CLINICAL SCIENCE

A real-life study of the effectiveness of different pharmacological approaches to the treatment of smoking cessation: re-discussing the predictors of success

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OBJECTIVE: To evaluate the effectiveness of nicotine replacement therapy (NRT), bupropion, nortriptyline and combination therapy and describe factors associated with treatment success.

INTRODUCTION: Clinical trials clearly demonstrate the efficacy of pharmacotherapy in smoking cessation. However, it is only after its use in real-life settings that clinical effectiveness and limitations of a treatment are fully known.

METHODS: Patients attended a four-session cognitive-behavioral program and received medicines free of charge. Abstinence from smoking was assessed at each visit.

RESULTS: A total of 868 smokers (68.8% women) were included. Their mean age was 49.6 years; the amount smoked was 25 cigarettes/day and the Fagerström Score was 6.6. Abstinence rates after 6 months and 1 year were 36.5% and 33.6%. In univariate analysis, male gender, age (>50), higher number of cigarettes smoked, cardiovascular comorbidities, longer interval from the last cigarette and combined treatment of nortriptyline plus NRT were predictive of abstinence, while neuropsychiatric comorbidities and the answer ''yes'' to the question ''Do you smoke more often during the first hours after waking'' were correlated with failure. In a multivariate model, predictors of abstinence were neuropsychiatric comorbidities, the answer ''yes'' to the question ''Do you smoke more often during the first hours after waking'' and combined treatment of nortriptyline plus NRT. Male gender and a longer period from the last cigarette were correlated with lower abstinence rate.

CONCLUSION: Satisfactory success rates were obtained in a teaching hospital. Factors such as age, daily cigarette consumption, number of pack-years and dependency score were not reliable markers of abstinence. The combination nortriptyline+NRT was independently associated with higher abstinence rates.

KEYWORDS: General practice; Nortriptyline; Cognitive-behavioral; Combined therapy; Weight gain.

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INTRODUCTION

Cigarette smoking remains one of the primary healthcare concerns world wide and continues to be the major cause of morbidity and mortality in the world. Five million people die yearly world wide owing to tobacco-related diseases. If current trends continue, tobacco will kill 1000 million people prematurely during this century.[1] Several studies have reported that 60–70% of smokers want to quit[2] and intend to stop, but only 3–5% of them remain abstinent for a year after an unassisted attempt.[3] ''Offer help to quit tobacco use'' in people addicted to nicotine is one of the six proven policies identified by WHO to expand the fight against the tobacco epidemic.

Pharmacological treatment is an important resource in smoking cessation. Several randomized, double-blind, placebo-controlled trials have reported significantly higher abstinence rates with first-line, and some second-line, drugs compared with placebo. These clinical trials provide scientific evidence of the efficacy and safety of nicotine replacement therapy (NRT),[4] bupropion (BUP),[5,6] varenicline[7,8] and nortriptyline (NOR),[9] a dopaminergic tricyclic antidepressant used as second-line smoking cessation therapy; however, the effectiveness and limitations of these drug regimens in real-life settings are still poorly documented.

Most randomized controlled trials have exclusion criteria, generally prohibiting entrance to the trial of patients with comorbidities and those with multiple or recent attempts to quit.[10] Those patients, especially those with cardiovascular and psychiatric disorders, frequently attend tertiary smoking cessation clinics such as ours.

The aim of this retrospective study was to assess the effectiveness of NRT, BUP, NOR and some combined schemes plus cognitive-behavioral intervention when used under clinical practice conditions and to investigate the role of different demographic and individual factors as predictors of abstinence.

MATERIALS AND METHODS

A retrospective interventional study was carried out among smokers motivated to quit attending the pulmonary division of Hospital das Clinicas, University of São Paulo Medical School (São Paulo, SP, Brazil) Smoking Cessation Clinic from 2003 to 2008. These smokers were included in the study, independently of the number of cigarettes smoked a day, number of pack-years or number of previous attempts to quit. All patients freely signed an informed consent form. Exclusion criteria were pregnancy and impossibility of attending the four sessions of the cognitive-behavioral program. Consultations were always held in the afternoons.

