoked. The presence of craving, withdrawal symptoms, use of other drugs, and the occurrence of adverse and other clinical events, were also evaluated. Compliance with treatment was evaluated at each visit by checking on the number of capsules taken since the last consultation.

### Statistical analysis

The sample size of 75 individuals in the control group and 25 in the intervention group (3:1) was based on an estimate of abstinence of 10% in the placebo group and 45% in the active treatment group, with an alpha error of 0.05, and power of 80%.

Data were analyzed with EPI-INFO, version 6.4 and SPSS, version 10. Efficacy was tested according a modified intention-to-treat analysis. The rate of abstinence in the groups was compared by the $\chi^2$-test, as well as the compliance to the drugs and the behavior therapies, and the occurrence of withdrawal symptoms. Relative

**Table 1** Baseline characteristics of smokers treated with sertraline plus buspirone ($n = 23$) or placebo ($n = 75$)

| Characteristics | Sertraline/Buspirone ($n = 23$) | Placebo ($n = 75$) |
|---|---|---|
| Age (year), mean ± SD | 44.0 ± 9.2 | 40.8 ± 9.8 |
| Female (%) | 14 (60.9) | 46 (61.3) |
| White (%) | 19 (82.6) | 69 (92.0) |
| Education (%) | | |
| <8 years | 13 (56.5) | 39 (52.0) |
| 8 < 11 years | 3 (13.0) | 17 (22.7) |
| 11–13 years | 5 (21.7) | 12 (16.0) |
| College graduate | 2 (8.7) | 7 (9.3) |
| Income (Brazilian minimum wages[a]) | 3.7 ± 3.0 | 4.2 ± 3.2 |
| Others smokers in household (%) | 14 (60.8) | 43 (57.3) |
| Years of smoking cigaretts, mean ± SD | 28.7 ± 10 | 24.0 ± 10.2 |
| No. of cigaretts smoked daily, mean ± SD | 21.9 ± 4.6 | 23.2 ± 6.9 |
| Alcohol drinking (%) | 13 (56.5) | 49 (65.3) |
| No previous attempts to quit (%) | 14 (60.9) | 50 (66.7) |
| Fagerström score[b] | 5.7 ± 1.6 | 5.8 ± 1.9 |
| Score ≥ 5 (%) | 17 (73.9) | 56 (74.7) |
| Nicotine physiological dependence—DSM-IV (%)[c] | 23 (100) | 75 (100) |
| History of major depression (%) | 0 | 8 (10.7) |
| Generalized anxiety disorder (%) | 0 | 8 (10.7 |

[a] Brazilian minimum wages (one wage is equivalent to US $ 163 per month)
[b] FTND, the range for the Fagerström Test for Nicotine Dependence score is 0–10, with scores ≥5 indicating higher levels of nicotine dependence (phyisiological dependence)
[c] Defined by the presence of tolerance or withdrawal

risk for continuous abstinence in the active treatment group was computed. The rate of quitting smoking was adjusted for the number of cognitive-behavioral therapy sessions attended, and the number of other smokers in household in a logistic regression model because these two conditions showed crude association with smoking abstinence.

## Results

### Baseline characteristics and rates of abstinence and compliance to the treatment program

Of the 102 randomized patients, four were lost of follow-up, two in each group (three moved to other cities and one abandoned the treatment because of adverse events). The participants randomized to the active and control group were similar in the distribution of prognostic factors (Table 1). Attendance at the cognitive-behavioral therapy sessions was low but similar in the two groups: 22% of the active treatment group and 25% of the placebo group attended to at least 12 sessions ($p = 0.73$).

At the end of the drug treatment period the continuous abstinence rate were 43.5% in the active group and 24.0% in the placebo group ($p = 0.07$). The rate of continuous abstinence after 6 months of ceasing smoking was greater in the active treatment group (10 out 23 participants, 43.5%) than in the control group (13 out 75, 17.3%, $p = 0.01$). Accordingly, treating four patients with sertraline and buspirone (associated with behavioral therapy) for 3 months lead to the abstinence for 6 months of one patient. The relative risk of continuous abstinence for the group treated with sertraline and buspirone against the placebo group was 2.51 (CI 1.27–4.95) and increased substantially after adjusting for confounding (Table 2). The rate of compliance to the treatment with medication was 16/23 individuals (69.6%) for the sertraline and 14/23 individuals (60%) for the buspirone in the active treatment group and 32/75 individuals (42.7%, $p = 0.089$) and 32/75 individuals (42.7%, $p = 0.126$), respectively, for the corresponding placebos.

