A randomized trial of smoking cessation

Medication versus motivation

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ABSTRACT

Objective: A prospective randomized study was undertaken to assess the effectiveness and side effect profiles of nicotine patch and bupropion therapies for smoking cessation.

Methods: Three hundred and fifty patients were referred to our smoking cessation program in the Department of Pulmonary Diseases, Gaziantep University between September 2002 and July 2003. Of these, only 131patients fulfilled the trial criteria. We randomized the patients into nicotine patch (n=50), bupropion (n=50) and control groups (n=31). Cases were followed up for 24 weeks. Questionnaires including the Fagerstrom test for nicotine dependence and Beck Depression Inventory were carried out at initial evaluation. Declaration of quitting and exhaled carbon monoxide level less than 10 ppm was accepted as success criteria.

Results: Success rates were 26% for nicotine patch group, 26% for bupropion and 16% for control group at the end of the 24th week (p=0.56). Beck depression inventory scores did not differ significantly between the groups, however none of the cases with scores greater than 13 succeeded regardless of the group. Mean body weight at baseline and change at 6 months did not differ significantly between the groups. Sleep disturbance was significantly more common in nicotine patch and bupropion groups than the control group (p=0.008).

Conclusion: The present study reinforces the role of medical doctors and importance of close follow up in smoking cessation, and directed counseling is quite as effective as pharmacologic therapy and is the sole approach without any adverse effects.

Saudi Med J 2007; Vol. 28 (6): 922-926

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Received 14th October 2006. Accepted 11th February 2007.

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Treatment of smoking habit can prevent many chronic diseases and complications. Smoking can cause approximately 40% of all deaths from cancer and 21% of deaths from cardiovascular disease.[1] The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association classifies tobacco dependence as an addiction. In such a dependency, the drug is needed to maintain an optimal state of well-being. Nicotine, the habituating constituent of tobacco, meets the criteria for addiction because a typical withdrawal syndrome occurs after smoking cessation. The most common smoking cessation methods are self quitting, group therapy, nicotine replacement therapy and bupropion treatment. We aimed to compare effectiveness and side effect profiles of nicotine patches and bupropion in patients who referred to our smoking cessation program in the Department of Pulmonary Diseases, Gaziantep University.

Methods. One hundred thirty-one patients were randomly selected from 350 patients who referred to our smoking cessation program between September 2002 and July 2003 and met the inclusion criteria. One hundred and thirty-one patients gave written informed consent. Members were randomly allocated to nicotine patch, bupropion and control groups. Cases aged 18 to 75 with a smoking history of at least 10 cigarettes for 1 year who were willing to quit smoking were recruited to the study. Current history of depression, pregnancy and lactation, symptomatic cardiac disease, regular psychotropic drug use, alcohol or drug abuse, chronic dermatological ailment for nicotine

patch group, history of head trauma or convulsion for bupropion group were not included in the study. Nicotine transdermal patches were applied daily 21 mg for the first 2 weeks (Nicotinell TTS®, 30 cm^2 Novartis, Istanbul), followed by 14 mg daily for 2 weeks (Nicotinell TTS®, 20 cm^2), and finally 7 mg daily for the next 2 weeks (Nicotinell TTS®, 10 cm^2). Bupropion sustained release tablets (Zyban® GSK, Istanbul) were prescribed as 150 mg for the first 3 days followed by 150 mg bid for 6 weeks. The control group (n=31) was advised to stop smoking and harmful effects of smoking and benefits of quitting were stressed. An information booklet about effects of tobacco smoke was provided for each case. Patients were advised to apply patches to the upper portion of the body, preferably on their shoulder or arms, switching after 24 hours and not to apply on the same site. Cigarette smoking during the first week was permitted for bupropion group and a quit day was set together. Questionnaires including the Fagerstrom test for nicotine dependence (FTND) and Beck Depression Inventory (BDI) were carried out at initial evaluation.[2,3] Cut-off scores for BDI-II are 0-13 minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression.[2] Physical exam, exhaled CO levels (Smokerlyzer, Bedfondt, UK), lung function measurements (System 2400, Sensormedics, USA), drug reactions and abstinence symptoms and weight gain were recorded at follow-up visits at 2, 4, 6, 8, 12, 24 weeks. Declaration of quitting and CO levels less than 10 ppm was accepted as success criteria. Smoking at least one cigarette per day was regarded as failure.

