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Efficacy of Nicotine Patch in Combination with Trazodone in Smoking Cessation

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ABSTRACT

Background: Treatment for tobacco dependency involves a combination of behavioral therapy, antidepressants, and nicotine replacement therapy. This study was conducted in order to compare the outcome of smoking cessation by using each of the four forms of nicotine replacement therapy (NRT) among participants using Trazodone tablet 50 mg.

Materials and Methods: In this non-randomized quasi-experimental study the efficacy of four mentioned forms of nicotine replacement therapy (NRT) including patches, gums and microtabs and two forms of NRT together was evaluated. Smoking cessation while using Trazodone was also studied. All the smokers who referred to the smoking cessation clinic of Iranian National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Tehran, Iran from Oct. 2005 to Oct. 2007 entered the study. They attended 4 weekly sessions followed by 2 sessions in the next 12 months.

Results: A total of 286 subjects participated in this study. Trazodone was prescribed for them and 253 used at least one form of NRT. There were 181 (74.6%) males. The mean age was 42.43 ± 13.4 yrs.

Thirty three cases selected nicotine patches, 99(39.4%) used nicotine gums, 64(25%) chose microtabs and 57(23%) preferred using two types of NRT simultaneously. A total of 152 participants (60%) quit smoking at the fourth session. At the fourth session, it was proved that nicotine patches had the highest success rate and were most efficient for quitting smoking (94%). Also, after 6 and 12 months follow-up it was found that nicotine patches were most effective for abstinence.

Conclusion: Nicotine patches used in combination with Trazodone tablets could result in higher success rates for smoking cessation. (*Tanaffos*2010; 9(3): 50-57)

Key words: Cigarette, Cessation, Nicotine replacement therapy, Nicotine patch, Trazodone

INTRODUCTION

Tobacco use, particularly cigarette smoking, is now a global pandemic (1) and is becoming increasingly common in Asia while quitting remains

rare (2). Furthermore, the expected morbidity and mortality from smoking-attributable diseases will continue to rise for the next 30 years (1).

Some studies estimated that unless current trends changed, some 30-40% of the 2.3 billion children and teenagers in the world would become smokers in early adult life (3,4) among which about 250 million

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will be killed by smoking. It is worth mentioning that, in countries where smoking is long established, almost all smokers begin before the age of 18 (3,5).

There are some observable facts about smoking and risks of life hazards. People who smoke are twice as likely to lose teeth as people who do not smoke (6). On the other hand, previous smokers had quality of life scores in between never smokers and continuous smokers in head and neck cancer (7). If a person who smokes has a heart attack, his or her risk of sudden death is twice as great as the risk of a person who does not smoke (8,9). People, who quit smoking before the age of 50, reduce by half their risk of dying in the next 15 years compared with continuing smokers (10). Smoking cessation for 10 years leads to the reduction of the risk of lung cancer by 30% to 50%, less severe asthma attacks, fewer respiratory illnesses; such as colds, flu, and pneumonia, and gradually declines the risk for developing cancers of the voice box (larynx), mouth, throat, esophagus, intestines, bladder, kidney, and pancreas (11).

Many young smokers think they can quit easily, but find that they are already addicted and develop withdrawal symptoms when they stop smoking (3,12). Tobacco dependency remains the major preventable cause of early mortality and morbidity in the developed world (11). It is also a strong factor that may partly explain the failure of a subpopulation of smokers to live abstinent (13,14). In order to reduce this negative impact on worldwide health, effective therapy to aid smoking cessation must be provided to current smokers.

Two recommended quit methods in standard cessation programs involve either gradual reduction of smoking prior to complete abstinence called "cut down" or abrupt abstinence from cigarettes called "cold turkey" (15). These ways of smoking cessation conclude no pharmacological or nicotine replacement

therapy.

Treatment for tobacco dependency involves the combination of behavioral therapy, pharmacological treatment (16), and nicotine replacement therapy.

There is evidence showing that the antidepressants in combination with NRT are effective in treatment of tobacco dependency (16).

Trazodone tablet 50 mg is known as a low cost and available therapy in Iran, acting as an inhibitor for dopamine reuptake in the mesolimbic dopaminergic system. This area of the brain is believed to mediate reward for nicotine use and for other drugs of dependence.

NRT is the most thoroughly researched method. Tests have shown that, if used correctly, it will double the chance of success, which is good news for those who have found withdrawal very hard on previous attempts (18). The aim of nicotine replacement therapy (NRT) is to replace cigarette nicotine. This reduces withdrawal symptoms associated with smoking cessation, helping resist the urge to smoke cigarettes afterwards (19). There are several forms of nicotine replacement available; such as patch, gum, lozenge, nasal spray, inhalator and lollipops. NRT reduces the cravings for cigarettes and the withdrawal symptoms associated with quitting (18).

