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Comparison of the Effectiveness of Varenicline, Extended-Release Bupropion and Nicotine Replacement Therapy on The Success and the Maintenance of a Smoking Cessation Program

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ÖZET:

Vareniklin, yavaş salınımlı bupropion ve nikotin yerine koyma tedavilerinin sigara bırakma programının sürdürümü ve başarısı etkilerinin karşılaştırılması

Amaç: Sigara bırakmayı düşünen ve bu konuda karar veren kişilere en etkin yaklaşım davranış eğitimi, motivasyonel destek ve farmakolojik tedavinin birlikte uygulanmasıdır. Bu çalışma bir eğitim ve araştırma hastanesi bünyesinde hizmet veren Sigara Bırakma Polikliniği'nde izlenen yetişkin sigara (nikotin) bağımlılarında nikotin yerine koyma tedavisi (NRT), yavaş salınımlı bupropion ve vareniklin tedavisinin tek başına veya kombine kullanımlarının sigara bırakma programının sürdürümü ve başarısı üzerine etkisini karşılaştırmayı amaçlamaktadır.

Yöntem: Sigara bırakma polikliniğine başvuran ve nikotin bağımlılığı tanısı doğrulanan 300 ardışık hasta randomize edilerek araştırmaya alınmıştır. Çalışma 251 hasta ile tamamlanmıştır. Bu çalışmada Fagerström nikotin bağımlılık testi, Hastane anksiyete ve depresyon ölçeği (HAD), karbonmonoksit (CO) düzeylerinin ölçümü amacıyla karboksimetre kullanılmış ve katılımcıların sosyodemografik bilgilerini edinmek ve klinik izlem için tarafımızca hazırlanmış olan yarı yapılandırılmış görüşme formu doldurulmuştur. Hastalar randomizasyona göre belirlenen farmakolojik tedavi seçeneğini 12 hafta boyunca kullanmıştır.

Bulgular: Tedavi grupları arasında hastaların yaşları, cinsiyet dağılımları ve eğitim durumları, açısından anlamlı ($p > 0.05$) farklılık yoktu. Sigara bırakma oranları bupropion grubunda (n= 77) (%57.1), NRT grubunda (n=73) (%54.8), varenicline grubunda (n=101) (%72.3) şeklinde bulunmuştur. NRT grubunda günlük tüketilen sigara miktarı ve Fagerstöm skorları bupropion ve vareniklin gruplarından anlamlı (p= 0.002) olarak daha düşük bulunmuştur. Bupropion grubunda ve NRT grubunda HAD-A 12. hafta ölçüm puanında başlangıç ölçümüne göre anlamlı (sırasıyla p=0.001 ve p=0.003) düşüş izlenmiştir.

Sonuçlar: Bu çalışmanın sonuçlarına göre 12 haftalık izlem boyunca çalışmaya katılan tüm hastaların %61.8'si sigarayı bırakma davranışını sürdürmüşlerdir. Vareniklinin sigara bırakma üzerine etkililiği ve bu etkinin devamı yavaş salınımlı bupropion ve nikotin yerine koyma tedavilerine göre sigara bırakma programı için daha üstün görünmektedir. Bupropion ve NRT gruplarındaki hastaların çalışma başlangıcına göre anksiyete seviyelerinin daha düşük olması bu tedavilerin başarı oranına ek katkı sağlamış olabilir.

Anahtar sözcükler: Yavaş-salınımlı bupropion, nikotin bağımlılığı, nikotin yerine koyma tedavisi, sigara bırakma, vareniklin

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ABSTRACT:

Comparison of the effectiveness of varenicline, extended-release bupropion and nicotine replacement therapy on the success and the maintenance of a smoking cessation program

Objectives: The most effective approach for individuals who decide to stop tobacco smoking is behavioral training complemented with motivational support and pharmacological therapy. This study aims to compare the effects of varenicline, extended-release bupropion and nicotine replacement therapy (NRT) on the success and the maintenance of a smoking cessation program.

