Brief Report

Effectiveness of Coadministration of Varenicline, Bupropion, and Serotonin Reuptake Inhibitors in a Smoking Cessation Program in the Real-Life Setting

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Abstract

Introduction: Varenicline has a significant impact on the ability to quit smoking. However, patients may have side effects similar to nicotine withdrawal symptoms. The aim of this study was to evaluate the effectiveness of varenicline in monotherapy or in combined therapy with bupropion and/or serotonin reuptake inhibitors (SRIs) in a specific cardiovascular smoking cessation service.

Methods: It is an outcome research of 427 patients that received varenicline monotherapy or combined pharmacotherapy and were followed for 52 weeks. Patients were oriented to take varenicline until week 12. During each medical visit, the patients were evaluated and in the cases of mood changes after varenicline use, SRIs were prescribed. Bupropion was combined in patients that did not achieve complete tobacco abstinence in 2 or 3 weeks after starting varenicline use or if the patient presented uncomfortable abstinent symptoms.

Results: The success (continuous abstinence rate in 52 weeks) in different drug regimens were: varenicline monotherapy (32.1%), varenicline + bupropion (55.0%), varenicline + SRI (50.6%), and varenicline + bupropion + SRI (57.7%). In a multivariate analysis of successful treatment predictors, compared with varenicline monotherapy, patients who used bupropion + SRI adjuvant treatment had an odds ratio (*OR*) of 5.05 (1.99–12.80) for a successful treatment response after 1-year follow-up, while patients who used bupropion or SRI had *OR* of 3.21 (1.68–6.14) and 3.58 (1.98–6.48), respectively.

Conclusions: Our results suggest that adjuvant treatment to varenicline therapy may be associated with improved success in smoking cessation, especially in patients with nicotine withdrawal symptoms. These results should be tested in randomized controlled trials.

Introduction

Smoking is a leading cause of preventable disease and is a significant modifiable risk factor for increased morbidity and mortality due to cancer, cardiovascular, and respiratory diseases. According to latest estimations by the World Health Organization, global tobacco-attributable deaths are expected to reach 6.4 million by 2015 and 8.3 million by 2030 (Mathers & Loncar, 2006).

Smoking cessation is associated with substantial decreases in morbidity and mortality and it is considered the most cost-effective intervention for disease prevention (U.S. Department of Health and Human Services, 1990).

In addition to counseling, pharmacotherapy has also presented a significant impact on the ability of individuals to quit smoking (Fiore, Jaen, & Baker, 2008). Varenicline received approval as a treatment aid for smoking cessation treatment in Brazil on September 18, 2006, and it is currently approved for marketing in 99 countries. Given the greater efficacy of varenicline compared with other drugs and the high risk of morbidity and mortality associated with continuous smoking, varenicline appears as a valuable element in the smoking cessation scenario according to European Medicine Agency (2011).

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In previous varenicline clinical trials, there were no important reports of psychiatric adverse events (Rigotti et al., 2010; Tonstad, Davies, Flammer, Russ, & Hughes, 2010). However, in the pos-marketing period, spontaneously reported psychiatric serious adverse events occurred. This fact induced U.S. FDA (Food and Drug Administration) to make a special alert about the risk of serious neuropsychiatric symptoms in varenicline users (U.S. Food and Drug Administration, 2008). Among patients taking varenicline, some patients can feel nicotine withdrawal symptoms as anxiety, depression, and mood imbalances, even if they are still smoking. In these cases, the medication suspension results in an increased chance of treatment failure. Then, it seems reasonable to treat these symptoms and to keep the treatment with varenicline.

In this scenario, the aim of this study was to evaluate the effectiveness of varenicline monotherapy compared to combined pharmacotherapy with bupropion and/or serotonin reuptake inhibitors (SRIs) in a sample of patients from a specific cardiovascular smoking cessation service.

Materials and Methods

Study Design and Patients

This retrospective outcome research included data of 476 consecutive patients who received a prescription for varenicline from a specific cardiovascular smoking cessation service from the Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, Brazil (September 1, 2007–December 31, 2009).

