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Original Article

Efficacy of Pharmacotherapy versus Combined Therapy in Tobacco Cessation: A Prospective Comparative Study

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Abstract

Background: *In view of skyrocketing number of cases leading to increased prevalence of tobacco use, especially in developing countries the interventions for smoking cessation have become an urgent need of the hour. The aim of the present study is, therefore, to know the effect of pharmacotherapy alone and pharmacotherapy with psychotherapy on tobacco cessation.*

Methods: *It is a prospective cohort study conducted in 75 subjects (Pharmacotherapy alone group, n= 38; pharmacotherapy with psychotherapy group n= 37). Subjects were randomly allocated into two groups. Medication was given to all the subjects with bupropion (300 mg) based on the severity of tobacco addiction while psychotherapies were individually tailored and delivered only in one group.*

Results: *Tobacco abstinence rates in both the groups differ markedly. The mean age of patients in the pharmacotherapy alone group and the combined group was 31.59±13.75 and 34.14±11.71 years, respectively. The mean age of starting tobacco use was 22.41±8.34 and 22.71±8.21 years in the pharmacotherapy alone group and the combined group, respectively. Overall, 22.7% (n=17) of the subjects were smoker while majority of them belonged to smokeless group (77.3%, n=58). The overall rates of continuous abstinence at 6, 8 and 12 weeks were 26.3%, 28.9% and 28.9% respectively in pharmacotherapy group, while in combined therapy group it was 47.3, 54.1, and 54.1 respectively. In Smokeless group it was 28.1% at week 6, 8 and 12 in pharmacotherapy group and 50%, 53.8% and 53.8% respectively in combined therapy group while in smokers abstinence rate at 6, 8 and 12 weeks was 16.7%, 33.3% and 33.3% respectively in pharmacotherapy group and 45.5%, 54.5% and 54.5% in combined therapy group ($p<0.05$).*

Conclusions: *Combined therapy was found to be significantly more effective than pharmacotherapy alone in both smoker as well as smokeless tobacco user group.*

Key words: *Tobacco cessation, Bupropion, Combined therapy.*

Introduction

Tobacco is a well known hazardous substance with increased prevalence of its use in different forms. So interventions for tobacco cessation became an urgent need because of its increased prevalence, especially in developing countries. Until the 1940s, tobacco was considered harmless, but subsequently, laboratory and clinical research studies have confirmed that tobacco is a hazard to health. On an average, smoke from a cigarette

contains around 4000 chemicals; some of which are highly toxic and about 40 of them can cause cancer. The World Health Organization (WHO) estimates that around 1.1 billion people worldwide use tobacco, constituting one-third of the entire population aged 15 years and above. Globally, 47% of men and 12% of women smoke.[1] By the year 2020, tobacco will become the single leading cause of death, causing one out of every eight deaths.[2] Worldwide, tobacco use causes nearly 6 million deaths per year, and current trends show that tobacco use will cause more than 8 million deaths annually by 2030.[2] According to a report from the Indian Council of Medical Research (ICMR), there are 184 million tobacco users in India, which include 40 million cigarette smokers, 80 million *bidi* smokers and 60 million using chewable forms of tobacco.

In India, tobacco use among the male and female population has been estimated to be around 23.2% and 4% in urban, and 33.6% and 8.8% in rural areas, respectively.[5] The mortality burden of tobacco-related deaths have been estimated at 800,000 deaths annually.[5] In developing countries such as India, where awareness levels are low, the first step towards a tobacco-free society includes anti-tobacco education and medical help for those willing to quit.[5] In the past few years, there has been an increase in tobacco research and several new therapeutic modalities have been developed. Tobacco cessation therapies that have proven effective range from simple counseling to intensive interventions using medications, either nicotine replacement therapy (NRT) or bupropion, in combination with cognitive-behavioural therapy.[6-10] Among these therapies, bupropion is the only antidepressant drug approved by the United States Food and Drug Administration (USFDA) for the treatment of tobacco addiction. In the United States, bupropion, which has potential side effects in patients predisposed to seizures, has been widely used.[11, 12] Other FDA approved drugs are Varenicline and NRT formulations.