**Table 2** Odds ratio for continuous abstinence in 6 months follow-up for smokers treated with sertraline plus buspirone ($n = 23$) versus placebo ($n = 75$)[a]

| | Odds ratio | 95% CI | $p$ |
|---|---|---|---|
| Treatment group | 4.74 | 1.5–14.99 | 0.008 |
| No. of smokers in household | 0.30 | 0.09–0.99 | 0.049 |
| No. of session in group therapy | 1.11 | 1.03–1.20 | 0.004 |

[a] Adjusted for number of smokers in the household and number of cognitive-behavioral sessions of therapy

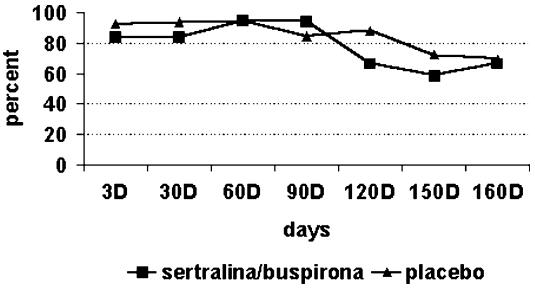


**Fig. 2** Self-report frequency of craving for cigarettes in treatment group of sertraline plus buspirone (S/B; $n = 23$) and placebo group ($n = 75$) in follow-up 180days. $\chi^2$-test $p > 0.05$

### Craving and nicotine withdrawal symptoms

Withdrawal symptoms of nicotine were common in both placebo and active treatment groups (98.7% vs. 95.5% $p = 0.371$), and were not different between groups for abstinent subjects. On the third day following the index day, 90.8% of the patients complained from craving (94.4% on placebo and 84.2% on sertraline plus buspirone; $p = 0.37$). There was a gradual decline with time in both groups (Fig. 2). Other frequent withdrawal symptoms were anxiety (62.8%), restlessness (56.3%) and appetite alterations (43.7%). The evolution of depression, anxiety, restlessness and changing in appetite was not different between the experimental groups along the experiment. Anger was the only characteristic that was of lower intensity in the group treated with the combi-

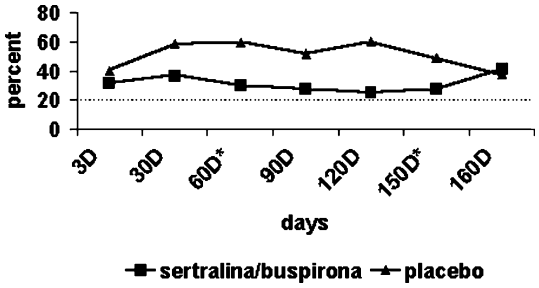


**Fig. 3** Self-report frequency (%) of anger in sertraline plus buspirone (S/B; $n = 23$) and placebo group ($n = 75$) in follow-up of 180 days. $\chi^2$-test, $^*p < 0.05$

**Table 3** Number of smokers ($n = 98$) treated with sertraline plus buspirone ($n = 23$) or placebo ($n = 75$) that complained of adverse events

| | Sertraline/buspirone *n* (%) | Placebo *n* (%) | *p* |
|---|---|---|---|
| Digestive symptoms | 19 (82.6) | 55 (73.3) | 0.366 |
| Drowsiness | 18 (78.3) | 52 (69.3) | 0.407 |
| Headache | 14 (60.9) | 51 (68.0) | 0.527 |
| Dizziness | 9 (39.1) | 35 (46.7) | 0.525 |
| Sexual Disfunction | 8 (34.8) | 18 (24.0) | 0.306 |
| Irritability | 8 (34.8) | 47 (62.7) | 0.018 |
| Insomnia | 8 (34.8) | 28 (37.3) | 0.824 |
| Lack of appetite | 6 (26.1) | 12 (16.0) | 0.274 |

nation of buspirone and sertraline (Fig. 3), but a play of chance can not be excluded since we did not adjust for multiple comparisons. Anger at baseline was inversely associated with continuous abstinence but did not reach statistical significance ($p = 0.193$).