Methods: 300 consecutive patients from a smoking cessation clinic, whose nicotine dependence was confirmed, were evaluated in a randomized manner. 251 patients completed the study. In this study, we used the Fagerström nicotine dependence test, a semi-structured clinic interview and the Hospital Anxiety and Depression scale (HAD) for clinical follow-up. Carbonmonoxide (CO) levels of the patients were measured with a carboxymeter. Patients had used the determined randomised pharmacological treatment option for 12 weeks.

Results: There were no significant differences between the therapy groups according to age, gender and education levels ($p > 0.05$). Smoking cessation rates were 57.1% in the bupropion group (n= 77), 54.8% in the NRT group (n=73) and 72.3% in the varenicline group (n=101). Fagerstöm scores and the number of cigarettes consumed per day in the NRT group were significantly lower than those of the other therapy groups (p =0.002). There was a significant decrease compared with the initial measurements in the HAD-A 12-week scores in the bupropion and NRT groups (p=0.001 and p=0.003, respectively).

Conclusions: According to our findings, 61.8% of all patients participating in this study continued the smoking cessation behavior during the 12 week follow-up period. It seems that varenicline is better than the other pharmacological therapy modalities for smoking cessation programs. The lower anxiety scores in the bupropion and NRT groups might have increased their success rates.

Key words: Extended-release bupropion, nicotine addiction, nicotine replacement therapy, smoking cessation, varenicline

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INTRODUCTION

Smoking (nicotine) addiction is the most common reversible risk factor across the world in terms of increases in morbidity and mortality (1). More than 20% of the population throughout the world suffers from nicotine addiction (2-4). Nicotine addiction is a chronic dependence progressing with relapses and it requires a long-term assessment (5). The most effective approach to those, who plan to quit smoking and have made up their minds to do this, is the concomitant administration of behavioral training, motivational support and a pharmacological therapy (2-4). The first line pharmacological therapies include nicotine replacement therapy(NRT), four forms of which are available in our country (nicotine patch, chewing gum, inhaler, and nasal spray), extended-release bupropion and varenicline (6-8). Nicotine shows its effect on the brain primarily through heterogenic acetylcholine receptors (nAChRs). By stimulating dopaminergic pathways, this activity causes an increase in dopamine and in this way contributes to the rewarding effect of nicotine (9-11). NRT helps stop smoking by alleviating the severity of cessation symptoms. There are no noteworthy differences among the nicotine replacement products in terms of their effects or efficacies on withdrawal symptoms, restlessness or despair (6,7). Bupropion is an antidepressant that has dopaminergic and adrenergic effects on the central nervous system (7,12). Since it is equally effective in nicotine addicts who have and do not have depression, its mechanism of action on smoking cessation is thought to be independent of its antidepressant effects (13). Bupropion may support smoking cessation behavior by blocking the reinforcing effects of nicotine, by alleviating the withdrawal symptoms or by reducing negative effects (14). Varenicline is a nicotinic receptor partial agonist. It is thought to reduce the withdrawal and craving symptoms while inducing some effects of nicotine by stimulating the $\alpha 4\beta 2$ subtype of the nicotinic acetylcholine receptor (6,15).

This study aimed at comparing the effect of NRT as well as extended-release bupropion and varenicline therapies, which are accepted as first line pharmacological therapies for nicotine addiction, on the success and maintenance of a smoking cessation program in adult cigarette (nicotine) addicts. This study was conducted at Erenkoy Mental and Neurological Diseases Training and Research Hospital Smoking Cessation Outpatient Clinic.