A number of studies have compared the medication therapy with placebo. However, there are only a few studies that had compared therapy involving pharmacotherapy alone with pharmacotherapy with psychotherapy (combined therapy). In the present study, pharmacotherapy alone was compared with combined therapy.

Material and Methods

Screening and Subjects

Patients were recruited from out patients department of University hospital (Sir Sunderlal Hospital) of Banaras Hindu University (BHU), Varanasi, India between January 2012 to July 2013. A total of 243 subjects who attended the OPD for tobacco cessation were assessed for eligibility criteria. Of this, 95 did not give written informed consent, 46 did not meet inclusion criteria (27 were excluded because of age <18 years, 8 were having past history of head injury, 6 had history of seizure disorder and 5 had history of cardiovascular disease). 27 subjects expressed inability to follow up due to far away distance.

75 cases that fulfilled the selection criteria were recruited for the present study and were followed up prospectively for 12 weeks. Subjects were eligible for inclusion in the study if they: were 18-65 years of age , used ST daily for at least one year, scored 4 or more points in Fagerstrom tolerance questionnaire, were in good general health, willing to complete all study procedures, willing to quit smoking and ST, and signed the informed consent. Subjects were excluded if they: have any predisposition to seizure disorder, history of head injury resulting in loss of consciousness for more than 1 hour, history of stroke or transient ischemic attack, being in poor general health, had a contraindication to the use of bupropion. The baseline assessment of the subjects included the following parameters: age, sex, religion, marital status, occupation, smokeless tobacco use, age at which smoking started, number of cigarettes/*bidis* smoked per day, level of nicotine dependence (through the Fagerstrom test), use of other potentially-addictive substances

(especially alcohol), previous attempts to quit tobacco use, physical health problems, family history of tobacco use, presence of concomitant diseases, reasons for starting tobacco use. The level of nicotine dependence was considered low for individuals with scores 0-4, average with scores 5-7, and high with scores above 7 in Fagerstrom test.[13,14] After baseline assessment subjects were randomly allocated into either group.

Treatment Period

Target quit date was preferentially two week after the start of Bupropion treatment. Patients were assessed at 2,4,6,8 and 12 weeks for the level of dependence. Combined therapy group was assessed at 2, 4, 6, 8 and 12 week and given a brief (≈ 45 minutes) individualpsychotherapy session for tobacco cessation. Specialist's advice was based on the National Cancer Institute's '5A', *i.e.*, Ask, Advice, Assess, Assist, Arrange.[15] Psychotherapy sessions focused on motivation, social support, problem solving, skills training and identification of tobacco use triggers and analysis of coping patterns.

Follow-up Period

A total of 5 follow-up visits were made by each subject. Follow-up assessment was done at 2,4,6,8 and 12 weeks, while baseline assessment was at 0 week. A brief face-to-face anti-tobacco advice was given at each visit. Follow-up assessment was made by self-reporting of abstinence at each visit. Withdrawal symptoms, such as craving, irritability, anxiety, depressed mood, difficulty in concentrating, restlessness, increased appetite, anger and difficulty in sleeping were recorded. The continuous abstinence and reduction in the number of cigarette/*bidi* smoked were assessed. The subjects were considered to be continuously abstinent if they had not smoked after the quit day. A subject was considered 'lost to follow up' when there was no follow up after the initial visit.

Statistical Analysis

For maintaining database, statistical analysis and data handling, SPSS software system was used. The results are presented in percentages and means with standard deviation (SD). Data analysis strategy consisted of two phases. First, baseline variable in the two groups was compared using the student's 't' and Chi-square tests to analyze continuous and categorical variables, respectively. Secondly, continuous abstinence rate was compared between the two groups. In this case, the dependent variable was continuous abstinence rate at week 12 and the independent variables were the baseline characteristics. A p value of less than 0.05 was considered significant.

