Original Article

Efficacy of Harm Reduction Programs among Patients of a Smoking Cessation Clinic in Tehran, Iran

Hooman Sharifi MD MPH¹, Roghieh Kharaghani MSc¹, Habib Emami PhD•¹, Zahra Hessami MD MPH¹, Mohammad Reza Masjedi MD²

Abstract

Background: Recently, harm reduction programs have been used to reduce mortality and morbidity among smokers. The main objective of this study was to evaluate the effect of harm reduction programs on the smoking patterns of subjects who presented to a smoking cessation clinic in Tehran, Iran.

Methods: This observational study was conducted between September 2008 – September 2009 on 132 patients who were unable to quit smoking. Patients were enrolled by the first come first service method. During the study period, subjects were assigned to either group or individual visits every 15 days in conjunction with the use of nicotine gum. The main objective of this study was to evaluate at the third and sixth months of follow-up: the number of smoked cigarettes, level of expired carbon monoxide (CO), and numbers of nicotine gum used. Data were analyzed by the Wilcoxon rank, Fisher's exact, and Pearson's chi-square tests and SPSS version 17 software.

Results: A total of 87.1% of the subjects were males. We noted decreases in the number of cigarettes smoked daily and the level of expired CO, whereas the amount of nicotine gum used significantly increased during the time interval between the first session and the third and sixth month follow-up visits (p <0.001 for all variables). During the follow up sessions, 64.4% of subjects reduced the number of cigarettes they smoked daily by at least 50% and 12.9% of subjects quit smoking.

Conclusion: Behavioral and pharmacological therapy in harm reduction programs result in a decrease in the number of cigarettes smoked daily and a reduction in the amount of expired CO. Therefore, these methods can be beneficial in achieving complete smoking cessation.

Keywords: Cigarette, harm reduction, nicotine, Tehran, treatment

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Introduction

Tobacco smoking is among the most common preventable causes of death worldwide. According to a report by the World Health Organization (WHO), the smoking-related death toll will reach 8 million by the year 2030, half of which will occur in developing countries. There are more than one billion smokers globally. In 2006, Iran became a member of the Framework Convention on Tobacco Control (FCTC) and legalized tobacco control. A primary action to reach the goal of tobacco control is to evaluate and acquire baseline information on the issues addressed in FCTC. Prior to FCTC, in 2005 the Islamic Republic has banned tobacco consumption in public places and subsequently passed a law (article 13) to penalize and fine those who disobey. Based on a report by the Ministry of Health and Medical Education in Iran, 24.1% of men and 4.3% of women (15-64 years old) are smokers.

Smoking is the cause of at least 85% of lung cancers, chronic

These behavioral and pharmacological therapies have increased the rate of 6-month abstinence to about 2 – 3 times.⁷ Following the effective steps taken by the US Tobacco Prevention and Control Center, the US smoking rate decreased from 42.4% in 1965 to 24.1% in 1998.⁸ However, many smokers who quit smoking relapse and others may never attempt to quit. In a study by the Smoking Cessation Clinic affiliated with the Tobacco Prevention and Control Research Center in Iran, 87.5% of participants who smoked quit tobacco smoking at the end of the first month of the study. In the mentioned study, 23.4% of participants relapsed dur-

bronchitis, and emphysema. The World Bank estimates the annual expenses of smoking-related diseases in the United States to be more than 200 million dollars, which is more than the profit from

Smoking is preventable. During the past decades there have

been remarkable improvements in nicotine-dependence treatment.

sales by multinational tobacco companies.6

to increase over time. 10 Finding new techniques for quitting smoking may be helpful in filling the gap between what the smoker hopes to accomplish and what he is capable of, since most smokers have repeatedly attempted to quit but with no success. 11

ing the first month, 40.7% during the third month, 47.2% during

the sixth month, and 52.4% during the first year following absti-

nence.9 Thus, the number of smokers resistant to treatment seemed

Harm reduction methods focus on reducing the harmful effects of tobacco products, rather than emphasizing nicotine withdrawal syndrome. ¹² These methods are designed to establish a temporary reduction in the number of cigarettes smoked by those who are un-

Authors' Affiliations: ¹Tobacco Prevention and Control Research Center (TP-CRC), Masih Daneshvari Hospital, Shaheed Beheshti Medical Science University, Tehran, Iran,²National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshvari Hospital, Shaheed Beheshti Medical Science University, Tehran, Iran

•Corresponding author and reprints: Habib Emami PhD, Tobacco Prevention and Control Research Center (TPCRC), Masih Daneshvari Hospital, Shaheed Beheshti Medical Science University, Shaheed Bahonar Avenue, Darabad, Tehran, Iran. Tel: +989127147041, Fax: +982126106003, Office: +9827122029, E-mail: emamihabib@yahoo.com.