METHOD

Study Design And Participants

This was a naturalistic clinical follow-up study. Before they were included in the study, all the participants had been duly informed and they signed a consent form. 300 consecutive patients between 18 and 60 years of age, who presented at the smoking cessation outpatient clinic operating at our hospital and who were administered the relevant section of the SCID-I and whose nicotine addiction diagnosis was verified under the DSM-IV (16), were included in the study on a voluntary basis and they were randomized to the pharmacological therapy groups. To support generalization, patients who met the following criteria were excluded from the study. A medical disease at a preterminal or terminal stage, a psychiatric disorder, pregnancy or breastfeeding, an eating disorder, abuse of or addiction to a substance other than alcohol, a diagnosis of epilepsy, head trauma or any other neurological disease, having a known allergy to any of the medications to be used in this study, and having an intelligence quotient under 80. During the research, 38 patients were excluded from the study due to the reasons listed above. This study was completed with a sample of 251 patients.

Measurements

The Fagerström test for nicotine dependence (17) and the Hospital Anxiety and Depression scale (HAD) (18) were used to evaluate nicotine addiction in the participants and a carboxymeter was used to measure exhaled carbon monoxide (CO) levels.

Diagnostic interviews were conducted by the research assistants, who administered the relevant section of the SCID-I; the interviews were supervised by an experienced psychiatrist. Moreover, a semi-structured interview form was filled out, which had been prepared by us to obtain the patients' sociodemographic information and to be used for clinical follow-up. This study was conducted through face-to-face clinical interviews held at baseline and once every month and by administering the psychiatric scales. The patients used the pharmacological therapy option they were assigned to by way of randomization for 12 weeks and maintained the cessation program during the subsequent non-pharmacological follow-up period of 12-16 weeks. The treatment was started for the patients in the varenicline group with a dose of 0.5 mg/day a week before the day they had identified as their target. The dose was raised to 1 mg/day at Day 4. The dose was increased to 2 mg/day at Day 8 (targeted smoking cessation day) and this dose was maintained until the end of Week 12. The treatment was started for the patients in the bupropion group with a dose of 150 mg/day, a week before the day they had identified as their target. The dose was raised to 300 mg/day on Day 4 and this dose was maintained until the end of the study. NRT was administered using either a nicotine patch or nicotine gum, or a combination of both. The nicotine patches were used transdermally in their three forms containing 21, 14 and 7 mg of active substance, which is released in 24 hours and in cases of excessive nicotine craving, 2 mg nicotine gum was used. For each dose of nicotine patches, 4 weeks of administration in decreasing doses was recommended. The nicotine gum was started between 12 and 24 doses (2 mg) a day and gradually decreased. All subjects were informed about the method of using the patches and gum.

The Fagerström test for nicotine dependence is a two and four-point Likert-type self-assessment scale containing 6 questions; it produces measurements between 0-1 and 0-3 and is used to evaluate the risk of physical dependence on nicotine in patients as well as to measure its level and severity. The validity and reliability testing of the Turkish version of the form was done by M. A. Uysal et al. in 2003 and its Cronbach's alpha value was found to be 0.56 (19).

The HAD is a self-assessment scale containing 14 questions that produce four-point Likert-type measurements between 0 and 3; it is used to determine the risk of anxiety and depression in patients and to measure their level and severity. Odd numbered questions measure anxiety and even numbered questions depression. The validity and reliability testing of the Turkish version of the form was done by Ö. Aydemir et al. in 1997 and its Cronbach's alpha value was found as 0.85 for the anxiety subscale and 0.77 for the depression subscale (20).

Statistical Analysis

Means, standard deviations, ratios and frequency values were used for descriptive statistics of the data. The distribution of the data was checked with the Kolmogorov test. The ANOVA, Kruskal-Wallis and Mann-Whitney u tests were used for comparisons. The chi-square test was used in analyzing proportional data. When the conditions for the chi-square test were not met, the Fisher's test was used. The Wilcoxon test was used for recurrent measurements. The analyses were carried out using the IBM SPSS 20.0 software.

RESULTS

There were no significant ($p>0.05$) differences between the three pharmacological therapy groups in terms of patient age, gender distribution and educational status.