Results

Out of 75 subjects assessed, only 70 completed the 12 weeks follow up and 5 drop outs. The overall, age range of the study sample was 18-65 years with mean age 33.56 ± 13.88 years. The mean age of patients in the pharmacotherapy alone group and the combined group was 31.59±13.75 and 34.14±11.71 years, respectively. Of the 75 patients, there were one female who belonged to the pharmacotherapy alone group and two belonged to combined therapy group. The mean age of starting tobacco use was 22.41±8.34 and 22.71±8.21 years in the pharmacotherapy alone group and the combined group, respectively. Overall, 22.7% (n=17) of the subjects were smoker while majority of them belonged to smokeless group (77.3%, n=58). The overall rates of continuous abstinence at 6, 8 and 12 weeks were 26.3%, 28.9% and 28.9% respectively in pharmacotherapy group, while in combined therapy group it was 47.3, 54.1, and 54.1 respectively. In Smokeless group it was 28.1% at week 6, 8 and 12 in pharmacotherapy group and 50%, 53.8% and 53.8% respectively in combined therapy group while in smokers abstinence rate at 6, 8 and 12 week was 16.7%, 33.3% and 33.3% respectively in pharmacotherapy group and 45.5%, 54.5% and 54.5% in combined therapy group.

Table: 1 Socio-demographic characteristics of the study sample

Socio-demographic characteristics	Number (N=75)%	Pharmacotherapy group (N=38)%	Combined therapy group (N=37)%
	Age		
≤ 40 *years*	58 (77.3)	26 (34.67)	32 (42.67)
> 40 *years*	17 (22.7)	12 (16)	5 (6.67)
	Sex		
Male	72 (96)	37 (49.33)	35 (46.67)
Female	3 (4)	1 (1.33)	2 (2.67)
	Marital status		
Married	46 (61.3)	15 (20)	14 (18.67)
Unmarried	29 (38.7)	23 (30.67)	23 (30.67)
	Residence		
Urban	23 (30.7)	12 (16)	11 (14.67)
Semi-urban	17 (22.7)	8 (10.67)	9 (12)
Rural	35 (46.7)	18 (24)	17 (22.67)
	Religion		
Hindu	71 (94.7)	34 (45.33)	37 (49.33)
Muslim	4 (5.3)	4 (5.33)	0
	Occupation		
Govt. job	12 (16)	9 (12)	3 (4)
Semiskilled	20 (26.7)	10 (13.33)	10 (13.33)
Student	18 (24)	6 (8)	12 (16)
Unskilled/agriculture	15 (20)	7 (9.33)	8 (10.67)
Unemployed	10 (13.3)	6 (8)	4 (5.33)
	Education*		
Illiterate	7 (9.3)	3 (4)	4 (5.33)
Primary	4 (5.3)	2 (2.67)	2 (2.67)
Middle	8 (10.7)	4 (5.33)	4 (5.33)
High school	11 (14.7)	6 (8)	5 (6.67)
Intermediate	12 (16)	7 (9.33)	5 (6.67)
Graduate	22 (29.3)	10 (13.33)	12 (16)
Postgraduate	11 (14.7)	6 (8)	5 (6.67)
	SES**		
Upper	2 (2.7)	1 (1.33)	1 (1.33)
Upper-middle	13 (17.3)	7 (9.33)	6 (8)
Lower-middle	32 (42.7)	17 (22.67)	15 (20)
Upper-lower	14 (18.7)	6 (8)	8 (10.67)
Lower	14 (18.7)	7 (9.33)	7 (9.33)
	Family Type		
Nuclear	38 (50.7)	18 (24)	20 (26.67)
Joint	37 (49.3)	20 (26.67)	17 (22.67)
Total	**75 (100)**	**38 (50.67)**	**37 (49.33)**