The Treatment Program

The treatment consists of an initial medical visit plus an average of five follow-up medical visits for 52 weeks. The follow-up was made by phone in patients who did not succeed in the smoking cessation treatment and/or did not continue to come on scheduled medical visits. In each follow-up visit, the presence and intensity of abstinence symptoms were monitored and adverse effects were collected by the structured questionnaire PAF (*Programa de Assistência ao Fumante*/Smoker Assistance Program, which is an electronic tool developed in our service to help in patient stratification, prescription, and follow-up). PAF is a psychometric tool, which evaluates the comfort according to the presence and degree (mild, moderate, and intensive) of the following symptoms: craving, irritability, anxiety, impatience, depressive mood, attention disturbance, appetite changes, insomnia, restlessness, and headache. PAF scale has not been validated yet, but it is in process (Issa, 2012). Clinical data, weight, and carbon monoxide concentration were collected in all visits. Demographic, socioeconomic and clinical data, the number of medical appointments, previous attempts to quit smoking, and the Fagerström score were also analyzed as predictor variables for success.

Patients received behavioral counseling and drug treatment from physicians specialized in smoking cessation. Varenicline was prescribed for patients who failed in previous attempts with nicotine replacement therapy or bupropion, or who smoke one or more cigarette pack(s) per day. We kept bupropion or SRI drugs in all patients who were already using these medications before the varenicline prescription (only 19 individuals were being treated with SRI before varenicline, and only 3 individuals were being treated with bupropion before varenicline initiation). In each medical visit, we analyzed the necessity of adding a new medication for the patients. Our indication to start the coadministration of bupropion at 150 mg/day was if the patient did not achieve complete abstinence after 2 or 3 weeks of starting varenicline use, or if the patient achieved complete abstinent, but presented moderate or intense discomfort abstinence symptoms. The coadministration of SRI, especially sertralin, occurred when the patient showed depression symptoms or mood imbalance after starting varenicline use, regardless of the smoking status.

Continuous abstinence rate (CAR) was investigated after 52 weeks as of starting varenicline. Patients were oriented to keep taking a dose of 2 mg/day until week 12, and continuous use of other drugs was defined according to medical evaluations. Patients were analyzed in four different drug treatment regimens: varenicline monotherapy, varenicline + bupropion, varenicline + SRI, and varenicline + bupropion + SRI. Smoking status (outcome) was divided into success group (patients who completed 52 weeks of CAR confirmed by carbon monoxide concentration), relapse group (patients who did not complete 52 weeks of CAR), and failure group (patients who never achieved CAR after starting varenicline treatment). The success group was followed for 52 weeks and the other groups were followed until the definition of smoking status (relapse or failure treatment).

Figure 1 presents a flow diagram of the varenicline treatment in our smoking cessation service.

Statistical Analysis

Categorical variables were presented as a percentage while continuous variables were presented as mean ± *SD* or median ± quartiles. The chi-square test was performed for comparative analysis of the adjuvant treatment groups and demographic and medical characteristics according to treatment response or according to treatment regimens. The chi-square test was also performed for comparing treatment response rate according to the drug regimen during follow-up. Analysis of variance tests were performed for comparing the demographic and medical characteristics according to the treatment response. Tukey's post-hoc test was performed to identify the different groups. A univariate analysis was performed for indicating successful treatment predictors and a multivariate approach was carried out to estimate the odds ratio (*OR*) for treatment response through the technique of logistic regression. Multiple testing corrections were not performed. All statistical analyses were carried out using the SPSS software (v. 16.0), with the level of significance set at $p \leq .05$.

Results

Baseline and General Characteristics of Studied Patients

Among 476 consecutive patients that received varenicline prescription, 49 have never started the use. We were able to collect complete information on 427 patients that started the varenicline treatment in our service. The patient group had a mean age of 49.9 ± 10.5 and 232 (54.3%) were female. From this

