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Original Article

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Success Rates of Pharmacological Therapies Used for Smoking Cessation and Factors that Affect Smoking Cessation Rates

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ABSTRACT

Smoking is still the most important cause of preventable diseases and premature deaths. Thus, smoking cessation interventions should include pharmacological therapies and/or counseling either alone or in combination. To analyze the demographic data of patients who presented to the smoking cessation polyclinic and received pharmacological therapies and determine the success rate of given therapies, and the factors that affect smoking cessation rates retrospectively. This retrospective study included patients who presented to the smoking cessation polyclinic and received pharmacological therapy (varenicline, bupropion or nicotine replacement therapy). Demographic data of patients, exhaled carbonmonoxide levels, and Fagerström test for nicotine addiction results were derived. Patients were reached by telephone survey in February 2013, and asked for their current smoking status and duration of therapy at the end of therapy. Patients were grouped into quitters and non-quitters. Differences between groups were assessed, and success rates of pharmacological therapies were compared.The study included 240 women and 509 men. Fagerström test for nicotine addiction results and exhaled carbonmonoxide levels were statistically higher in the non-quitter group than the quitter group. We did not find any significant difference between the groups in variables such as profession, age, gender, marital status and education levels. Varenicline had the highest smoking cessation rates at the end of therapy, and the rates were significantly different from others. Smoking cessation rates for varenicline, bupropion and nicotine replacement therapy were 50.9%, 35.9%, and 35.2%, respectively (p<0,05). However, long-term success rates (3-12 months) were similar for all pharmacotherapies. Long-term success rates of pharmacological interventions used for smoking cessation were not significantly different among groups. To prevent relapses, patients should be monitorized closely and new interventions should be developed to keep patients' motivation high for long-term abstinence.

Key words: *Aadiction, smoking cessation, pharmacological therapies*

Sigara Bırakma Tedavisinde Kullanılan İlaçların Başarı Oranları ve Sigara Bırakma Oranlarını Etkileyen Faktörler

ÖZET

Sigara bilinen en önemli erken ölüm ve önlenebilir hastalık nedenidir. Bu nedenle sigara bırakma yaklaşımları farmakolojik tedaviler ve danışmanlık hizmetlerini tek başına ya da kombine olarak içermelidir. bu çalışmada sigara bırakma polikliniğine başvuran ve farmakolojik tedavi verilen hastaların demografik verilerinin incelenmesi, farmakolojik tedavilerin başarı oranları ile sigara bırakma başarısını etkileyen faktörlerin belirlenmesi amaçlandıSigara bırakma polikliniğine başvuran ve farmakolojik tedavi (vareniklin, bupropion ya da nikotin replasman tedavisi) verilen hastalar retropsektif olarak çalışmaya dahil edildi. Hastaların demografik verileri, Fagerström nikotin bağımlılık testi sonuçları ve ekshale karbonmonoksit değerleri kaydedildi. Hastalar telefonla aranarak mevcut sigara içme durumları soruldu.Hastalar sigarayı bırakanlar ve bırakamayanlar olarak iki gruba ayrıldı ve gruplar arasında değişkenler açısından fark olup olmadığına bakıldı. 240 kadın 509 erkek hasta çalışmaya dahil edildi. Fagerström nikotin bağımlılık testi ve ekshale karbonmoksit seviyeleri sigarayı bırakamayan grupta anlamlı olarak daha yüksek saptandı. Yaş, cinsiyet, meslek ve eğitim seviyesi gibi değişkenler açısından iki grup arasında fark saptanmadı. Tedavi bitiminde vareniklin kullanan hasta grubunun sigara bırakma oranı bupropiyon ve nikotin replasman tedavisi alan gruplardan anlamlı olarak daha yüksek saptandı (sırasıyla %50.9, %35.9, %35.2, p<0,05). Ancak uzun dönem başarı oranları açısından gruplar arasında fark saptanmadı. Sigara bırakma tedavisinde kullanılan farmakolojik ajanların uzun dönem başarı oranları açısından anlamlı farklılık saptanmadı. Relapsları önlemek için hastalar sigarayı bıraktıktan sonra da yakından takip edilmeli ve uzun dönem başarı için hastaların motivasyonunu üst seviyede tutmak için yeni yaklaşımlar geliştirilmesi gereklidir.