Table: 2 Clinical characteristics of the study samples

Characteristics	Total sample (N=75)	Smokers (Mean±SD)	Smokeless (Mean±SD)
Mean age of onset tobacco use	22.64±8.18 (10-47 years)	22.41±8.34 (10-42 years)	22.71±8.21 (10-47years)
Mean duration of intake of tobacco	10.87±7.74 (1-30 years)	9.06±8.56 (1 to 30 years)	11.40±7.48 (1-30 years)
Baseline mean Fagerstrom score		6.12±1.453 (Range 4-10)	6.28±1.412 (Range 4-9)
No. of quit attempt	1.85±2.97	2.00±2.37	1.81±3.15
No. of sessions	3.95±1.03	4.09±0.94	3.88±1.07
Precipitating factors for the intake of tobacco use	**N (%)**	**N (%)**	**N (%)**
No	1 (1.3)	0	1 (1.3)
Peer Pressure	51 (68)	9 (12)	42 (56)

Underlying stress	23 (30.7)	8 (10.7)	15 (20)
Total	**75 (100)**	**17 (22.7)**	**58 (77.3)**
Past psychiatric illness			
Nil	46 (61.3)	13 (76.5)	33 (56.9)
BPMD	11 (14.7)	1 (5.9)	10 (17.2)
Schizophrenia	9 (12)	1 (5.9)	8 (13.8)
Depression	5 (6.7)	1 (5.9)	4 (6.9)
Anxiety disorder	1 (1.3)	0	1 (1.7)
OCD	2 (2.7)	0	2 (3.4)
Substance dependence	1 (1.3)	1 (5.9)	0
Total	**75 (100)**	17 (100)	58 (100)
Type of tobacco used	**N (%)**		
Smoker	17 (22.7)		
Smokeless	58 (77.3)		
No. of quit attempt	**N (%)**	**Smokers**	**Smokeless**
Nil	46 (61.3)	8 (10.7)	38 (50.7)
1-2	7 (9.3)	4 (5.3)	3 (4)
3-4	7 (9.3)	1 (1.3)	6 (8)
5+	15 (20)	4 (5.3)	11 (14.7)
Total	**75 (100)**	**17 (22.7)**	**58 (77.3)**
Types of therapy	**N (%)**	**Smokers**	**Smokeless**
Pharmacotherapy	38 (50.7)	6 (8)	32 (42.7)
Combined therapy	37 (49.3)	11 (14.7)	26 (34.7)

P=0.036

Table: 3 Comparison of pharmacotherapy vs combined therapy among the smokers on the basis of FTND score (at each visit)

FTND score for smokers	**Pharmacotherapy group (Mean±SD);** n=6	**Combined therapy group (Mean±SD);** n=11	**p-value***
Baseline	7.33±1.366	6.45±1.036	0.152
Week 2	5.67±1.751	4.09±0.944	0.037
Week 4	4.50±1.378	2.64±1.629	0.037
Week 6	3.17±0.722	1.36±0.748	0.0002
Week 8	2.50±0.975	1.27±0.494	0.003
Week 12	2.33±0.862	1.09±0.578	0.002

*unpaired student's t test

Table: 4 Comparison of pharmacotherapy vs combined therapy among the smokeless tobacco user on the basis of FTND-ST score (at each visit)

FTND-ST score for smokeless	**Pharmacotherapy group;** n=32 **(Mean±SD)**	**Combined therapy group (Mean±SD);** n=26	**t-value**	**p-value***
Baseline	6.25±1.437	6.31±1.408	-0.153	0.879
Week 2	4.59±1.266	4.54±1.174	0.171	0.865
Week 4	4.03±1.513	3.38±1.602	1.577	0.121
Week 6	3.25±1.796	2.35±2.038	1.794	0.078
Week 8	2.81±1.655	1.85±1.870	2.087	0.041
Week 12	2.66±1.516	1.73±1.823	2.111	0.039

*unpaired student's t test

Discussion

Tobacco addiction is a chronic remitting and relapsing addictive disorder requiring specific treatment. It is widely prevalent, harmful and neglected condition. The present study is a modest attempt to compares the effectiveness of pharmacotherapy alone versus combined pharmacotherapy and behavioral therapy in smoking cessation and smokeless tobacco users, over a period of 12 weeks, in patients attending the Psychiatric Outpatient Department of Sir Sunderlal Hospital, Banaras Hindu University,

IMS, Varanasi , India. Overall this study reflected that after 12 weeks of treatment, combined treatment proved to be superior to pharmacotherapy alone.