All smokers received a standardized program for smoking cessation including pharmacological and cognitive-behavioral interventions, consisting of four 60-minute structured group sessions (dealing with aspects of smoking-related morbidity and mortality, key issues of nicotine addiction and the development of a specific action plan for stopping smoking) during the pretreatment period. Pharmacotherapy consisted of NRT, NOR, BUP and NRT combined with NOR or BUP and was assigned depending on availability (supplied by the public health system, free of charge) and physician's discretion. Treatment always began 2 weeks before the target quit day for BUP and NOR users and on the day before quitting for patients receiving NRT. Pharmacological therapy was prescribed for at least 12 weeks.

Patients attended follow-up control visits at weeks 2, 4, 8 and 12 after the scheduled quit day and monthly until the sixth month. Abstinence at 1 year was assessed, when possible, by telephone call.

Patients who missed their appointments or did not answer the phone calls were considered smokers (intention-to-treat analysis).

At baseline a detailed smoking history and health data, using a three-domain structured anamnesis, were gathered. Questionnaires included questions on gender, age, cigarette initiation, number of cigarettes per day and Fagerström test for nicotine dependence (FTND), time from last cigarette, previous attempts to quit, presence of other smokers in the household and former and current diseases and medications. Self-reported cigarette consumption, exhaled CO level (COex), weight and possible adverse effects were measured at all follow-up visits. Effectiveness was measured as 7-day point prevalence abstinence rate confirmed by COex levels of $\leq$9 ppm from week 2 through the sixth month.

Psychiatric comorbidity was assessed using the Diagnostic and Statistical Manual of Mental Disorders,[11] fourth edition (DSM-IV) and self-reported diagnostics. Weight was recorded at every appointment. Data were first entered into a relational database (Microsoft Excel, Microsoft Corp, Redmond, Washington, USA) and then converted into an SAS file (SAS 9.0, SAS Institute Inc, North Carolina, USA). In the descriptive analysis, categorical variables are expressed as proportions, and continuous variables as mean (with standard deviation) and median, when they have no normal distribution.

Univariate (crude) analysis of variables from the entire population was performed using a χ^2 test and two-sample test for continuous data. Data were expressed as an odds ratio and 95% confidence interval. All tests used a significant level of 0.05.

Multivariate logistic regression was used to identify independent predictors (adjusted odds ratio and 95% confidence interval) associated with abstinence. Models were fitted, including all factors associated with the outcome, in a stepwise procedure. Factors were subsequently eliminated from the model if the χ^2 statistic of likelihood ratio test indicated no statistical significance.

RESULTS

Of a total of 1112 patients who attended the first appointment and began the treatment, 244 (21.9%) refused to participate in the structured program and did not attend the following meetings for group therapy.

Of the 868 patients who were assisted by the program, 597 were women (68.8%) and 271 men (31.2%), with a mean age of 49.6 years (range 21–82), who smoked an average of 25 cigarettes per day and 39.7 pack-years.

Baseline information and demographic characteristics of the participants are reported in Table 1.

The mean age of initiation was 15 years (SD 5.7); the distribution of subjects according to age of initiation is shown in Figure 1.

The results of the FTND (Figure 2) showed a sample of individuals with a moderate-to-high degree of dependence (mean score 6; median 7; SD 2).

About 81.8% of patients had made at least one previous attempt to stop smoking.

Of the women who had at least one pregnancy (n = 379), 272 (71.8%) smoked during gestation.