Anahtar kelimeler: *Bağımlılık, sigara bırakma, ilaç tedavisi*

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INTRODUCTION

Smoking remains the most important cause of preventable diseases and premature death worldwide(1). Smoking is both physiologically and psychologically addictive, making it extremely difficult to quit (2). Quitting smoking is beneficial to health at any age, and cigarette smokers who quit before age 35 years have similar mortality rates to those who never smoked (3). Approximately 70% of those who smoke indicate that they would like to quit. However, among the more than 40% of smokers who do make a quit attempt each year, only about 5% experience long-term (3–12 months) success (2). The majority of tobacco users persist in tobacco use for many years and typically cycle through multiple periods of remission and relapse (4). The methods used for attempting to quit smoking include self help, counseling, and pharmacological interventions. Combination of these methods (Counseling and pharmacological interventions) is more successful than use of these methods alone and generally a lot of quitting attemps are needed for success (2). The first-line drugs for smoking cessation approved by the United States Food and Drug Administration (FDA) are varenicline, bupropion and nicotine replacement therapies (NRT) (5). All pharmacologic agents have been shown to be effective in smoking cessation with odds ratios between two and four when compared to placebo treatment. Absolute smoking cessation rates that vary in range from 5% to 35%depend on the particular pharmacologic agent used and the intensity of concomitant counseling (5). NRTs reduce smoking motivation and physiologically and psychologically symptoms that appear during smoking cessation. Various dosages of patches, chewing gum, lozenge, sublingual tablet, sprays and inhaler (absorbed by oral or nasal mucosa) forms are available (1). However, in Turkey only gum and various dosages of patches are available. NRT was developed in 1970s, and has been prescribed widely since then. It is sold without prescription in many countries. Bupropion which is a weak dopamine and nor-epinephrine reuptake inhibitor was developed as a non-tricyclic antidepressant. It is preferred by patients who do not want to use nicotine-based therapy or patients who failed with NRT(1,6). Varenicline is an α4ß2 nicotinic receptor partial agonist and was licensed for only smoking cessation therapy in USA in 2006 and in European Union in 2006/2007(1,6). Smoking cessation interventions generally include counseling and/or pharmacological therapies like varenicline, bupropion, and NRT alone or in combination. Research findings suggest that smoking-cessation self-help strategies alone are usually ineffective while counseling and pharmacotherapy either alone or in combination can improve abstinence rates (7). The comparison between bupropion and NRT suggests no advantage for either treatment. But varenicline is shown to be superior both to single forms of NRT and to bupropion(1). In a review, 5 forms of NRT were all found more effective than placebo with an odds ratio of 1.77, and abstinence rates were significantly higher than placebo (17% vs 10%, respectively) (8). Another randomized controlled trial that compared different dosages of bupropionand placebo, showed that the rates of abstinence were significantly better in the bupropion 150 mg and 300 mg groups (p=0.02 and p=0.01, respectively) than placebo and bupropion 50 mg BID (9). In another study, effectiveness of various dosages of varenicline was assessed, and pooled abstinence rates for 0.5 mg BID and 1 mg BID were 49% and 44% at weeks 12, respectively, and 22.4% and 18.5% at weeks 52 respectively (10).