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Table 1. Baseline socio-demographic characteristics of participants.

Variables	Numbers	Percent
Sex (male)	115	87.1
Age:		
Males (years)	37.3±10.7*	_
Females (years)	40.7±12.2*	_
Education		
Illiterate and primary	10	7.5
Guidance and high school	31	23.5
Diploma and higher	91	68.8
Social class		
Clerical or non-manual skilled	65	49.2
Manual skilled	47	35.6
Unskilled or semiskilled	20	15.2
Tenure		
Owner occupied	69	52.3
Rent/other	63	47.7
Marital status		
Married	85	64.4
Single	35	26.5
Widowed, divorced or other	12	9.1
* = Mean±standard deviation		

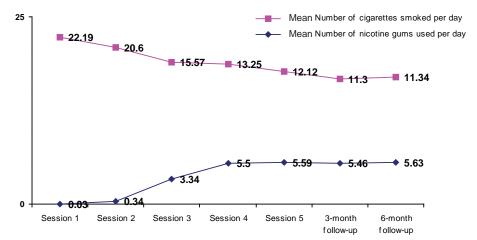


Figure 1. Mean number of cigarettes smoked and number of nicotine gums used per day from baseline to 6-month follow up. Differences were all statically significant (p < 0.001).

able to quit completely.13,14

Nicotine replacement drugs contain small amounts of nicotine which is gradually released and somehow prevents cigarette craving. ¹⁵ Use of these nicotine-containing products for a long time is not harmful and it is definitely superior to smoking cigarettes. ^{16,17}

Considering the prevalence of smoking, large number of exsmokers who relapse, and limited number of smoking cessation interventions in Iran, the present study has sought to determine if prolonged smoking cessation programs in which nicotine replacement products used by current smokers helped to decrease daily cigarette consumption and exhaled carbon monoxide (CO). This study was conducted to assess the efficacy of harm reduction programs for smoking cessation clinic patients. The main objectives of this study were to evaluate: i) the number of cigarettes smoked per day, ii) exhaled CO levels, and iii) number of nicotine gums used per day.

Materials and Methods

Study design

This pre-post design interventional study was conducted at an inner-city smoking cessation clinic with approximately 1000 participants between September 2008 and September 2009 in Tehran, Iran.

Sample selection

The Tobacco Prevention and Control Research Center's Smoking Cessation Clinic was considered as the main setting for sample selection. The inclusion criteria were: participants who had previously attended smoking cessation programs in this center, those who were unsuccessful in quitting smoking or relapsed after quitting, and those willing to participate in this study who offered their

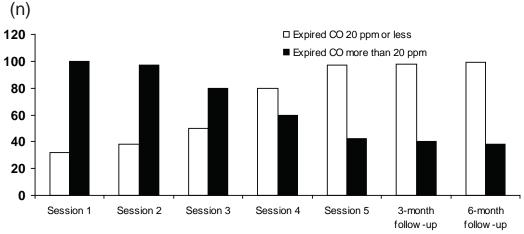


Figure 2. Expired carbon monoxide (CO) levels from baseline to 6-month follow up. Differences were all statically significant on Fisher's exact test (p < 0.001).

consent. The exclusion criteria were the inability to actively participate in the study or not having enrolled in a smoking cessation program. A total of 132 patients were enrolled.

Data collection

A questionnaire was designed according to International Union Against Tuberculosis and Lung Diseases (IUATLD) and WHO-structured questionnaires, pilot tested, and revised. The first two sections of the questionnaire were self-administered, whereas the third section was completed by counselors during the smoking cessation course. The questionnaire included demographic data, history, and pattern of smoking. Before beginning the course, in order to assess nicotine use, the Fagerström Test for Nicotine Dependence (FTND) was performed.

The social status of the participants was determined based on the Registrar General Model of Social Classes, and participants were classified into 6 groups.¹⁸

The numbers of cigarettes smoked daily and consumed nicotine gums were recorded at every visit.