Only 4% female tobacco users sought guidance for tobacco cessation despite a considerably higher percentage of female tobacco users in urban areas. This suggests that because of social stigma females are not coming for help. This problem needs to be addressed if they are to be benefited from tobacco cessation interventions.15

The average age of the subjects in our study was 33.56±12.15 (18-65 years) years and most of the tobacco users had no tobacco-related diseases suggesting that middle aged persons were most likely to seek help for smoking cessation. Most of the subjects were self-motivated to quit tobacco showing that these subjects had the will power to quit and they wanted to be helped at the clinic. These findings suggest that majority of the tobacco users belongs to younger age group. Characteristically this finding appears to comprise of youngest population as compared to other studies (Ahluwalia et al., 2002, Swan et al., 2003, Dale et al., 2007). The average age at which thesubjects began tobacco use was 22.41±8.34 (range 10-42 years) in smokers and 22.71±8.21 (range 10-47 years) in smokeless tobacco users.

Present study revealed that the mean age of onset of tobacco use among smokers was 22.41$\pm$*8.34* (range 10-42 years) and among smokeless tobacco users it was 22.71 $\pm$*8.21* (range 10-47 years). These findings were somewhat closer to what was reported by D'Souza et al., 2012 (smoker: 20.8$\pm$*8.5* and smokeless: 25.8$\pm$*11.3*).

Mean duration of tobacco intake in smokers was 9.06$\pm$*8.56* (range 1-30 years) and in smokeless tobacco users was 11.46±7.53 (Range is 1 to 30 years). In other studies mean duration of tobacco use was on higher side as reflected in the study by Dale et al. (2007) mean years of regular smokeless tobacco use was 18.7(±9.9) and by Swan et al.(2003) mean years of smoking was 25.9(±11.3) years. Mean duration of tobacco use was 23.0(±15.4), 14.6(±12.2) and 8.9(±12.4) years for beedi smokers, cigarette smokers and chewers, respectively.

In our study we have found that most of the subjects have started taking tobacco due to influence of peer group. We observed that 68% of subjects have started tobacco with effect of peer group and 30.7% have started because of some underlying stress like failure in examination, loss of job, unemployment and relationship problem. While other studies did not focus on the reason of start of tobacco (Ahluwalia et al., D'Souza et al., Hurt et al.).

In our study total no. of smoker were 22.7% (n=17) and smokeless tobacco users were 77.3% (n=58) while majority of the studies conducted earlier, had either smoker or smokeless tobacco users (Dale et al., Hurt et al. and Swan et al.). In another study by D'Souza et al. (2012) distribution by type of tobacco use was: Beedi only (22%), cigarettes only (49%), beedi and cigarettes (18%), chewing only (2%) and smoking and chewing (9%).

This study revealed that majority of the participants did not try to quit by their own which comprised 61.3% (n=46), in which smokers were 10.7% (n=8) and smokeless was 50.7% (n=38). Participants having 1-2 quit attempt in the past were 9.3% (n=7), 9.3% had 3-4 quit attempt and 20% (n=15) had more than 5 unsuccessful quit attempt. Dale et al. (2007) reported serious stop attempts in 79% subjects: 1-2 attempts (42%), 3-4 attempts (23%) and 5+ attempts (16%). Number of previous attempts to quit was 5.4 (±9.5) and 4.3 (±5.4) by Swan et al. (2003) and Hurt et al. (1997) respectively.

All tobacco users who had made a prior quit attempt (38.7%) presented on their own without any help from a physician or the use of any medication. This is very important, as a physician's advice encourages tobacco cessation. A meta-analysis done in 1988 by Kottke et al. showed an overall cessation rate of 8.4% at six months with brief (less than 15 minutes) physician's advise. Since then, there have been several large studies on physician's advise that

have shown quit rates of up to 10 percent, (Cummings et al. 1889, Strecher et al. 1991).

In the present study, the quit rate at six week and 12 week by pharmacotherapy were 26.3% and 28.9% respectively and by combined therapy quit rate was 47.3% and 54.1% respectively.