The aims of the present study were to analyze demographic data of patients who presented to the smoking cessation unit, compare the success rates of these three therapies (NRT, bupropion and varenicline), and determine the factors that affect smoking cessation rates

MATERIAL AND METHODS

The participants of the study consisted of patients who presented to the smoking cessation unit of the Uzun Mehmet Chest and Occupational Diseases Hospital, Zonguldak, Turkey between January 2012 and November 2012. Demographic data of the patients including age, gender, marital status, professions and, daily cigarette consumption were derived from the records of the smoking cessation unit. Also, exhaled carbonmonoxide (CO) levels and results for the Fagerström Test for Nicotine Addiction (FTNA) were obtained. The FTNA is a 6-item questionnaire structured to help health care professionals determine a patient's degree of nicotine dependence; a score of ≥5 of 10 indicates a high level of nicotine dependence (Table 1). The study included patients who were given pharmacological therapies (varenicline or bupropion or NRT). In February 2013, we conducted a telephone interview with the patients. Patients who accepted to participate in the study were asked for their smoking status at the end of the smoking cessation therapy. They were also asked about duration of the therapy they used for smoking cessation. The patients were grouped

Table 1. Questions, answers, and scoring for Fagerström Test for Nicotine Addiction

	Answers	Points
How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
	6-30 minutes	2
	31-60 minutes	1
	After 60 minutes	0
Do you find it difficult to refrain from smoking in places where it is forbidden (e.g. at the library, in the cinema, etc.)?		
	Yes	1
	No	0
Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
How many cigarettes/day do you smoke?	≤10	0
	11-20	1
	21-30	2
	≥31	3
Do you smoke more frequently during the first hours after waking up than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

into quitters and non-quitters. Data were assessed using the PASW Statistics 18.0 for Windows. Variables like age, gender, education level, profession, marital status, daily cigarette consumption, FTNA scores and exhaled CO levels and success rates of pharmacotherapies were comparedusing the Student's t test. Nonparametric variables were compared using the Chi-square test. p value <0.05 was considered significant.

RESULTS

A total of 1145 patients presented to the smoking cessation unit between January 1st, 2012 and November 30th, 2012. Two hundred and eighty two patients who were not given a pharmacological therapy and 114 patients who could not reached by telephone were excluded. A total of 749 patients, 240 females (32%) and 509 males (68%) were eligible. Their demographic data are shown in Table 2. The mean FTNA scores and exhaled CO levels were significantly higher in the non-quitter group than the quitter group. The number of the patients who were given varenicline, bupropion, and NRT were 106 (14.1%), 264 (35.2%) and 360 (48.0%), respectively. Only 19 patients (2.5%) were given a combination therapy (NRT + bupropion or varenicline). Quitting rates were similar between males and females (36.7% and 38.3%, respectively). There was no significant difference between groups in age, education levels, and marital status (Table 3). The mean FTNA scores were significantly lower in bupropion group than in varenicline and NRT groups. Varenicline group had higher quitting rates than NRT and bupropion groups at the end of therapy, and the difference was significant (p=0.002). At the end of the therapy, quitting rates for varenicline, NRT and bupropion were 50.9%, 35.2% and 35.9%, respectively (Table 4). However, long term (3-12 months) abstinence rates were not significantly different among the groups (30.1 % for varenicline, 27.5% for NRT and 25.3% for bupropion, respectively). At the end of the therapy (3-12 week), quitting rate was 37.8% for all groups, but

Table 2. Demographic data of patients

	Quitted	Not Quitted	Total	p value
Age (year)	39.78 ±12.5	40.14±11.05	40.00±11.61	0.687
Fagerström	6.36±2.1	6.73±2.03	6.6±2.06	0.022
Exhaled CO (ppm)	10.91±6.39	12.76±6.56	12.09±6.55	0.001
Cigarette (per/day)	23.20±8.78	23.79±8.74	23.57±8.75	0.37
Duration of therapy (day)	25.41±9.61	25.73±10.41	25.61±10.1	0.67
Education level (year)	8.84±3.51	9.03±3.93	8.95±	0.64