The amount of daily cigarette consumption was significantly ($p<0.05$) higher in the NRT group than in the bupropion and varenicline groups. No significant difference ($p>0.05$) was seen in the amount of daily cigarette consumption between the bupropion and varenicline groups. At baseline, the Fagerström dependence score in the NRT group was significantly ($p<0.05$) lower than those in the bupropion and varenicline groups. No significant

Table 1: Distribution of the smoking cessation according to the treatment groups

	Bupropion		Varenicline		Nrt		
	n	%	n	%	n	%	p
Stopped smoking	44	57.1%*	73	72.3%	40	54.8%*	0.032
Did not stop smoking	33	42.9%	28	27.7%	33	45.2%	

Chi-square test, *p< difference with Varenicline group

Table 2: Distribution of the nicotine dependence and some data according to the smoking status of patients

	Stopped smoking Mean ± SD	Did not stop smoking Mean ± SD	p
Age	45.8 ± 12.4	40.8 ± 10.7	0.001
Daily cigarette quantity	22.99 ± 9.426	25.57 ± 12.253	0.189
Cigarette quantity (boxes/year)	23.62 ± 11.119	23.26 ± 12.103	0.830
Fagerström score	5.9 ± 2.3	6.7 ± 2.4	0.003

Independent sample t test / Mann-Whitney u test

Table 3: Logistic regression analysis of smoking cessation in our sample.

	Mean	95 % Confidence interval		p
		Lowest	Highest	
Therapy (varenicline /bupropion)	1.96	1.04	3.66	0.036
Therapy (varenicline/NYKT)	2.05	1.19	3.52	0.010
Therapy (bupropion/ NYKT)	0.95	0.69	1.32	0.772
Fagerström (≤ 6/ > 6)	2.37	1.40	4.01	0.001
Age (> 60 / ≤ 60)	6.64	1.96	22.49	0.002

difference (p>0.05) was seen in the Fagerström scores of the bupropion and varenicline groups at baseline.

The rate of smoking cessation was significantly (p<0.05) higher in the varenicline group (72.3%) than in the bupropion group (57.1%) and the NRT group (54.8%). The rate of smoking cessation showed no significant (p>0.05) difference between the bupropion group and the NRT group (Table 1).

No significant (p>0.05) difference was found between the three therapy groups in terms of their HAD-D and HAD-A scores at baseline, Week 4 and Week 12. There was no significant (p>0.05) difference between the therapy groups in terms of the changes in their HAD-D and HAD-A scores measured at baseline and Week 12. A significant (p<0.05) decrease was seen in the HAD-D scores of the bupropion and varenicline groups at Week 12 as compared to their baseline scores. The HAD-D score did not show a significant (p>0.05) change in the NRT group. There was a significant (p<0.05) decrease in the HAD-A scores of the bupropion and varenicline groups at Week 12 as compared to their baseline scores. The HAD-A score did not show a significant (p>0.05) change in the varenicline group as compared to the score at baseline.

The age of the patients who stopped smoking were significantly (p<0.05) higher than those who did not stop smoking. There was no significant (p>0.05) difference in the numbers of daily or yearly cigarettes used by the patients who stopped or did not stop smoking. The Fagerström scores of the patients who stopped smoking were significantly (p<0.05) lower than those of the patients who did not stop smoking (Table 2).

The likelihood of smoking cessation was 1.96 (1.04-3.66) (p=0.036) times more in the varenicline group than in the bupropion group. The likelihood of smoking cessation was 2.05 (1.19-3.52) (p=0.010) times more in the varenicline group than in the NRT

group. The likelihood of smoking cessation was 0.95 (0.69-1.32) (p=0.772) times more in the bupropion group than in the NRT group and this was not a significant difference. The likelihood of smoking cessation increased 2.37 (1.40-4.01) (p=0.001) times in those whose Fagerström scores were ≤6 as compared to those whose Fagerström scores were >6. The likelihood of smoking cessation increased 6.64 (1.96-22.49) (p=0.002) times in those whose age was >60 as compared to those whose age was ≤60 (Table 3).