There is no or little doubt about the reliability of the responses on questionnaires administered in the first visit of smoking cessation clinics, however many smokers mispronounce their situation during follow-up sessions. ¹⁹ In studying nicotine replacement therapies such as nicotine gum, cotinine cannot be used as a marker of cigarette abstinence, because cotinine is a metabolite of nicotine. Accordingly, cotinine's first use for verification of self reports of abstinence during treatment is limited to non-nicotine containing medications. ^{20,21}

Since the determination of breath CO levels is noninvasive, inexpensive, and yields immediate results, it is the method of choice in research and clinical practice.²² In this study, CO level was measured using a hand-held portable CO monitor (Bedfont Micro Smokerlyser, Kent, England) that had previously been shown to be effective in validating the participants' self-reports regarding smoking status.^{23,24}

CO has a 3-6 hour half-life, which depends on the level of exercise and environmental CO. Previous studies have shown that smoking within the past 24 hours generally results in elevated breath CO levels which are above the normal physiological range. However, this could depend on both the quantity of cigarettes smoked and the last time a cigarette was smoked.²⁵ One study has

shown a strong, statistically significant relationship between level of reported smoking during the past 24 hours and breath CO levels.²²

Although presumed unsuitable for epidemiological studies that gather information during a single visit, breath CO testing could be a valuable tool for monitoring abstinence from smoking during cessation trials that have regular follow-up intervals.²⁶

The Smokerlyzer measures breath CO levels in parts per million (ppm) based on the conversion of CO to CO₂ over a catalytically active electrode. On breath holding, the CO in the blood forms equilibrium with CO in the alveolar air; therefore, there is a high degree of correlation between breath CO levels and COHb concentration. This enables the Smokerlyser to accurately estimate the blood COHb concentration from the breath CO level. We have calibrated the Smokerlyzer weekly by using a mixture of 50 ppm CO in air.

Procedures

Patients were initially asked to participate in this study by phone contact using their previous records. Those who met the inclusion criteria were scheduled for their initial assessment visit following the first group therapy session. All 132 participants who consented to enroll in this study were divided into 10 groups of 5 – 15 participants each. Participants were visited approximately every two weeks, on weekdays, and a smoking counselor attended each session. Participants came to the Smoking Cessation Clinic at 2, 4, 6, 8 and 10-week intervals following initiation of the study to participate in group therapy, and at 3 and 6 months for follow up assessments. In all sessions respiratory CO levels were assessed.

The study protocol was approved by the Research Committee of the Tobacco Prevention and Control Research Center.

Intervention

No new intervention was implemented following the completion of all measurements. Subjects were monitored to achieve a certain percentage of reduction in smoking rate (at least 50%). Therefore, 2 mg nicotine gums were administered to all subjects, the same as in the cessation program.

The treatment procedure was started in a routinely conventional cessation program and categorized in three steps: i) one session as a baseline assessment; ii) two sessions for gradual reduction

Table 2. Baseline smoking status, habits, and dependence.

Variables	Mean±standard deviation	
Age at smoking onset (years)	18.5±5.6	
Number of cigarettes smoked per day	22.1±10.4	
Expired carbon monoxide (CO) level	101 (76.5)**	
Number of nicotine gums used per day	0.03±0.43	
Pack of cigarettes smoked per year	22.3±16.9	
Q-MAT* score	14.9±4.1	
HAD† score	16.9±6.7	
FTND‡ score	5.9±2.8	
* Motivation to quit smoking; ** Number (percent); † Hospital anxiety and depression test; ‡ Fagerström Test for Nicotine Dependence;		

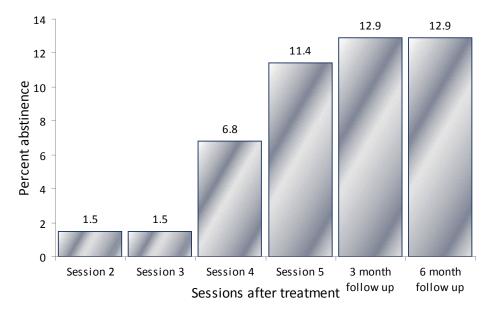


Figure 3. Percent abstinence after treatment from second session until 6-month follow up.

that used 2 mg nicotine gums; and iii) two maintenance sessions (steady amount of nicotine gum and cigarettes) following two maintenance sessions that aimed at further reduction or cessation of smoking. During the first session (baseline assessment), subjects precisely stated the mean number of cigarettes they smoked daily and their reduction amount for each day for 2 weeks, considering the counselor's advice. Based on the recordings of the first session regarding smoking status, subjects were advised to decrease smoking over a 2-week period by 50% (reduction goal). In case of any difficulty following the schedule, the reduction pace was lessened. Upon achieving the 50% reduction goal, subjects were advised to further decrease their consumption or quit smoking completely.