Values were given as mean±SD

Table 3. *Descriptive data of patients*

		Quitted n (%)	Non quitted n (%)	Total n (%)	p value
Profession					
	Employeed	162 (36.9)	276 (63.1)	438(67.8)	0.055
	Retired	44 (57.6)	33 (42.3)	77 (11.9)	
	Housewife	26 (31.7)	56 (68.3)	82 (12.7)	
	Jobless	29 (59.1)	20 (41.1)	49 (7.6)	
	Total	261 (40.4)	385 (59.6)	646 (100)	
Marital status					
	Married	125 (35.1)	227 (64.5)	352 (59.3)	0.505
	Single	30 (36.1)	53 (63.9)	83 (40.7)	
	Total	235 (32.8)	480(67.2)	715(100)	
Gender	Male	195 (38.3)	314 (61.7)	509 (67.9)	0.363
	Female	88 (36.7)	152 (63.3)	240 (32.1)	
	Total	283 (37.8)	466 (62.2)	749 (100)	
Cigarette per day					
	0-20	168(35.1)	310 (64.9)	478 (63.8)	0.265
	>20	115 (42.4)	156 (57.6)	271 (36.2)	
	Total	283(37.8)	466(62.3)	749 (100)	

long term (3-12 months) abstinence rates dropped to 26.2%. Relapse rates were similar for all groups (Table 4). The mean duration of therapy for varenicline, bupropion and NRT were 37.0, 28.6, and 25.9 days, respectively. There was no correlation between quitting rates and duration of therapy.

DISCUSSION

The present study showed that the patients who used varenicline for smoking cessation therapy had a significantly higher quitting rate than those who used NRT and bupropion at the end of therapy (at weeks 4-12). Several studies that assessed the success rate of pharmacological therapies reported different rates. In a meta analysis, Eisenberg et al. (11) identified 70 published reports of 69 placebo-controlled randomized trials that involved a total of 32908 participants, and reported that varenicline, bupropion and the NRT (chewing gum, tablets, nasal spray, and patch) were all more efficacious than placebo, with ORs of about 2. Also in a direct comparison of varenicline that had an active bupropion arm (3 trials, 1881 patients), varenicline was superior to bupropion (OR 2.18). Another placebo controlled study (12) that compared nicotine patch, bupropion alone and combination of nicotine patch and bupropion, showed that both bupropion and combination of bupropion and nicotine patch had significantly higher rates of abstinence than placebo and nicotine patch alone either at 6 months and 12 months (both $p < 0.001$).

In this study, despite the higher abstinence rates with varenicline compared to NRT and bupropionat the end of the therapy, the long-term abstinence rates were not significantly different among the groups (30.1 % for varenicline, 27.5% for NRT and 25.3% for bupropion). Abstinence rate was 37.8% at the end of the therapy (4 to 12 weeks) for all groups, but during follow up (3 to 12 months), it dropped to 26.2%. One third of patients relapsed during follow up period. In a randomized controlled trial, Jorenby et al. (13) who compared the efficacy of vareni-

Table 2. *Pharmacological therapies and smoking cessation rates*

	Duration of therapy (day)	Quitted n (%)	Not Quitted n (%)	Relaps n (%)	Total n (%)
NRT (%)	25.9±7.8 (10-56)	127 (35.2)	233 (64.8)	28 (22.0)	360 (48)
Varenicline	37.1±13.4 (15-80)	54 (50.9)	52 (49.1)	22 (40.7)	106 (14)
Bupropion	28.93 ±10.8 (12-60)	95 (35.9)	169 (64.1)	28 (29.4)	264 (35.2)
Combination#	31.2 ±9.5 (20-60)	7 (36.8)	12 (63.2)	1(14.2)	19 (2.8)
Total	34.75 ±10.3	283 (37.8)	466 (62.3)	79 (27.9)	749

** values were given as mean ± standart deviation,(range) #: varenicline± NRT or bupropion ± NRT, †: p= 0,006*

cline and bupropion for smoking cessation and reported that continuous smoking abstinence rates at weeks 9-12, 24 and 52 were 43.9%, 29.7%, and 23% respectively for varenicline, 29.8%, 20.2%, and 14.6%, respectively for bupropion, and 17.6%, 13.2%, and 10.3%, respectivel for placebo. Similarly Eisenberg et al. (11) reported that the number of patients who remained abstinent from smoking at follow-up was low. Most of the randomized controlled trials included in their meta-analysis reported that the point prevalence of abstinence at 12 months was well under 30% among patients in the treatment groups.