Table 1 - Demographic data and descriptive analysis

Characteristics	Value
Number	868
Gender, M/F (%)	31.2/68.8
Age (years)	49.6 $\pm$ 10.7
Educational status (years)	8.5 $\pm$ 5.3
Weight (kg)	67 $\pm$ 15
FTND Score*	6 $\pm$ 2 (0–10)
COex (ppm)	22 $\pm$ 12
Age of initiation (years)*	15 $\pm$ 5.7 (3–62)
Number of cigarettes/day	25 $\pm$ 20
Pack-years	39.7 $\pm$ 21.7
Respiratory comorbidities (%)	25
Cardiovascular comorbidities (%)	34
Neuropsychiatric comorbidities (%)	51
Time from last cigarette at first appointment (min)	120 $\pm$ 232 (2–1440)

*Expressed in mean $\pm$ SD (range).
COex = exhaled CO; FTND = Fagerström test for nicotine dependence; SD = standard deviation.

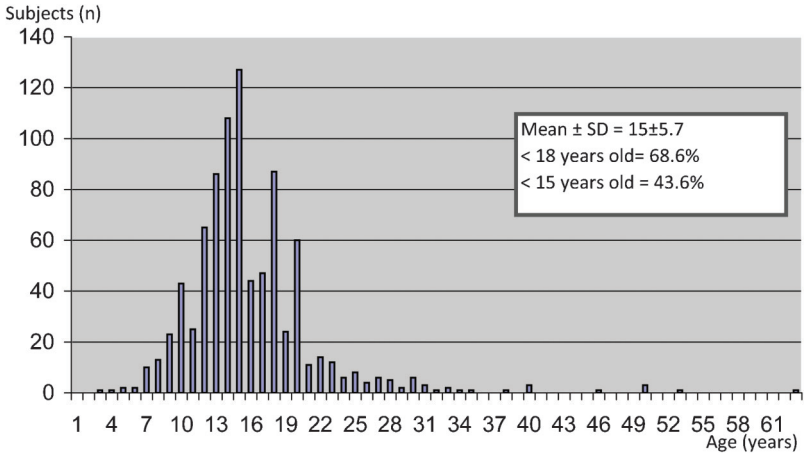


Figure 1 - Age of initiation (years).

More than a third of subjects had an associated disease (25% respiratory, 34% cardiovascular and 51% psychiatric comorbidity). Of those subjects, 82.5% had made at least one previous attempt to quit smoking and 41.8% had another smoker (or smokers) at home.

The distribution of treatment options was as follows: 74% NRT (n = 642), 8% NOR (n = 69), 8% NOR plus NRT (n = 70), 6% BUP plus NRT (n = 52) and 4% BUP alone (n = 35).

Success rates at 4 weeks, 8 weeks, 16 weeks, 6 months and 1 year are summarized in Figure 3.

For the variable ''time from last cigarette at first appointment'', values above and below the cut-off point at the median (120 min) were chosen in order to make this variable categorical. Intervals were also described as quartiles to study trends.

In the logistic procedure for multivariate analysis, there were no statistically significant differences in 7-day point prevalence at 1 year for age, gender, COex, FTND Score, pack-years, comorbidities (cardiovascular, mental and respiratory) and type of drug therapy used. Only the time from last cigarette at first appointment >120 min (OR = 1.17; 95% CI 1.07–1.28, $p<0.0001$) was a predictor of success. There was a linear relationship between the time from the last cigarette (separated into quartiles) at first visit and abstinence rate after 1 year (Cochran–Armitage Trend Test, $p = 0.0038$). The greater the time, the greater the success rate (Figure 4)

Having analyzed the success rates according to the combination of drugs used, we obtained the results shown in Figure 5. The combination of NOR+NRT was the most effective option (46.4% in 1 year). There was a statistically significant difference between the result of this combination and other treatment options (OR = 1.6; 95% CI 1.1–2.4, $p<0.05$). There was no statistically significant difference among the other treatment options.