Outcome measures

Outcome measures in this study included the decrease in the number of cigarettes smoked per day and the amount of nicotine gums used per day. Successful reduction was defined as a self-reported reduction by 50% in the number of cigarettes smoked per day.

Data analysis

First, the estimated prevalence was calculated for all variables through numbers, percentages, means and standard deviations. Second, in order to determine the efficacy of the intervention, the

Wilcoxon rank test was used since two outcome variables (number of cigarettes and nicotine gums used per day) did not have normal distributions as shown by the Kolmogorov-Smirnov test. Pearson's chi-square test was used to determine the efficacy of intervention in decreasing CO levels. All data were analyzed using SPSS version 17.0 software. Statistical tests used were two-tailed with 5% significance level.

Results

Characteristics of the subjects

Among participants, 87.1% (n=115) were men with a mean age of 37.33 ± 10.72 years and 12.9% (n=17) were women with a mean age of 40.70 ± 12.24 years. A total of 64.4% (n = 85) of the subjects were married, 26.5% (n = 35) were single, and the remainder were divorced, widowed or separated. Regarding their level of education, approximately 69.2% (n = 90) had a high school diploma or lower educational level. Homeowners comprised about 52.3% (n = 69) of subjects. All were from low class strata; most (49.6%, n = 65) were employed in clerical work or non-manual skilled labor, whereas 6.8% (n = 9) were unemployed (Table 1).

Smoking pattern and nicotine dependence

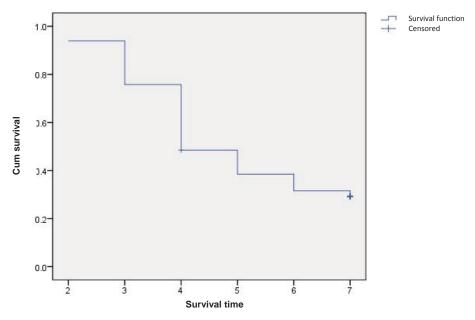


Figure 4. Estimated survival curves for 50% reduction in daily cigarette consumption through 3 months.

The mean age of smoking initiation was 18.5 ± 5.6 years and the mean number of cigarettes smoked daily was 22.19 ± 1.03 . The mean amount of expired CO for 76.5% (n = 101) of subjects was more than 20 ppm. According to FTND, the mean score of nicotine dependence was 5.9 ± 2.8 . The mean score for readiness to quit smoking was 14.9 ± 4.1 based on motivation to quit smoking questionnaire (Questionnaire de motivation à l'arrêt du tabac) (Q-MAT) and according to the Hospital Anxiety and Depression test (HAD), the mean score for suffering from depression or anxiety was 16.9 ± 6.7 (Table 2).

Treatment efficacy

During the first 6 months, the number of cigarettes smoked daily significantly decreased; the number of nicotine gums used significantly increased. At the beginning of the study these rates were 22.9 for number of smoked cigarettes and 0.03 for the number of nicotine gums used. This declined to 11.34 for the number of cigarettes smoked and 5.63 for number of nicotine gums used at the 6-month follow up. All were statistically significant (p < 0.001; Figure 1). According to the chi-square test, differences in expired CO levels were statistically significant (p < 0.001 for all; Figure 2). In this study, 85 subjects (64.4%) decreased their number of daily cigarettes by a minimum of 50%. During the follow-up visits, the number of subjects who quit gradually increased. Finally at 3 and 6-month follow-up visits, 17 subjects (12.9%) quit smoking (Figure 3). After 4 weeks of observation there was a minimum of 50% reduction in daily cigarette consumption among the participants (Figure 4).

Discussion

This study explained the feasibility of reduction and eventual cessation of cigarette smoking among Iranian people who previously failed to quit. The reduction in level of expired CO was statistically significant, even at the 6-month follow up, which validated the efficacy of smoking reduction programs in this study.