At week 2, the mean FTND score for smokers was 5.67 (±1.751) in pharmacotherapy group versus 4.09 (±0.944) in the combined therapy group, (P=0.037) and FTND-ST score for smokeless tobacco users was 4.59 (±1.266) in pharmacotherapy group versus 4.54 (±1.174) in the combined therapy group, (P=0.865, t=0.171), showed significant reduction in score.

At week 4, the mean FTND score for smokers was 4.50 (±1.378) in pharmacotherapy group versus 2.64 (±1.63) in the combined therapy group, (P=0.037) and FTND-ST score for smokeless tobacco users was 4.03 (±1.51) in pharmacotherapy group versus 3.38 (±1.60) in the combined therapy group, (P=0.121, t=1.577), reflected significant reduction in FTND score.

At week 6, the mean FTND score for smokers was 3.17 (±0.722) in pharmacotherapy group versus 1.36 (±0.748) in the combined therapy group, (P=0.0002) and FTND-ST score for smokeless tobacco users was 3.25 (±1.796) in pharmacotherapy group versus 2.35 (±2.038) in the combined therapy group, (P=0.078, t=1.794), at this time reduction in score was highly significant.

At week 8, the mean FTND score for smokers was 2.50 (±0.975) in pharmacotherapy group versus 1.27 (±0.499) in the combined therapy group, (P=0.003) and FTND-ST score for smokeless tobacco users was 2.81 (±1.655) in pharmacotherapy group versus 1.85 (±1.87) in the combined therapy group, (P=0.041, t=2.087).The cessation rate of smoking was 33.33% in pharmacotherapy group versus 54.54% in combined therapy group while cessation rate of smokeless tobacco use in pharmacotherapy group and combined group was 28.1% and 53.8% respectively.

At week 12, the mean FTND score for smokers was 2.33 (±0.862) in pharmacotherapy group versus 1.09 (±0.578) in the combined therapy group, (P=0.002) and FTND-ST score for smokeless tobacco users was 2.66 (±1.52) in pharmacotherapy group versus 1.73 (±1.823) in the combined therapy group, (P=0.039, t=2.11), showed significant reduction in score. The cessation rate for smokeless tobacco in combined group was nearly double that of pharmacotherapy group 53.85% and 28.12%, respectively and cessation rate in smokers were 33.33% in pharmacotherapy group alone and 54.54% in combined group.

In our study, the overall rates of continuous abstinence at 6, 8 and 12 weeks were 26.3%, 28.9% and 28.9% respectively in pharmacotherapy group, while in combined therapy group it was 48.6, 54.1, and 54.1, respectively. In Smokeless group it was 28.1% at week 6, 8 and 12 in pharmacotherapy group and 50%, 53.8% and 53.8% respectively in combined therapy group while in smokers abstinence rate at 6, 8 and 12 week was 16.7%, 33.3% and 33.3% respectively in pharmacotherapy group and 45.5%, 54.5% and 54.5% in combined therapy group. We found varied result in other studies like study by Tonstad et al. (2003) of 629 subjects, it has been found that the continuous abstinence rates from week 4 to 26 and 4 to 52 continued to be more than double for bupropion SR compared with placebo (27 vs 11%; 22 vs 9%). Another randomized, placebo-controlled trial of 509 smokers, Aubin et al. (2004) revealed that the continuous abstinence rates in bupropion group and placebo group were 41% and 21% for week 4 to 7, and 25% and 13% for weeks 4 to 26, respectively. Confirmed abstinence rates at the end of seven weeks of treatment were found to be 36% in the bupropion SR group and 19% in the placebo group, Ahluwalia et al. (2002). These finding clearly shows that continuous abstinent rate was consistently higher in the combined therapy group than the medication only group. This again robustly supports the supremacy of

combined therapy over pharmacotherapy alone in overall study sample (P=0.027), in smoker group (P=0.402) and in smokeless tobacco user group (P=0.046). This highlights the effectiveness of bupropion with behavior therapy for tobacco cessation in Indian subjects as well.

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