Weight gain was an important concern in our study (Table 2), affecting 79.5% and 57.4% of patients, after 6 months and 1 year, respectively. From those who showed a weight increase, the mean gain was 7.5% (SD 6.1%) or 4.9 kg, at 6 months and 6.8% (SD 8%) or 5 kg, after 1 year. A

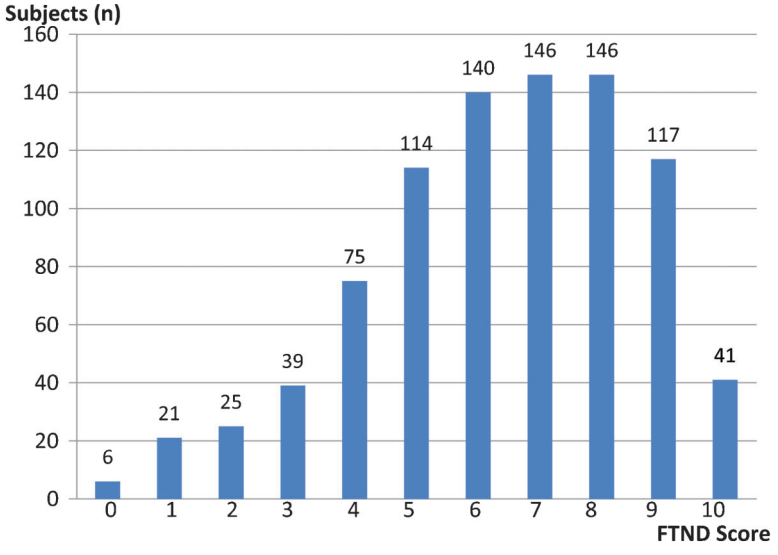
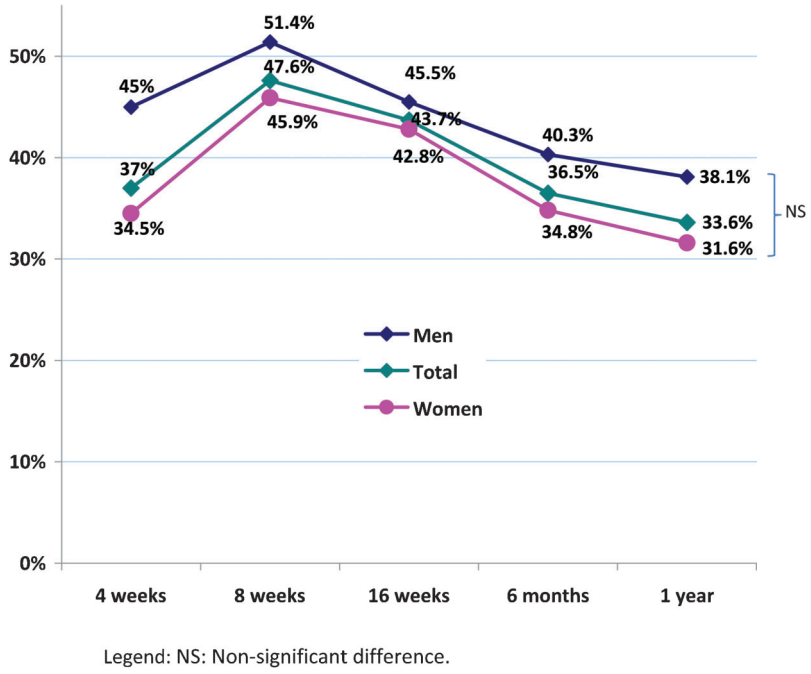


Figure 2 - Distribution of Fagerström test for nicotine dependence (FTND) Scores.



Legend: NS: Non-significant difference.

Figure 3 - Seven-day point prevalence abstinence rates at 4 weeks, 8 weeks, 16 weeks, 6 months and 1 year, according to gender.

comparison of people who had stopped smoking with those who continued to smoke showed a statistically significant difference in both period.

In univariate analysis (Table 3), gender (male), age (>50 years), cigarettes smoked (above the median of 35 pack-years), the presence of cardiovascular comorbidities, the interval from the last cigarette smoked before the first consultation (fourth quartile versus others) and the combined treatment of NOR+NRT were predictive of abstinence after 1 year, while the existence of neuropsychiatric comorbidities and the answer ''yes'' to the question ''Do you smoke more often during the first hours after waking than during the rest of the day?'' of Fagerström's Questionnaire were predictive of failure.