Data was recorded to SPSS 9 statistical software (Statistical Package for Social Science). Comparisons between groups were achieved by one way ANOVA test. P<0.05 accepted as significant.

Results. Physical exam, exhaled carbon monoxide (CO) levels, spirometric variables were similar between the groups (p<0.05) (**Table 1**). In 131 subjects, 106 were male. Mean age was 36.3 ± 12 for nicotine patch, 36.0 ± 10 for bupropion and 36.0 ± 10 for control groups (p>0.05). Abstinence rates at 2, 4, 8, 12 and 24 weeks were 50%, 36%, 28%, 26%, 26% respectively for nicotine patch group while bupropion group achieved 58%, 46%, 38%, 34%, 26% success rates. These rates were determined as 41.9%, 22.5%, 16.1%, 16.1% for the control group. The rates of abstinence at any time period did not reach statistically significant difference between the 3 groups (p=0.56). Mean age at onset of smoking was 19.0±5.4. There was no difference between onset of smoking age and success rates between groups (p=0.17). Twenty-five of 106 (23.5%) males and 6 of 25 (24%) females were successful at the 24th week. No statistically significant difference was found with regard to gender (p>0.05). Compliance with nicotine patch therapy in the first week was 100% while rates decreased to 82% in the second week, 56% in the fourth and 22% in the sixth week. Compliance with bupropion treatment was 100%, 90%, 50% and 40% respectively. The difference between groups were not statistically significant (p>0.05). Four patients discontinued bupropion treatment because of oral aphthae (n=1), hallucination (n=1) and sexual dysfunction (n=2), whereas one patient discontinued nicotine patch therapy due to oral aphthae formation. The BDI is used mostly to monitor change in the severity of depressive symptoms over time in individuals receiving treatment for depression or taking part in research studies of depression. Beck Depression Inventory score was 7.0±6.8 for nicotine patch group, 6.6 ± 5.7 for bupropion group and 8.2 ± 6.2 for control group (p>0.05). Quitting rates were significantly higher for those with BDI score ≤13 irrespective of the

Table 1 - Characteristics of the groups.

Characteristics	Nicotine patch (n=50)	Bupropion (n=50)	Control group (n=31)	*P* value
Age (year)	36.3 ±12.7	36.0 ±10.5	36.0±10.6	0.9
Male (%)	80	88	70	0.6
Female (%)	20	12	30	0.7
Age at onset of smoking	17.6±5.5	20.1±5.5	18.8±4.6	0.13
Basal CO (ppm)	19	22	17	0.1
Basal weight (kg)	70	75	72	0.09
Basal FEV_1 (L)	3.5	3.2	3.4	0.21
Basal PEF (L/min)	7.4	7.3	6.7	0.37
BDI score	7	6.6	8.2	0.53
FTND score	4.5	4.8	3.9	0.29

BDI - Beck Depression Inventory, FTND - Fagerstrom Test for Nicotine Dependence,
FEV1 - forced expiratory volume in first second, PEF - Peak forced expiratory flow.

Table 2 - Abstinence symptoms by group.

Abstinence symptoms	Nicotine patch n (%)	Bupropion n (%)	Control n (%)	*P* value
Anxiety	9 (18)	8 (16)	3 (9.6)	0.75
Restlessness	13 (26)	8 (16)	6 (19.2)	0.10
Irritability	12 (24)	13 (26)	3 (9,6)	0.21
Sleep disturbance	19 (38)	18 (36)	3 (9.6)	0.008
Headache	21 (42)	16 (32)	9 (29)	0.73
Concentration deficit	20 (40)	16 (32)	12 (38.7)	0.39
Increased appetite	24 (48)	16 (32)	8 (25.8)	0.06
Depression	17 (34)	13 (26)	12 (38.7)	0.29
Desire to smoke	44 (88)	43 (86)	27 (87)	0.42

Table 3 - Adverse effects of nicotine patch therapy.

Adverse effects	n	(%)
Headache	10	(20)
Nervousness	10	(20)
Insomnia	9	(18)
Dry mouth	7	(14)
Urticaria	5	(10)
Dizziness	4	(8)
Nausea	2	(4)
Tremor-palpitation	2	(4)
Chest pain	2	(4)
Gastric symptoms	1	(2)

Table 4 - Adverse effects of bupropion therapy.