Smoking reduction may encourage smoking cessation by allow-

ing smokers to gradually take control of this habit. Similar studies that have aimed to decrease smoking in those trying to quit noted complete smoking cessation in a significant number of smokers. ^{27–31} In our study, the gradual reduction in smoking was followed by a 12.9% successful quit rate.

One concern in harm reduction programs is that smokers who reduce the number of daily cigarettes may balance their intake of tobacco by smoking fewer cigarettes but more forcefully. In this study, reduction in expired CO levels and number of daily cigarettes is statistically significant. Therefore, even if this hypothesis is true, we have reached a significant reduction in expiratory CO levels due to the consumption of nicotine gums while participants still smoked.

Some researchers suggest that high dose nicotine replacement therapy should be used to reduce the health risks due to compensatory smoking.³¹

Nicotine Replacement Therapy (NRT) increases lasting abstinence rates by 50% to 70%, irrespective of the method of prescription in smokers motivated to quit.³² The 6-month abstinence rate in our study (12.9%) was the same as that observed in a number of previous studies on NRT products for smoking reduction (8% – 12%),²⁷⁻³⁰ but lower than observed in a recent trial by Kralikova et al. which showed that 18.7% of participants quit smoking in an intervention group that used nicotine gums.³³ This was possibly due to the fact that Kralikova and colleagues recruited smokers who wanted to manage their smoking, which meant either decreasing cigarette consumption or immediate cessation; whereas, in the present study our participants were smokers who had failed to quit.

The NRT-assisted reduction phase aims to promote cessation and engage smokers who are ready to quit in a time-limited course of structured reduction to reach a quitting endpoint. The reduce-to-quit approach is not the only technique that uses NRT. A comparable approach, described as "cut down to quit", encourages smokers who are not currently interested in quitting to use NRT for smoking reduction over a period of up to 12 months. The meta-analysis conducted by Wang et al. in 2008 have reported that this approach was successful but less cost effective than immediate cessation. The

two approaches address different populations with different plans, making it difficult to compare the results.³⁴

Our data suggest that although prolonged observation is not included in conventional smoking cessation programs, we could design our interventions for a longer period of time to address cessation in smokers. Moreover, a structured treatment on the first two months of the course with regular follow-ups could clearly enhance the quit rate.

This study's strengths include the presence of detailed data on smoking pattern and biochemical measures of smoke exposure. Another strong point is the report of smoking prevalence in a 6-month period instead of point prevalence at the end of a conventional treatment, which is a less relevant outcome.

In summary, this study shows that reduction in smoking can be achieved through prolonged counseling sessions and NRT. Smoking reduction in people unable to stop smoking immediately seems to be a step forward towards improved health and may finally proceed to complete smoking cessation.

The results of this study support the efficacy of harm reduction programs. This is particularly useful for smoking cessation counselors to know that continuation of conventional programs can augment the success rate of quitting in smokers. We hope that the results of this study may be useful for tobacco control programs and policy making. Further studies are also recommended in this regard.

Last but not least, similar studies in other regions and countries can help support and generalize our findin

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References

- WHO Report on the Global Tobacco Epidemic. Implementing smokefree environments. 2009. Available from: URL: http://www.who.int/ tobacco/mpower/en/index.html. (Accessed 2011 August 20).
- Ortiz A, Martinez M, Torres A, Casal J, Rodriguez W, Nazario S. Predictors of smoking cessation success. *Puerto Rico Health Science Journal*. 2003; 22: 173 – 177. Available from: URL: http://www.biomedexperts.com/Abstract.bme/12866142/Predictors_of_smoking_cessation_success. (Accessed 2011 August 20)
- General Surgeon Report. Important factors in smoking cessation; women and smoking, a Report of the Surgeon General. 2007. Available from: URL: http://www.cdc.gov/mmwr. (Accessed 2011 August 20).
- Ministry of Health and Medical Education. Center for Disease Control. A national profile of non-communicable disease risk factors in the Islamic Republic of Iran. 2005. Available from: URL: http://www.who.int/chp/steps/IR_IranSTEPSReport.pdf. (Accessed 2011 August 20).
- Slama K. Tobacco Control and Prevention. A Guide for Low-income Countries. Paris: IUATLD; 1998. Available from: URL: http://www. iuatld.org/pdf/en/guides_publications/tobac coguide.pdf. (Accessed 2011 August 20).
- Curbing the epidemic: Governments and the economics of tobacco control. The World Bank. Tobacco Control. 1999; 8: 196 – 201. Available from: URL: http://www.worldbank.org/tobacco/. (Accessed 2011 August 20).
- US Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and