This study was conducted in order to compare the outcome of smoking cessation by using four pharmacological forms of NRT (patches, gums, microtabs or using two of them together) among smokers using Trazodone.

MATERIALS AND METHODS

This study was carried out as a non-randomized quasi-experimental study in which the efficacy of four mentioned forms of NRT was evaluated in participants using Trazodone medication.

- **Subjects:** All smokers who referred to the smoking cessation clinic of Iranian National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Tehran, Iran from Oct. 2005 to Oct. 2007 entered this study and were followed for 12 months.

- **Methods:** After registering, all cases were given a questionnaire based on the WHO and IUATLD questionnaires that contained three parts: motivation section, reasons of smoking, and Fagerstrom questionnaire. Motivation section had four questions about the importance, decision, reason and predictive outcomes of quitting in smokers' point of view. The second section was about cigarette-induced concentration, behavior, well being, relaxation, addiction, weight loss, and automatism in smoking. The Fagerstrom questionnaire is a well-known instrument to evaluate cigarette (nicotine) dependency in smokers in which time, situations and places of smoking as well as number of cigarettes smoked per day are evaluated in order to find nicotine dependence rate.

- **Methods of quitting:** After filling out the questionnaire, smokers were examined for vital signs, respiratory and cardiac auscultation and expiratory CO (carbon monoxide) concentration using PICO. Then the participants' readiness to quit smoking was improved through necessary educations about changing the routine smoking habits for each person. Treatment was started at the first session by using Trazodone, 1 tablet daily for 1 week, followed by 2 tablets daily for the next week and 3 tablets daily for the next 5 weeks.

The second session was held a week later when participants were asked about the side effects and their medical and mental status was evaluated by asking them about the problems. At this session, treatment was adjusted and behavioral therapy along with shift in smoking habits was completely planned. The participants were requested to allocate a quit

date to give up smoking. Indeed, in this study, we mixed the "cold turkey" method of cessation with pharmacological treatment, nicotine replacement plus cognitive behavioral therapy to get better outcomes of cigarette cessation. The third session was coming one week later in order to confirm the quit date, start NRT, and complete behavioral therapy for patients. Every referee could select their favorite NRT method based on the received consulting guidance and the cost of each method.

Four weeks later the participants were visited to know if they had given up smoking, and also withdrawal symptoms, quit-related problems, relapses impending smoking cessation were all evaluated in them.

The first follow up was 6 months later and the second one was within a one-year interval from the quit date. The flow diagram of smoking cessation process is summarized in Figure 1.

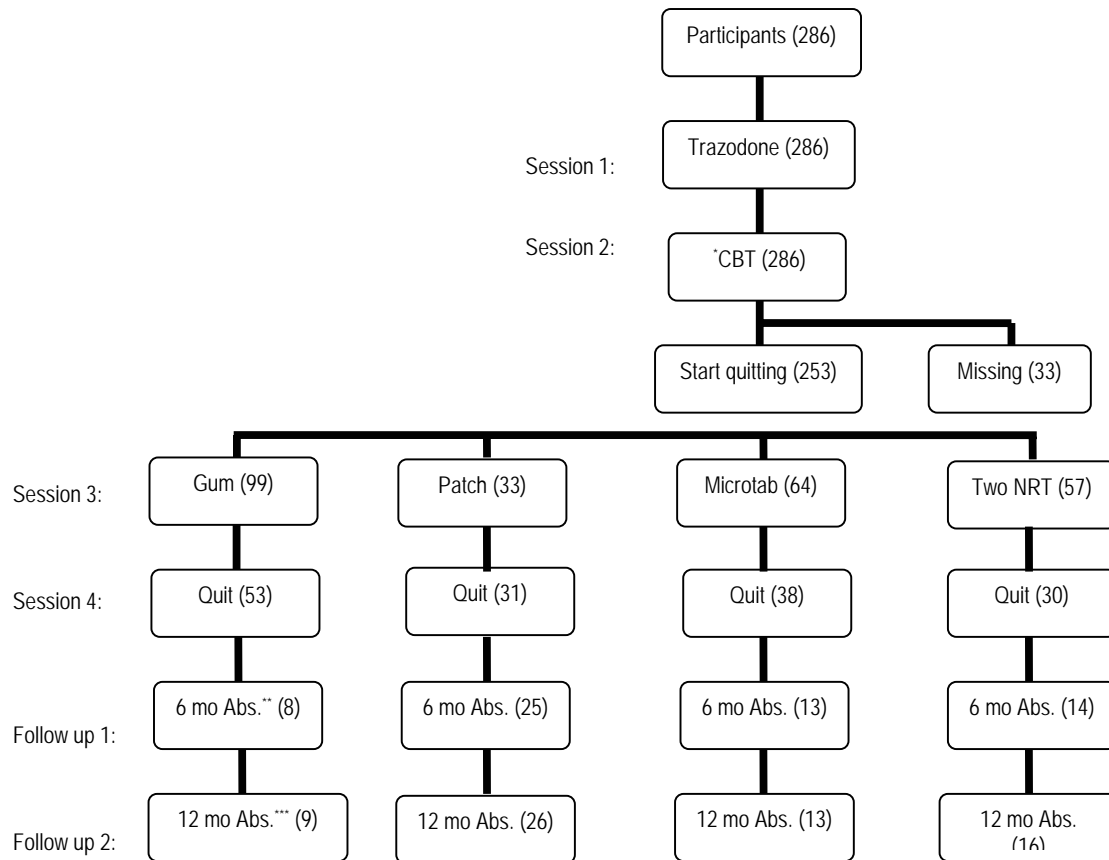
- **Nicotine replacement therapy:** At first, type of NRT, instructions for use, cost of each method and also the most suitable form of NRT for each case were determined. The participants selected their favorite NRT method considering the above-mentioned factors. The duration of NRT was at least 6 weeks. The NRTs used in this study were patches, gums and microtabs. Some participants chose using 2 forms of NRT together.