### Adverse events

The majority of patients of both groups complained of adverse events: 91.3% in the active treatment group and 88.0% in the placebo group, $p = 1.0$. There were no serious adverse events and no patient required specific management for an adverse event. Table 3 presents the most frequent adverse events. The most frequent complaints in both groups were digestive symptoms, drowsiness and headache. Only irritability was more frequent in the placebo than in the intervention group ($p = 0.018$), but again we did not adjust for multiple comparisons. Only one patient from the active treatment abandoned the treatment due to intolerance to the study medication (because of diarrhea).

## Discussion

We demonstrated that the use of the combination of sertraline and buspirone for 3 months promoted higher rates of smoking cessation for six months in smokers without psychiatric comorbidity. This efficacy—a four times greater probability to be continuously abstinent—is highly significant in clinical terms. The absence of smokers in the household was also a protective factor and may be secondary to a genetic trace related to the serotonergic system function [6], or to an environmental influence. Although, similar rates of continuous abstinence have been reported by other authors [20, 32], the rate observed in this study both for the placebo and intervention groups was higher than predicted. This may be explained by a high motivation to quit smoking. Patients must be in the Prochaskás action stage [31] to be included in the study and they were spontaneously seeking for treatment not attending an advisor for clinical trial. In the randomized clinical trial of varenicline [21] the rates of continuous smoking abstinence for weeks 9 through 12 at the end of treatment were similar to our findings. The self-report of smoking cessation might have artificially increased the proportion of quitters, but not the difference between groups, in view of the double-blind design of our trial. On the other hand, the CBT for both groups until the end of the study may have contributed for this rates. Attending CBT was an independent predictor for abstinence, but the rate of compliance was low. The very different frequency of visits scheduled for the cognitive-behavioral sessions and to receive the agents may be among the reasons for the low-rate of adherence to the CBT.

The efficacy of sertraline plus buspirone to promote smoking cessation has not been demonstrated to date [17, 18]. Both drugs had variable efficacy when used separately [4, 7, 17, 18]. Craving, depression, anxiety, restlessness and change in appetite varied similarly in both groups, suggesting that other mechanisms may be involved in the cessation of smoking, such as those related by Schiffman et al. [35]. The lower rate of anger in the active treatment group was previously described by Coccaro et al. [5], and Fishbein et al. [11], who have demonstrated that antagonizing the diminution of serotonin is associated with impulsive aggressive behavior. Sertraline plus buspirone might reduce the sensitivity to stimulus that causes rage and that are antagonized by the use of nicotine by smokers [19, 26].

Buspirone acts selectively on the pre-synaptic 5-hydroxi-tryptamine 1A ($5HT_{1A}$) receptors as a serotonergic antagonist and presents a partial agonist action on the post-synaptic receptors thereby affecting anxiety, depression, sexual behavior, temperature, arterial pressure, pain [13, 34] and, possibly, also plays a role in serotonergic modulation of the sleeping Rapid Eye Movement (REM) [36]. Its influence on parameters of sleep REM [37] and an increase in sleepiness might modify the effect of the buspirone on patients seeking to quit smoking. Sertraline does not show affinity for the $5HT_{1A}$ receptors [2, 22, 33]. Its anti-depressive action seems to be mediated by direct influence on the cerebral serotonergic neurones that activate the noradrenergic neurones in the *locus ce-*

*ruleus.* This activation of the *locus ceruleus* provokes the down-regulation of the post-synaptic beta-receptors and the pre-synaptic alpha-receptors, which differentiates sertraline from fluoxetine [2, 8, 22, 33]. These drugs also do not present anti-cholinergic effects, which could accentuate the withdrawal symptoms related to the diminution of the liberation of acetylcholine that occurs in the absence of nicotine when smoking ceases [27]. Furthermore, the increase in extra-cellular serotonin is related to the modulation rate of liberation of acetylcholine in the central nervous system that has been attributed to nicotine [12].