In the multivariate model, however, only five of these factors were correlated with the outcome. The presence of neuropsychiatric comorbidities, the answer ''yes'' to the question ''Do you smoke more often during the first hours after waking than during the rest of the day?'' and the combined treatment of NOR+NRT predicted higher odds of abstinence at 1 year. Male gender and longer period from last cigarette at the first attendance were correlated with lower odds of abstinence at 1 year.

DISCUSSION

This retrospective study shows data on tobacco abstinence after a period of clinical treatment for smoking cessation with real-life pharmacological schemes and cognitive-behavioral intervention and, also, analyzes markers of success in an off-trial clinical context.

The effectiveness data presented in this study are slightly better than those reported in the original clinical trials.[12] The corresponding real-setting abstinence rates at

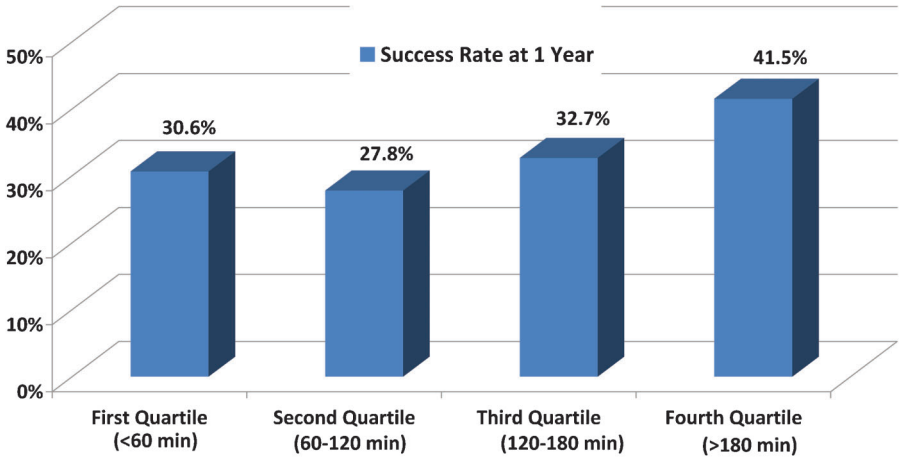


Figure 4 - Success rates at 1 year, according to time from last cigarette at first appointment, displayed in quartiles.