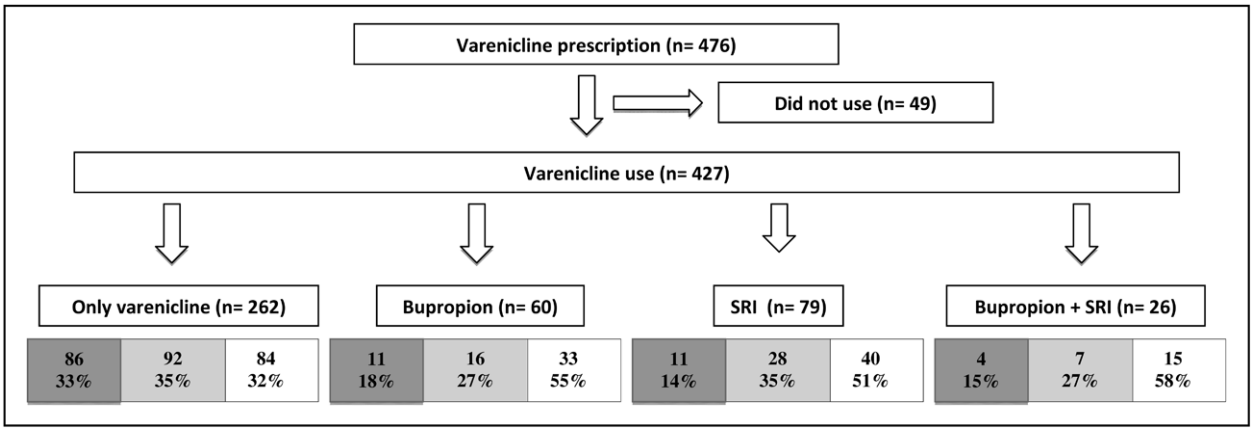

Figure 1. Flow diagram of the varenicline treatment in smoking cessation service. SRI, serotonin recaptation inhibitors. Dark gray box, failure; light gray box, relapse; white box, success.

Table 1. Demographic and Medical Characteristics of Studied Patients According to Treatment Response

	Failure (n = 112)	Relapse (n = 143)	Success (n = 172)	p value
Gender, male %	45.5	42.0	48.8	.50
Age, years	51.8 ± 10.5	49.2 ± 10.9	49.1 ± 10.0	.07
University education, %	39.3	54.5	58.7	<.01
Ethnicity, Caucasian descent, %	81.3	89.5	86.6	.14
Baseline weight, kg	74.9 ± 16.1[a,b]	71.3 ± 22.4[a]	76.1 ± 19.0[b]	.05
Final weight, kg	75.3 ± 16.6[a]	76.2 ± 19.1[a]	80.4 ± 20.0[b]	<.01
Weight gain, kg	0.7 ± 2.4[a]	2.1 ± 7.9[a,b]	5.7 ± 5.8[b]	<.01
Clinical visits	1.9 ± 1.2[a]	3.3 ± 2.2[b]	4.4 ± 2.5[c]	<.01
Fagerström score	7.6 ± 2.6	7.1 ± 2.6	7.3 ± 2.5	.21
Hypertension, %	36.6	26.6	25.0	.08
Coronary artery disease, %	7.1	9.8	6.4	.51
Myocardial infarction, %	10.7	9.8	7.6	.62
Dyslipidemia, %	28.6	21.0	19.2	.16
Chronic obstructive pulmonary disease, %	15.2	11.9	12.8	.73
Type 2 diabetes mellitus, %	4.5	3.5	1.7	.39
Hypothyroidism, %	4.5	4.2	8.1	.26
Depression, %	25.9	30.1	17.4	.03
Bipolar disorder, %	1.8	2.8	0.6	.52
Panic disorder, %	0.9	1.4	7.0	.02
Anxiety disorder, %	9.8	11.9	9.9	.81
Number of coexisting diseases, median	1.0 (0–2.5)	1.0 (0–2.0)	1.0 (0–2.0)	.82
Number of drugs other than for smoking cessation, median	1.0 (0–3.0)	1.0 (0–3.0)	0 (0–2.0)	.06
Retreatment, %	3.6	7.7	1.7	.03
Number of previous attempts, mean	1.69 ± 1.96	1.62 ± 1.45	1.32 ± 1.12	.07

Note. Baseline weight was adjusted for age and gender. Weight gain and final weight were adjusted for age, gender, and baseline weight. Values for the weight and clinical visits with different superscript letters are significantly different (Tukey's post-hoc test).

sample, 112 (26.2%) failed the treatment, 143 (33.5%) relapsed, and 172 (40.3%) were not smoking after a 1-year follow-up (successful treatment).

Demographic and medical information according to treatment response from the entire cohort is described in Table 1. Patients of the success group had a higher number of clinical visits (4.4 ± 2.5) and a higher university education frequency (58.7%) compared with patients from the failure group (1.9 ± 1.2, 39.3%; $p < .01$). Patients of the success group had also a higher weight gain (5.7 ± 5.8 kg) compared with individuals from the failure group (0.7 ± 2.4 kg) ($p < .01$), even after an adjustment for age, gender, and baseline weight (Table 1). No association of the treatment response with the number of coexisting diseases or with the total number of drugs other than for smoking cessation was observed ($p = .53$ and $p = .06$, respectively).