The combination of sertraline and buspirone had no effect on craving. This result is consistent with the observed in studies with bupropion [19] and nortriptyline [22], but not with the findings of Jorenby et al. [21]. These authors recorded reduction of total craving with varenicline and with bupropion compared with placebo. In other trial [7], craving was considerably reduced by sertraline in comparison with placebo.

The incidence of adverse events was high but similar in both groups, being irritability the only statistically significant difference possibly reduced by combination of sertraline and buspirone (Fig. 3). Probably some symptoms attributed to the treatment were confounded by nicotine withdrawal symptoms. Only one patient in the active treatment group withdrew because of adverse events, which indicate that the combination of sertraline and buspirone was well tolerated. Probably as a result of the small doses used [23], only 26.1% of participants treated with sertraline complained of lack of appetite.

The relatively small sample size and the absence of evaluation of the intensity of symptoms of abstinence are potential weakness of our study. Our 3:1 allocation rate was employed in view of budget limitation (supply of active treatment). An alpha error is unlikely, however, but the size of benefit may be taken only as an estimation of the real efficacy. Another limitation was the absence of documentation of abstinence by carbon monoxide and cotinine measurement, but a reasonable agreement between informed and measured compliance with the recommendation to stop smoking has been reported [14, 25].

In conclusion, we demonstrated the efficacy of the combination of sertraline and buspirone with cognitive-behavioral therapy to help smokers to quit smoking. Further comparisons of this association with other established pharmacological interventions are necessary to confirm if this therapy may be of value for smoking cessation.

## References


1. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn (DSM-IV). Washington, DC
2. Byerley WF, McConnell EJ, McCabe RT, Dawson TM, Grosser BI, Wamsley JK (1987) Chronic administration of sertraline, a selective serotonin uptake inhibitor, decreased the density of B-adrenergic receptors in rat frontoparietal cortex. Brain Res 421:377–381
3. Cerveri I, Accordini S, Verlato G, Corsico A, Burney P, de Marco R, for the European Community Respiratory Health Survey (ECRHS) Study Group (2001) Variations in the prevalence across countries of chronic bronchitis and smoking habits in young adults. Eur Respir J 18:85–92
4. Cinciripini PM, Lapitsky L, Seay S, Wallfisch A, Meyer WJ, Vanvunakis H (1995) A placebo-controlled evaluation of the effects of buspirone on smoking cessation: differences between high- and low-anxiety smokers. J Clin Psychopharmacol 15:182–191
5. Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL (1989) Serotonergic studies in patients with affective and personality disorders. Arch Gen Psychiatry 46:587–599
6. Coccaro EF, Silverman JM, Klar HM, Horvath TB, Siever LJ (1994) Familial correlates of reduced central serotonergic system function in patients with personality disorders. Arch Gen Psychiatry 51:318–324
7. Covey LS, Glassman AH, Stetner F (2002) A randomized trial of sertraline as a cessation aid for smokers with a history of major depression. Am J Psychiatry 159:1731–1737
8. Doogan DP, Caillard VJ (1988) Sertraline: a new antidepressant. J Clin Psychiatry 49(suppl):46–51
9. Epping-Jordan MP, Watkins SS, Koob GF, Markou A (1998) Dramatic decrease in brain reward function during nicotine withdrawal. Nature 393:767–769
10. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ, Assessment Collaborating Group (2002) Selected major risk factors and global and regional burden of disease. Lancet 360:1347–1360
11. Fishbein DH, Lozovsky D, Jaffe JH (1989) Impulsivity, agression, and neuroendocrine responses to serotonergic stimulation in substance abusers. Biol Psychiatry 25:1049–1066
12. Garcia-Colunga J, Awad IN, Miledi R (1997) Blockage of muscle and neuronal nicotinic acetylcoline receptors by fluoxetine (Prozac). Proc Natl Acad Sci USA 94:2041–2044
13. Gelenberg AJ (1994) Buspirone: seven-year update. J Clin Psychiatry 55:222–229
14. Glassman AH, Stetner F, Walsh BT (1988) Heavy smokers, smoking cessation, and clonidine: results of a double-blind randomized trial. JAMA 259:2863–2866
15. Heatherton TF, Kozlowski LT, Frecker RC (1991) The Fagerström Test for Nicotine Dependence: a revision of the Fagerström tolerance questionnaire. Br J Addict 86:1119–1127
16. Hilleman DE, Mohiuddin SM, Delcore MG (1994) Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. J Clin Pharmacol 34:222–224
17. Hughes JR, Stead LF, Lancaster T (2006) Antidepressants for smoking cessation (Cochrane Review). In: The Cochrane Library, Issue 1. Oxford: Update software
18. Hughes JR, Stead LF, Lancaster T (2006) Anxiolytics for smoking cessation (Cochrane Review). In: The Cochrane Library, Issue 1. Oxford: Update software
19. Jamner LD, Shapiro D, Jarvik ME (1999) Nicotine reduces the frequency of anger reports in smokers and nonsmorkers with high but not low hostility: an ambulatory study. Exp Clin Psychopharmacol 7:454–463
20. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB (1999) A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 340:685–691
21. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR, for varenicline Phase 3 Study Group (2006) JAMA 296:56–63