Using patches had three steps: 52.5, 35 and 17.5 mg/cm² patches were used each for 2 weeks with daily replacement.

Nicotine gums were prescribed up to 12 pieces and nicotine microtabs were prescribed up to 8.

Using two forms of NRT together included using patch with gum or microtab.

- **Research ethics:** All participants selected their NRT method of choice and were free to walk out whenever they wished to do so. Registration forms and charts were firmly protected by researchers in order to prevent any propagation, abuse or jobbery.



* CBT = Cognitive Behavioral Therapy
 ** 6 mo. Abs. = Abstinence at 6th month
 *** 12 mo. Abs. = Abstinence at 12th month

Figure 1. The flow diagram of smoking cessation process.

- **Outcome measures:** Through the one-year period of study, smoking no cigarette at all was considered as “quit” and smoking even one cigarette was considered as “relapse”. Consequences of quitting were evaluated during three separate sessions followed by the fourth session, 6 months and 12 months follow ups. This study aimed to compare the effect of the four types of NRT on the quit rate. Obviously, the process of cognitive behavioral therapy, filling the questionnaires and Trazodone therapy was the same. We scored Fagerstrom questionnaire by mild, moderate, and severe dependence considering the participants scores:
 0 to 4: mild dependence

5-7: moderate dependence
 8-10: severe dependence.

- **Data analysis:** Demographic data as well as the results of questionnaires and follow up sessions were entered and analyzed using SPSS16 software. Chi-square test was done and in some cases, when needed, “Fisher exact test” was used to evaluate the correlation between two variables. Also, logistic regression was performed to find the odds ratio of efficacy of each NRT method.

RESULTS

A total of 286 individuals participated in this study and were prescribed Trazodone with the

mentioned dosage and 253 used at least one form of NRT.

There were 181 (74.6%) males and 70 (25.4%) females. The mean age was 41.2 ± 11.5 yrs (range 18-86 years) and the median was 42.

Fagerstrom test scores demonstrated that 29% had mild (0-4), 36% had moderate (5-7) and 35% had severe nicotine dependence (8-10). Despite no significant deference, frequency of severe dependency was a little bit higher among males (38%) whereas, moderate dependence was seen more frequently in females (44%). ($P=0.128$)

There was no significant relationship between the forms of NRT selected by the participants in terms of nicotine dependence rate. ($P=0.24$)

Table 1 shows the rate of each NRT form chosen based on gender.

Table 1. Form of NRT chosen according to gender.

NRT	Gum	Patch	Microtab	Two NRTs
Gender	n(%)	n(%)	n(%)	n(%)
Male	66 (36.5)	18 (9.9)	50(27.6)	47 (26)
Female	33 (47.1)	15 (21.4)	12(17.1)	10 (14.3)
Total	99 (39.4)	33 (13.1)	62(24.7)*	57 (22.7)

* Two cases with missing sex

Of all cases, 33(13%) selected nicotine patches, 99(39.4%) used nicotine gums, 64(25%) chose microtabs, and 57(23%) preferred two types of NRT simultaneously.

As it is indicated in Table 2, 151 participants (60%) quitted smoking by the fourth session, whereas, 101 had cut down smoking significantly by that time. Outcomes of participants at the 4th session and the other two follow up sessions based on gender and age group are summarized in Table 2. A statistically significant correlation was detected between genders in the quit rate only in the first evaluation ($p = 0.048$).