Adverse effects	n	(%)
Dry mouth	23	(46)
Headache	22	(44)
Insomnia	20	(40)
Agitation	17	(34)
Confusion	15	(30)
Urticaria	8	(16)
Postural hypotension	8	(16)
Abdominal discomfort	7	(14)
Nausea	6	(12)
Depression	6	(12)
Anxiety	6	(12)
Decreased appetite	6	(12)
Chest pain	3	(6)
Tachycardia	3	(6)

treatment arm. There were 111 cases with BDI score less than 14 among whom 31 were successful at the end of 24 weeks whereas none of the cases with BDI score >13 (n=20) was successful . Quit rates did not differ significantly with respect to FTND scores (p>0.05). The mean increase in weight was 2.3±1.5 kg in nicotine patch group, 0.9±3.0 kg for bupropion group and 2.5±2.2 kg for control group (p=0.24). We reported abstinence symptoms similarly by the groups (**Table 2**). Sleep disturbance was more common in the treatment groups compared to control group (p=0.008). The most common side effects for nicotine patch group were headache (20%), and nervousness (20%) (**Table 3**); whereas dry mouth (46%) was the most common side effect reported by the bupropion group (**Table 4**).

Discussion. In this controlled randomized study, we found abstinence rates at 24th week as 26% for nicotine patch group, 26% for bupropion group and 16% for control group. Quitting rates were detected 8.4-40% with just doctors' advice in many studies.[4-7] This success emphasizes us the importance of health care worker's role in smoking cessation. Every doctor has to give advice to every patient who refers to any hospital. Daughton et al found quitting rates as 39% for nicotine patch group, 13.5% for placebo group after 4 weeks therapy at 24th weeks.[8] A study involving 935 patients, nicotine patches were applied to subjects during 6 weeks and quit rate was 61% for active treatment group whereas it was 27% for placebo group.[9] A meta-analysis summarizing the randomized controlled trials for the effectiveness of bupropion therapy found 21-35% quit rates for treatment and 10-19% for placebo groups.[10] Jorenby et al[11] reported quit rates as 21.3% for nicotine patch, 34.8% for bupropion and 38.8% for the combined therapy group with bupropion and nicotine patch after 24 weeks of treatment.[11] In an