22. Koe BK (1990) Preclinical pharmacology of sertraline: a potent and specific inhibitor of serotonin reuptake. J Clin Psychiatry 51B:13–17
23. Levin ED, Briggs SJ, Christopher NC (1993) Sertraline attenuates hyperphagia in rats following nicotine withdrawal. Pharmacol Biochem Behav 44:51–61
24. Li X, Rainnie DG, McCarley RW, Greene RW (1998) Presynaptic nicotinic receptors facilitate monoaminergic transmission. J Neurosci 18:1904–1912
25. Manfredi C, Crittenden KS, Warnecke R, Engler J, Cho YI, Shaligram C (1999) Evaluation of a motivational smoking cessation intervention for women in public health clinics. Prev Med 28:51–60
26. Marques ACPR, Campana A, Gigliotti AP (2001) Consensus on the treatment of nicotine dependence. Rev Bras Psiquiatr 23:200–214
27. Marshall L, Schooley M, Ryan H, Cox P, Easton A, Healton C, Jackson K, Dvis KC, Homsi G, Centers for Disease Control, Prevention (2006) Youth tobacco surveillance–United States, 2001–2002. MMWR Surveill Summ 55(3):1–56
28. Masur J, Monteiro MG (1983) Validation of the CAGE alcoholism screening test in Brazilian psychiatric hospital setting. Braz J Med Biol Res 16:215–218
29. Moreira LB, Fuchs FD, Moraes RS, Bredemeier M, Cardoso S (1995) Prevalence of smoking and associated factors in a metropolitan area of southern Brazil. Rev Saúde Pública 29:46–51
30. Nuesch R, Schroeder K, Dieterle T (2001) Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: a prospective case-control study. Br Med J 323:142–146
31. Prochazka AV (2000) New developments in smoking cessation. Chest 117:169S–175S
32. Prochazka AV, Weaver MJ, Keller RT, Fryer GE, Licari PA, Lofaso D (1998) A randomized trial of nortriptyline for smoking cessation. Arch Int Med 158:2035–2039
33. Sanders-Bush E, Breeding M, Knoth K, Tsutsumi M (1989) Sertraline-induced desensitization of the serotonin 5HT-2 receptor transmembrane signaling system. Psychopharmacology 99:64–69
34. Schweizer E, Rickels K (1997) Strategies for treatment of generalized anxiety in the primary care setting. J Clin Psychiatry 58:27–31
35. Shiffman S, Johnston JA, Khayrallah M, Elash CA, Gwaltney CJ, Paty JA, Gnys M, Evoniuk G, DeVeaugh-Geiss J (2000) The effect of bupropion on nicotine craving and withdrawal. Psychopharmacology (Berlin) 148:33–40
36. Ursin R (2002) Physiological review–Serotonin and sleep. Sleep Med Rev 6:57–69
37. Wetter DW, Carmack CL, Anderson CB (2000) Tobacco withdrawal signs and symptoms among women with and without a history of depression. Exp Clin Psychopharmacol 8:88–96