The number of clinical visits was significantly higher in the success group ($p > .01$) (Table 1). However, we can identify among our success patient samples that the patient group using only varenicline had a lower number of visits (3.1 ± 2.1) compared to the bupropion success group and SRI success group (4.3 ± 2.3 to 6.3 ± 3.3) ($p < .001$).

Follow-up Information

Clearly, a significantly higher prevalence of adjuvant therapy was observed in the success group (19.2%, 23.3%, and 8.7% for use of bupropion, SRI, and bupropion + SRI, respectively) compared with the relapse group (11.2%, 19.6%, and 4.9%) and with the failure group (9.8%, 9.8%, and 3.6%) ($p < .001$).

A lower success rate (CAR in 52 weeks) and a higher failure rate were also observed in patients who used only varenicline (32.1% and 32.8%) compared with patients who used varenicline + bupropion (55.0% and 18.3%), varenicline + SRI (50.6% and 13.9%), and varenicline + bupropion + SRI (57.7% and 15.4%) ($p < .001$ and $p = .003$, respectively) (Supplementary Figure 1).

According to our PAF's data bank, the main reasons for treatment failure were lack of compliance (38.4%), interruption of treatment (20.5%), and intensive side effects (15.2%—especially nausea and abnormal dreams); while the main reasons for treatment relapse were stressful situations (39.2%) and carelessness (13.3%). The relapse rate was different according to the follow-up: 57.5% of them occurred before 12 weeks of the varenicline treatment, 25.0% between weeks 12 and 24, and 17.5% after 24 weeks of treatment.

Univariate Analysis of Successful Treatment Predictors

Next, we aimed at the identification of baseline or at treatment variables that could be associated with a successful varenicline treatment. We compare success versus no-success (failure + relapse) groups. From this analysis, we were able to identify retreatment—patients who had already tried to quit smoking in our service ($p = .05$, $OR = .28$), the number of previous treatment attempts ($p = .03$, $OR = .85$), baseline weight ($p = .01$, $OR = 1.02$), the number of drugs (other than for smoking cessation) at baseline ($p = .02$, $OR = .91$), and receiving at least one adjuvant drug during varenicline treatment ($p < .001$). Interestingly, we were not able to observe a statistically significant additive effect with both bupropion and SRI (bupropion: $OR = 2.59$, 95% $CI = 1.46–4.58$; SRI: $OR = 2.17$, 95% $CI = 1.30–3.63$; bupropion + SRI: $OR = 2.89$, 95% $CI = 1.27–6.56$).

Multivariate Analysis of Successful Treatment Predictors

In Supplementary Table 1, we present adjusted coefficients and confidence intervals for a multivariate model with all significant variables from univariate analyses. Treatment with adjuvant drugs, whether bupropion or SRI, was still significantly associated with a higher odds of a successful treatment response after a 1-year follow-up. Patients who used the bupropion + SRI adjuvant treatment had an *OR* of 5.05 (1.99–12.80) for a successful treatment response, while patients who used bupropion or SRI had *OR* of 3.21 (1.68–6.14) and 3.58 (1.98–6.48), respectively (Supplementary Table 1).

Discussion

Our data suggest that coadministration of bupropion and/or SRI with varenicline in heavy smokers is associated with increased success rates at a 1-year follow-up.

Of the 262 patients who received only varenicline, 86 (32.1%) had treatment failure (Supplementary Figure 1). The main hypothesis for this was the lower number of medical visits in this group and this was not enabling clinical reevaluation and thus not permitting pharmaceutical association in case the patient presented discomfort symptoms with varenicline monotherapy. One can anticipate the several consequences of this fact. In the scenario of a smoking cessation program, the number of medical visits is associated with a reduction in failure treatment for several reasons; we suggest that one is the impossibility of the adjuvant medication prescription. The number of clinical visits can affect treatment success according to the literature. However, we can identify among our success patient samples that the patient group using only varenicline had a lower number of visits (3.1 ± 2.1) compared to the group whose patients that needed to add more drugs (4.3 ± 2.3 to 6.3 ± 3.3) ($p < .001$) suggested that these patients, indeed, needed more medical visits. Here, of the 427 studied patients, 165 (38.6%) used the adjuvant treatment because they did not achieve complete tobacco abstinence in 2 or 3 weeks after starting varenicline, or had presented, in follow-up visits, discomfort with abstinence symptoms or mood changes. For these patients, our multivariate analysis indicated that the bupropion + SRI adjuvant treatment had an *OR* of 5.05 (1.99–12.80) for a successful treatment response, while *OR*s of 3.21 (1.68–6.14) and 3.58 (1.98–6.48) were observed for bupropion and SRI, respectively.