The studies from Turkey reported that long-term smoking cessation rates were 30.9 to 55.2% for bupropion, 6.7 to 21% for NRT and 50 to 55% for varenicline. Success rates reported for all groups ranged from 21.6 to 43.7%. Ten percent of patients resumed smoking after finishing their therapy(14-18). All pharmacological therapies seem successfull in the short-term, but their long-term effects are unclear. A long-term maintenance therapy may be considered for continous abstinence. In a double blind randomized controlled trial, Tonstad et al. (19) showed that longer duration of therapy with varenicline was associated with higher rates of quitting. They compared the effectiveness of a 24-week varenicline treatment versus a 12-week treatment, and found significantly higher quitting rates with the 24-week treatment. However, quitting rates of both treatment groups and placebo group were higher than those reported in the literature (continuous abstinence rates for 12-week varenicline treatment, 24-week varenicline treatment and placebo were 70.5%, 49 and 36.9%, respectively).

The mean FTNA scores and exhaled CO levels were significantly higher in non-quitters than quitters. But interestingly, one of the parameters used in FTNA, daily cigarette consumption, was not statistically significant different among the groups. This may indicate that nicotine addiction may not only be associated with the number of cigarettes smoked.The other paramaters used in FTNA such as the time of the first cigarette smoked after wake up, or having difficulty to refrain from smoking in places where it is forbidden, may be more important to predict addiction. Mc Ewen et al. found that more dependent smokers, as measured by the FTNA, were less likely to be abstinent(10). On the other hand, Raherison et al. (20) reported that the number of cigarettes smoked and FTNA results were not different between the groups. Similarly, Robles et al. (7) reported that in black patients who did not completely abstain, the mean number of cigarettes smoked was not significantly different between the groups.

We did not find any significant difference between the groups in terms of mean age, gender, marital status, education levels and professions.So, smoking is a condition that affects people ofany ages, gender and social status.

In the present study, mean duration of therapy was short in all groups. This could be due to side effects or high cost of drugs. Also patients generally tend to discontinue medication after they quitted smoking. A recent study from China showed that 84% of participants used NRT for less than 4 weeks, and 44% used it for less than 7 days (21). The same problem might have occurred in our study population, with an impact on the success rates.

Our study had some limitations: firstly, it was a retrospective study. If it was a prospective study, abstinence rates would have been higher. But Jorenby et al. (13) concluded that randomized controlled trials in general involve highly selected patients who may not be representative of patients in actual practice. Similarly, Aubin et al. (22) pointed out that smoking cessation medications have no useful applications in "real-world" settings. Thus, our study may havea significance in showing real-world results. Secondly, smoking status and drug use were assessed based on self-reporting. Exhaled CO levels or plasma cotinine levels were not determined. However, Raherison et al. (20) reported that self reported abstinence rates were correlated with biochemical assessment of exhaled CO or plasma cotinine levels. Another limitation was that the number of patients was not equal among the groups (n:360 for NRT, n:105 for varenicline and n:264 for bupropion), which may have resulted in higher rates in the varenicline group. We could not reach all patients at the end of one-year follow-up period. If we were able reach all patientsat 12 months, success rates might have been lower. However regardless of these limitations, long term abstinence rate for all groups was 26.7%, and it was consistent with the literature findings.

Smoking is an important public health problem in both our country and worldwide. Smoking should be regarded as a chronic disease, and patients should be monitorized closely after quitting smoking. Most of the studies showed that all of the pharmacological therapies are more successful than placebo. Short-term success rate of varenicline seems superior to other pharmacotherapies, but the long-term effects are similar. Thus, patients who present for smoking cessation should be assessed for pharmaco-

logical therapies,if not contraindicated, to improve the success rate.We need to develop new strategies to keep patients' motivation at high levels for long-term abstinence, and maintenance therapy may be considered in order to achieve continued abstinence.

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