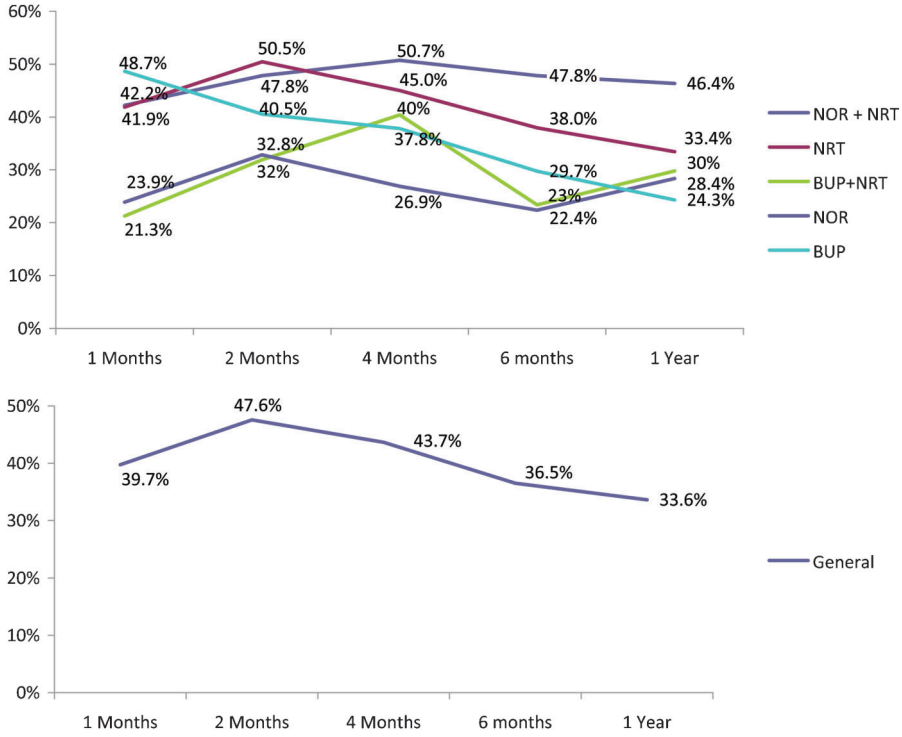


Figure 5 - Seven-day point prevalence abstinence rates according to drug options. BUP = bupropion; NOR = nortriptyline; NRT = nicotine replacement therapy.

52 weeks ranged from 38.1% for men to 31.6% for women, with no statistically significant difference between the two groups.

Identification of individual characteristics that predict success in smoking cessation is highly desirable, but not always feasible. A number of common predictors have been described as personal, social and psychological factors. In our population, however, age of initiation, educational status, dependency score (FTND), cigarette consumption, exhaled carbon monoxide level and the existence of respiratory comorbidities did not predict smoking cessation.

We observed data on gender differences that are similar to those found in previously published reports. There is evidence that women are more likely to seek assistance in their attempts to quit than are men[3], but there is some controversy about whether women benefit from specific pharmacological interventions (NRT, for instance) as much as men.[13,14]

Our study clearly demonstrates an early initiation into smoking, with over 68% of patients having started smoking before the age of 18 years. The median smoking initiation age in our group was similar to that described by Menezes and colleagues,[15] both for the city of São Paulo (16.2 and 18.3 years for boys and girls, respectively) and for the average of other Latin American cities studied (18.2 years).

Weight gain in our population was also similar to that in other studies, such as that reported by Klesges et al.,[16] which demonstrated a mean increase of 5 kg in abstinent patients after 1 year. In contrast to data published by Williamson and colleagues,[17] weight gain, which is strongly related to smoking cessation, occurred in the majority of those who stopped smoking. Some potential cosmetic effects of weight gain may negatively interfere with attempts to quit and thus, should be considered as an important problem in a cognitive-behavioral approach and counseling, especially for women.

In our center, with highly motivated patients, many of them with comorbidities, a high Fagerström Score was not a predictor of lower abstinence rates. Another intriguing finding was that smoking more in the early hours of the day was not confirmed in multivariate analysis as a factor related to treatment failure. Perhaps the restrictions on smoking indoors (which can directly influence the number of cigarettes smoked during the day and times at which one smokes more—possibly after the work shift) may explain these findings and signal the eventual need for future

Table 2 - Weight gain in 6 months and 1 year, according to subgroup analysis.

	6 Months		1 Year	
	Absolute gain (kg ± SD)	Percentage gain (% ± SD)	Absolute gain (kg ± SD)	Percentage gain (% ± SD)
General	4.3 ± 4.6	5.8 ± 7.1	1.5 ± 7.5	2.2 ± 10
Abstinent*	4.2 ± 4.3	6.8 ± 6.7	5.0 ± 7.0	7.1 ± 9.8
Present smokers	5.1 ± 2.4	3.7 ± 7.7	-0.4 ± 5.7	-0.4 ± 6.7

*$p<0.05$ compared with present smokers in 6 months and 1 year.

Table 3 - Predicting factors for abstinence in 1 year.