observational prospective study in general practice one year abstinence rate was 22% among 227 motivated people.[12] We did not observe significant difference between the success rates of study groups. This could be attributed to low compliance with therapy. Compliance rates with high quit rates reported in the literature reach 90% at 6 weeks,[9] while compliance rates to nicotine patch and bupropion therapies were 84% and 90% for second week, whereas 22% and 20% for the 6th week, respectively in our study. Jorenby et al have called study subjects for 8 times during the study period in order to maintain high motivation.[11] We called the participants 3 times during 24 weeks. We believe that if subjects were contacted more often the success rates could have been higher. Can et al[13] had observed that the majority of the participants were reluctant to apply nicotine patches and most of them were noncompliant to the prescribed therapy after the first week. Some of the subjects in our study would not use the study medications because of insufficient economic resources. This high level of noncompliance rates, because of restricted supplies, may have greatly influence the success rates. Quit rates among the compliant subjects for nicotine patch and control group were 36% and 22.5% at the end of fourth week, 28% and 22.5% at the end of 8th week, respectively. There was a positive correlation between compliance to therapy and success rates. When the economic burden induced by the diseases related to tobacco addiction is taken into account then the coverage of treatment strategies by social policies is entirely justified. Studies have demonstrated that quit rates doubled when lung function tests and CO test were performed. Uzaslan et al reported one year abstinence rates as 40% with motivational support and frequent follow up visits.[14] We also performed lung function tests and CO test for each visit. We suggest that these factors may have influenced the high success rate observed in the control group relative to the treatment groups. Abstinence symptoms between 3 groups were desire to smoke, depression, increased appetite, concentration deficit, headache, sleep disturbance, anxiety, restlessness, irritability. Sleep disturbance was more common in nicotine patch (38%) and bupropion groups (40%) compared to control group (9.6%). Similarly, sleep disturbance has been reported 30-45% as a consequence of bupropion treatment 300 mg/day.[15] We consider that sleep disturbance is a treatment related side effect because the control group suffered significantly less. Compatible with the literature we observed nervousness in nicotine patch group, dry mouth in bupropion group, headache and insomnia in both groups as the most common treatment related adverse effects. In nicotine patch group oral aphthae (n=1) and in bupropion group oral aphthae (n=1), hallucination (n=1), sexual dysfunction (n=2) led to the discontinuation of therapy. There are several reports concerning effects of bupropion therapy on sexual function. Masand et al evaluated thirty-nine patients who had received Serotonin Selective Reuptake Inhibitor (SSRI) therapy for at least 6 weeks evaluated for sexual dysfunction. There was no difference between adjunctive low-dose sustained-release bupropion and placebo for the treatment of SSRI-induced sexual dysfunction.[16] A fixed dose of 150 mg/day of bupropion SR was taken in the morning does not appear to be effective in the treatment of SSRI-induced sexual dysfunction.[17] However, in another report bupropion was used as an antidote for SSRI-induced sexual dysfunction and the drug successfully reversed a variety of sexual dysfunctions caused by SSRIs in 31 (66%) of 47 patients.[18] Clayton et al[19] have also found that bupropion SR seemed to be an effective antidote to SSRI-induced sexual dysfunction. Although we could not explain the mechanism of sexual dysfunction in our cases, this can be attributed to bupropion. There are several contradicting reports favoring either sex in nicotine patch treatment.[20-25] We did not find any difference between smoking cessation rates with respect to gender. High scores of BDI have been related to higher relapse rates in several reports.[26,27] Jorenby et al reported BDI scores as 3.9 for nicotine patch, 4.4 for bupropion, 3.5 for combined therapy and 4 for placebo group,[11] whereas we observed BDI scores for nicotine patch (7%), bupropion (6.6%) and control group (8.2%), which in turn may have influenced the success rates. High BDI scores predicted worse outcome in our study. We emphasize that cases except minimal depression are prone to failure and we suggest that determination of high BDI scores in the initial interview necessitates combination therapy and frequent follow-up. We observed that the mean change in weight was less in the bupropion group (0.9 ± 3.0 kg) compared to nicotine patch (2.3 ± 1.5 kg) and control group (2.7 ± 2.2 kg) at the end of 24th week, but the difference did not reach statistical significance. There are several studies reporting that weight gain is less with bupropion.[28] It is obvious that medications and also methods that can prevent weight gain will influence treatment options and patient compliance. The limitation of our study is low compliance in treatment groups. This limitation reminds us of economic problems that have to be overcome and smoking cessation modalities should be covered by health insurance agencies or compensated by government.

In conclusion, the results of this study emphasizes that motivation with doctors' advice and regular follow up visits are effective as medications, and BDI as a good prognostic predictor of outcome. Nicotine addiction is difficult to treat despite intensive programs; therefore, preventive interventions are essential.