DISCUSSION

According to the results of this relatively large-scale prospective clinical follow-up study, where the efficacies of the nicotine replacement therapy (NRT), extended-release bupropion therapy and varenicline therapy, which are accepted as the first line pharmacological treatments for nicotine addiction, were compared with respect to maintenance of the smoking cessation program, 61.8% of all the patients who participated in the study maintained their smoking cessation behaviors during the 12-week follow-up period. According to the relevant literature, when non-pharmacological therapies (consultation, recommendation-education, cognitive behavioral therapy, etc.) are administered in combination with pharmacological therapies, the rate of success increases (4,21,22). The nicotine craving reducing effect of NRT was particularly emphasized in previous studies (23). During a process of nicotine clearance by NRT, overcoming deprivation gradually and preventing craving due to deprivation are made possible, so that compliance with the treatment program and thus the success of the treatment is increased (21-23). Bupropion similarly restricts nicotine craving and withdrawal symptoms by its dopaminergic activity on rewarding pathways in the mesolimbic system and nucleus accumbens (26). Bupropion also acts like a nicotine acetylcholine receptor antagonist and this function may be critical for smoking cessation behavior (24-26). As a partial nicotine receptor agonist, varenicline reduces the withdrawal symptoms associated with smoking cessation by stimulating fixed dopamine release at a moderate level in the nucleus accumbens (25). Additionally, varenicline binds to nicotinic receptors competitively to help diminish the reinforcing effects of nicotine in smokers (25).

The main finding of our study was that the rate of smoking cessation was significantly higher in the varenicline group than in the other pharmacological therapy groups. This result is similar to the results of the previous randomized controlled studies comparing the efficacy of bupropion and NRT with that of varenicline on smoking dependence (24,27,28). The Fagerström dependency scores at baseline of the group using varenicline were significantly higher as compared to those of the NRT group. According to the results of this study, when all the participants were considered, the fact that the smoking cessation behavior was stronger in the varenicline group, although those who had lower Fagerström dependency scores at baseline had higher rates of smoking cessation, might be a good indication that varenicline would be a more effective treatment option in the pharmacotherapy of nicotine addiction in the short and long run.

Another finding of our study was that there was a significant decline in the baseline HAD-D and HAD-A scores of the smokers in the bupropion group at Week 12. The bupropion and NRT groups had better results in coping with the anxiety associated with nicotine deprivation than the varenicline therapy. Bupropion and varenicline were more successful in reducing depressive symptoms than NRT. However, the effectiveness of bupropion in maintaining smoking cessation was not as strong as its anti-anxiety and anti-depressant effects. This may be a result supporting the fact that its effects on smoking cessation behavior are independent of its anti-depressant effect.

According to the results of this study, those whose Fagerström nicotine dependence scores were under 6 and those whose ages were above 60 were more successful in maintaining a smoking cessation behavior. We think that this outcome was due to the fact that older cigarette addicts had more smoking-related physical complaints, sensed the damage caused by smoking more or had their

quality of life impaired more. It can also be linked to the fact that older individuals had a higher motivation to quit smoking. The results of our study showed that the amount of cigarette consumption did not affect the smoking cessation behavior in cigarette addicts.

Our study had some limitations. First of all, the pharmacological agents used in the study were administered in a standard manner for the therapy groups to which the patients were randomized. Thus, personal characteristics of each patient and pharmacological side effects could not be assessed separately. For example, each of the patients who received NRT used both nicotine patches and nicotine gum. Nevertheless, no adverse event was reported during the study. A second limitation was the lack of consideration of how the duration of smoking and the previous smoking cessation attempts related to the success in the current smoking cessation program.

In conclusion, similar to a recent meta-analysis on the subject, varenicline seems superior to the other pharmacological therapies for smoking cessation (29). The results of this study should be taken into consideration when developing clinical practice guidelines.

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