Factors	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Gender (male)	1.20	0.99–1.45	0.78	0.57–1.08
Age (>50 years)	1.39	1.15–1.68	1.01	0.99–1.03
Age of initiation (>15 vs. <15)	1.04	0.86–1.26		Not included
Educational status (>8 years)	0.87	0.77–1.23		Not included
FTND (High vs. low)	0.93	0.69–1.26		Not included
Cigarettes/day (>20)	0.97	0.80–1.17		Not included
Pack-years (>36)	1.17	0.97–1.41	0.95	0.68–1.33
COex (>20)	0.91	0.76–1.10		Not included
Cardiovascular comorbidities	1.13	0.93–1.37	0.93	0.80–1.10
Respiratory comorbidities	1.01	0.82–1.23		Not included
Neuropsychiatry comorbidities	0.84	0.69–1.01	1.11	0.96–1.28
How soon after you wake up do you have your first cigarette (within 5 min)	1.08	0.90–1.31		Not included
Do you smoke more frequently during the first hours after waking than the rest of the day? (Yes)	0.80	0.67–0.97	1.41	1.06–1.89
Time from last cigarette at first appointment (4th quartile vs. others)	1.37	1.14–1.66	0.62	0.46–0.84
BUP vs. others	0.71	0.40–1.27		Not included
NRT vs. others	0.97	0.79–1.20		Not included
NOR vs. others	0.83	0.56–1.23		Not included
BUP + NRT vs. others	0.87	0.56–1.37		Not included
NOR + NRT vs. others	1.37	1.03–1.81	1.69	1.01–2.83

BUP = bupropion; COex = exhaled CO; FTND = Fagerström test for nicotine dependence; NOR = nortriptyline; NRT = nicotine replacement therapy.

reviews of the questionnaire and its descriptors in light of recent changes in the pattern of cigarette consumption.

In univariate analysis, the variable defined as the time elapsed since the last cigarette and the first visit proved to be a predictor of success, which encourages the hypothesis that this factor could be recognized as an indicator of dependence (ie, the shorter the time, the higher the degree of dependence). However, this hypothesis was not confirmed in the multivariate model, indicating the need for confirmation in prospective studies.

A particular aspect of our study is the use of NOR, a tricyclic antidepressant with some evidence of efficacy in smoking cessation in small studies,[18,19,20] but classified in guidelines as a second-line drug owing to its side effects profile and conflicting results in larger controlled trials.[21] From our point of view, and in agreement with the findings from the meta-analysis of Wagena and colleagues,[22] it is a significant treatment option, given its efficacy (comparable to those first-line options), safety and, especially, its low cost and wide availability. Perhaps, considering the threat of a global tobacco epidemic—and even more significant impacts on the less affluent nations—the inclusion of NOR in the therapeutic arsenal of smoking cessation may be a promising step towards a wider access to treatment, especially in developing countries.

Based on our findings, we propose the inclusion of NOR among the list of first-line drugs for smoking cessation.

The major limitation of this report is that it was retrospective, uncontrolled and not randomized. The available options of treatment regimens were chosen by individual criteria on a case-by-case basis or according to the availability of medicines in the public health system.

Another significant limitation of our study was that the sample size allocated to each treatment group was very different, which may have compromised, to some extent, the validity of the comparison between them and, eventually, the reliability of these data.

Nevertheless, the proof of results previously demonstrated in randomized controlled clinical trials shows that treatment of smoking cessation in clinical practice is feasible and effective.

CONCLUSIONS

Despite the broad therapeutic armamentarium available, smoking cessation is still a therapeutic challenge all around the world. The different individual or combined pharmacotherapy regimens provide modest success rates—around 30–35% in 1 year. Another potential difficulty is translating the results observed in clinical trials into daily clinical practice, which in part can be explained by the fact that ''real'' patients do not always resemble those subjects participating in randomized controlled studies.

In a teaching hospital with students in training, our group has achieved satisfactory success rates, treating patients with high levels of dependence and high prevalence of comorbidities. Combining NRT with NOR yielded more favorable results.

Factors such as gender, age, number of pack-years, dependency score were not good predictors of success or markers of lower abstinence rates in smoking cessation treatment in this particular group of patients.

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