References

1. Rakel RE, Blum A. Nicotine Addiction. In: Rakel RE, editor. Rakel Textbook of Family Practice. 6th ed. USA: W. B. Saunders Company; 2002. p. 1523.
2. Beck AT, Steer RA. Internal consistencies of the original and the revised Beck Depression Inventory. ***J Clin Psychol*** 1984; 40: 1365-1367.
3. Hisli N. Beck Depresyon Envanterinin gecerligi üzerine bir çalısma. ***Psikoloji Dergisi*** 1988; 22: 118-126.
4. Fiore M, Jorenby D, Baker T, Kenford S. Tobacco dependence and the nicotine patch. ***JAMA*** 1992; 268: 2687-2694.
5. Kottke TE, Battisska RN, Difriese GH, Brekke ML. Attributes of successful smoking cessation intervention in medical practice: a meta analysis of 39 controlled trials. ***JAMA*** 1988; 259: 2882-2289.
6. Cummings SR, Coates TJ, Richard RJ, Hansen B, Zahnd EG, Vandermartin R. Training physicians in counseling about smoking cessation's randomized trial of the 'quit for life' program. ***Ann Intern Med*** 1989; 110: 640-647.
7. Strecher VJ, O'Malley MS, Villagra VG, Campbell EE, Gonzalez JJ, Irons TG et al. Can residents be trained to counsel patients about quitting smoking? Results from a randomized trial. ***J Gen Intern Med*** 1991; 6: 9-17.
8. Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN et al. Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy: a randomized, placebo controlled, double blind study. ***Arch Intern Med*** 1991; 151: 749-752.
9. Transdermal nicotine for smoking cessation. Six-month results from two multicenter controlled clinical trials. Transdermal Nicotine Study Group. ***JAMA*** 1991; 266: 3133-3138.
10. Hays JT, Ebbert OJ. Bupropion sustained release for treatment of tobacco dependence. ***Mayo Clin Proc*** 2003; 78: 1020-1024.
11. Jorenby D, Leischow S, Nides M, Rennard SI, Johnston JA, Hughes AR et al. A controlled trial of sustained-release bupropion a nicotine patch or both for smoking cessation. ***N Engl J Med*** 1999; 340: 685-691.
12. Wilkes S, Evans A, Henderson M, Gibson J. Pragmatic, observational study of bupropion treatment for smoking cessation in general practice. ***Postgrad Med J Nov*** 2005; 81: 719-722.
13. Çan G, Öztuna F, Özlü T. Karadeniz Teknik Üniversitesi Tıp Fakültesi Sigara Bırakma polikliniği sonuçlarının degerlendirilmesi. ***Tuberk Toraks*** 2004; 52: 69-74.
14. Uzaslan E, Özyardımcı N, Karaya M. The physician's intervention in smoking cessation: results of the five years of smoking cessation clinic. ***Ann Med Scien*** 2000; 9: 63-69.
15. Johnston JA, Fiedler-Kelly J, Glover ED, Sachs DP, Grasela TH, DeVeaugh-Geiss J. Relationship between drug exposure and the efficacy and safety of bupropion sustained release for smoking cessation. ***Nicotine Tob Res*** 2001;3 :131-140.
16. Masand PS, Ashton AK, Gupta S, Frank B. Sustained release bupropion for selective serotonin reuptake inhibitor induced sexual dysfunctional randomized, double placebo-controlled, parallel-group study. ***Am J Psychiatry*** 2001; 158: 805-807.
17. De Battista C, Solvason B, Poirier J, Kendrick E, Loraas E. A placebo-controlled, randomized, double-blind study of adjunctive bupropion sustained release in the treatment of SSRI-induced sexual dysfunction. ***J Clin Psychiatry*** 2005; 66: 844-848.
18. Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction. ***J Clin Psychiatry*** 1998; 59: 112-115.
19. Clayton AH, Warnock JK, Kornstein SG, Pinkerton R, Sheldon-Keller A, McGarvey EL. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. ***J Clin Psychiatry*** 2004; 65: 62-67.
20. Bjornson W, Rand C, Connett JE, Lindgren P, Nides M, Pope F, et al. Gender differences in smoking cessation after 3 years in the Lung Health Study. ***Am J Public Health*** 1995; 85: 223-230.
21. Swon GE, Jack LM, Ward MM. Subgroups of smokers with different success rates after use of transdermal nicotine. ***Addiction*** 1997; 92: 207-217.
22. Perkins KA. Nicotine discrimination in men and women. ***J Pharmacol Biochem Behav*** 1999; 64: 295-299.
23. Sachs DP, Sawe U, Leischow SJ. Effectiveness of a 16 hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. ***Arch Intern Med*** 1993; 153: 1881-1890.
24. Fortmann SP, Killen JD. Nicotine gum and self help behavioral treatment relapse prevention: results from a trial using population based recruitment. ***J Consult Clin Psychol*** 1995; 63: 460-468.
25. Demir T, Tutluoglu B, Koç N, Bilgin L. Sigara bırakma poliklinigimizin bir yıllık izlem sonuçları. ***Tuberk Toraks*** 2004; 52: 63-68.
26. Shiffman S, Johnston JA, Khayrallah M, Elash CA, Gwaltney CJ, Paty JA. The effect of bupropion on nicotine craving and withdrawal. ***Psycopharmacologia*** 2000; 148: 33-40.
27. Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC et al. A comparison of sustained release bupropion and placebo. ***N Engl J Med*** 1997; 337: 1195-1202.
28. Perkins KA, Marcus MD, Levine MD, D'Amico D, Miller A, Broge M et al. Cognitive behavioral therapy to reduce weight concerns improves smoking cessation outcome in weight-concerned women. ***J Consult Clin Psychol*** 2001; 69: 604-613.