Table 2. Quit and abstinence rate at each evaluation session considering genders.

Gender	Male n(%)	Female n(%)	Total n(%)	P-value
Quit	100(55.2)	51(73)	151(60)*	0.00
After 6 mo	37(34)	23(47)	60(38)	0.08
After12 mo	38(35)	26(53)	64(40)	0.02

* One case with missing sex

We had no drop out or no show at the first and second follow ups.

A significant correlation was found between NRT form and quit rate at three evaluation sessions using chi square test ($P < 0.001$). At the fourth session, patch users were proved to have the highest quit rate (92%). After 6 months follow-up it was found that nicotine patches had the best effect during abstinence and patch users had a better outcome at the end of the program. Outcomes are summarized in Table 3.

Table 3. Outcomes based on NRT types.

Outcome	Quit N (%)	Abstinence After 6 months N (%)	Abstinence After 12 months N (%)
Category			
Gum	53(53.5)	8(22)	9(24)
Patch	31(94)	25(76)	26(79)
Microtab	38(60)	13(20)	13(20)
Two NRTs	30(52)	14(54)	16(61.5)
Total	152(60)	60(37.5)	64(40)
Significance	0.000	0.000	0.000

At the fourth session patches were found to be about 3 times more effective than other forms of NRT by using logistic regression with an accessible significance ($p=0.039$).

DISCUSSION

Implementation of smoking cessation methods is an essential issue in tobacco control programs. It is shown that in some countries smoking cessation services are offered widely at low prices (10).

Smoking cessation methods are provided in two general forms of personal and interventional methods. In personal method the success rate is lower but it can be generalized to the whole society and smokers can follow it with no help. In the interventional method, the success rate is higher and the smokers use self-help materials or medicines, and therefore they have to spend some money in this method (15).

Many studies evaluated the cost effectiveness of smoking cessation programs in comparison with continuation of smoking and found out that smoking cessation is more acceptable (15,16,18).

Besides, in many studies the efficacy of nicotine replacement therapy in smoking cessation has been proven (18,19).

The aim of this study was to find the best method of smoking cessation through specialized smoking cessation services and counseling, and provide the most acceptable method of nicotine replacement therapy.

According to our study results nicotine gum was the most common form of NRT used for smoking cessation by our understudy population maybe because of its easy use, accessibility and low price. It was especially popular among women (47%). However, there was a significant difference between the consumption of gum among two genders; and other forms of NRT were mostly used by men.

On the other hand, the success rate shows that 60% of smokers quit smoking at the end of the fourth session and this rate was significantly higher among women. After six months the abstinence rate reached 38%, but it was still higher among women (47% versus 34%) but the difference was not statistically significant. However, after 12 months follow up the abstinence rate was 40% (53% among women and 35% among men) which showed a probable

significant difference according to the gender and perhaps revealed a more effective method for treatment of depression and nicotine replacement among women.

These issues are rarely mentioned in foreign studies (16-18). Nicotine patch users had the highest success rate which was statistically significant. They also had the highest quit and abstinence rate during the first year (94%, 76% and 79%, respectively). After the nicotine patch, the second most effective method was using two forms of nicotine replacement therapy at the same time which respectively resulted in success rates of 52%, 54%, and 61.5%. The first point to consider is that when using two forms of nicotine replacement therapy, surely one of them was nicotine patch and the other one was microtab or nicotine gum. Researchers failed to find any reason for the decreased quit rate while using microtab or nicotine gum along with nicotine patch; therefore, the need for further complementary studies on this issue is undeniable.

Another point to consider in this study is the estimation of golden time in abstinence. According to the observations, the first 6 months after quit date is a critical time, as it can predict the abstinence for one year if no relapse happens, because the results show a little increase in 12 months abstinence rate (37.5% versus 40%).

Interestingly, this study showed that nicotine patch was quite popular among the participants despite its high price. The success rate of this study suggests using this method as the preferred method of NRT. It would be ideal to start making nicotine patches in our country.

In similar foreign studies, no significant difference has been reported between different forms of nicotine replacement therapies; only in some cases the relative privilege of using nicotine patch has been

reported (18). Further studies are required to evaluate the significant effect of this method on smoking cessation in Iran.

Study strengths and weaknesses

A great aspect of this study is that the participants were followed up for one year along which probably the effect of time could be evaluated on quit and abstinence rates especially in correlation with gender as well as NRT forms, costs and other characteristics.

No missing data was the greatest strength in this study, but we failed to accept or reject any hypothesis powerfully because of low number of cases in this study.

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