Moore, Furberg, Glenmullen, Maltsberger, and Singh (2011) analyzed the FDA's Adverse Event Reporting System database from 1998 to September 2010 and found elevated rates of suicidal or self-injurious behavior or depression among patients using any cessation aid. Patients taking varenicline were more than 8 times as likely as those using nicotine replacement products to experience such adverse events. Patients using bupropion presented about 3 times the risk of such an adverse event compared with nicotine replacement users (Moore et al., 2011).

The main finding of this study was that the varenicline treatment combined with bupropion and/or serotonin recaptation inhibitors presented a higher success rate compared to varenicline monotherapy. Probably, the negative symptoms developed by patients during the smoking cessation process were identified and treated and consequently the patients kept the medication use and medical visits. Whether the effect of adjuvant drugs was due to specific pharmacotherapy effects, the possibility of positive reinforcement in an increased number of medical visits, or a combination of both, remains to be tested in more controlled scenarios. Interestingly, coadministration of varenicline and bupropion was only tested in a simple arm trial, and the abstinence rate in 6 months was 58% (Ebbert et al., 2009), similar to our results in 1 year.

The continuous use of varenicline despite not achieving complete abstinence from smoking during the first weeks of treatment has been associated with increased success rates

(Rennard et al., 2011). Therefore, it is difficult to dissect the specific therapeutic advantage of adjuvant therapy use. Several hypotheses could be raised: (a) counter balance of varenicline side effects leading to more medical visits and increased varenicline use and (b) an additive or synergistic effect of varenicline, plus bupropion and SRI.

Perhaps, some of the side effects may have been confounded by symptoms typically seen in people who had stopped smoking and were experiencing withdrawal from nicotine, such as anxiety, depression, and humor changes (Hughes & Hatsukami, 1986). The results of a number of preclinical studies support the hypothesis that varenicline has a dual mechanism of action at the α4β2 receptor, acting both as a partial agonist to moderate the levels of dopamine in the mesolimbic system, and as a power antagonist agent, blocking the effects of nicotine after smoking (Coe et al., 2005; Rollema et al., 2007). Thus, this powerful nicotine blocking effect could be the possible reason to explain the much higher risk of psychiatric adverse events associated with varenicline than those associated with other cessation drugs (Moore et al., 2011).

Since no other smoking cessation drug blocks the nicotine receptor, when the patient smokes, he can feel relief from abstinent symptoms. This cannot be achieved with varenicline. Therefore, it seems reasonable to suppose that the psychiatric adverse events related to varenicline could, indeed, be abstinence symptoms, even though the user is still smoking. In our patients, no severe psychiatric and cardiovascular adverse event was observed. Similarly, Rigotti et al. (2010) in a varenicline trial in patients with cardiovascular disease did not observe an increased cardiovascular risk in varenicline users.

There are some limitations in our study. First, our findings were identified in heavy smokers; thus, the results may not be equal in "lighter" smokers. Second, the duration of treatment with adjuvant drugs was not included as a covariate, and one cannot estimate what could be the reasonable duration of adjuvant treatment in this scenario. Third, our study did not allow identifying the effect of the number of clinical visits on treatment response. In fact, only randomized clinical trials could test these conditions and bring out the individual role of an adjuvant treatment and the number of clinical visits. Here, probably the two variables—the number of drugs and the number of visits—are inseparable. Fourth, our sample size for patients using varenicline + bupropion + SRI is very small precluding the determination of narrow risk estimative from this particular subgroup.

In conclusion, our data suggest that it is relevant to evaluate and to treat uncomfortable symptoms during the varenicline treatment, even if the presence of the symptoms could be related or not to varenicline uses. The risk of continuous smoking is much higher than serious adverse events (European Medicine Agency, 2011) and a benefit–risk approach should be adopted when considering treatment with varenicline.

Supplementary Material

Supplementary Table 1 and Figure 1 can be found online at http://www.ntr.oxfordjournals.org

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Declaration of Interests

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