- Health. The health consequences of smoking: The changing cigarette. A report of the Surgeon General. 1981. Available from: URL: http://www.quit-smoking-stop.com/articles-tobacco-health.html. (Accessed 2011 August 20).
- Centers for Disease Control and Prevention (CDC). Cigarette smoking among adults-United States, 1998. Morb Mortal Wkly Rep. 2000;49: 881 – 884
- Masjedi M, Azaripour MH, Hosseini M, Heydari G. Effective factors on smoking cessation among the smokers in the first "Smoking Cessation Clinic" in Iran. Tanaffos. 2002; 1: 61 – 67. Available from: URL: http://www.sid.ir/en/VEWSSID/J_pdf/100220020403.pdf. (Accessed 2011 August 20).
- Irvin JE, Hendricks PS, Brandon TH. The increasing recalcitrance of smokers in clinical trials II: Pharmacotherapy trials. *Nicotine Tob Res*. 2003; 5: 27 – 35. Available from: URL: http://ntr.oxfordjournals.org/ cgi/reprint/5/1/27.pdf. (Accessed 2011 August 20).
- Lindson N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. Cochrane Database Syst Rev.2010, Issue 3. Art. No.: CD008033. DOI: 10.1002/14651858.CD008033.pub2...
- Frances RJ, Miller SI, Marck AH. Clinical Textbook of Addictive Disorders. 3rd ed. Location of publishing company? The Guilford Press. Available from: URL: http://www.informaworld.com/smpp/content~content=a911177929~db=all~jumptype=rss. (Accessed 2011 August 20).
 - Warner KE, Slade J, Sweanor DT. The emerging market for long-term nicotine maintenance. *J. Am. Med. Assoc.* 1997; 278: 1087 1092. Available from: URL: http://jama.ama-assn.org/cgi/content/abstract/278/13/1087. (Accessed 2011 August 20).
 - Kunze M. Maximizing help for dissonant smokers. *Addiction*. 2002;
 95: 13 17. DOI: 10.1046/j.1360-0443.95.1s1.1.x
 - Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr. Mortality from tobacco in developed countries: Indirect estimation from national vital statistics. *Lancet*. 1992; 339: 1268 – 1278. DOI: 10.1016/0140-6736(92)91600-D
 - Tilashalski K, Rodu B, Cole P. Seven year follow-up of smoking cessation with smokeless tobacco. *J Psychoactive Drugs*. 2005; 37: 105 108.
 Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed/15916256. (Accessed 2011 August 20).
 - Rodu B. Swedish tobacco use: Smoking, smokeless and history. ACSH Health Facts and Fears. 2004. Available from: URL: http://www.acsh. org/factsfears/newsID.362/news_detail.asp. (Accessed 2011 August 20).
 - Currie CE, Elton RA, Todd J, Platt S. Indicators of socioeconomic status for adolescents: The WHO Health Behavior in School-aged Children Survey. Health Education Research. 1997; 12: 385 397. Available from: URL: http://her.oxfordjournals.org/cgi/reprint/12/3/385.pdf. (Accessed 2011 August 20).
 - Barrueco M, Jiménez Ruiz C, Palomo L, Torrecilla M, Romero P, Riesco JA. Veracity of smokers' reports of abstinence at smoking cessation clinics [Article in Spanish]. Arch Bronconeumol. 2005; 41: 135 – 140.
- Ahluwalia JS, Harris KJ, Catley D, Okuyemi KS, Mayo MS. Sustained-release bupropion for smoking cessation in African Americans: A randomized controlled trial. J Am Med Assoc. 2002; 288: 468 – 474.
- Hall SM, Humfleet GL, Reus VI, Munoz RF, Hartz DT, Maude-Griffin R. Psychological intervention and antidepressant treatment in smoking cessation. Arch Gen Psychiatry. 2002; 59: 930 – 936.
- Javors MA, Hatch JP, Lamb RJ. Cut-off levels for breath carbon monoxide as a marker for cigarette smoking. *Addiction*. 2005; 100: 159

 167.
- Jarvis MJ, Belcher M, Vesey C, Hutchison D C S. Low cost carbon monoxide monitors in smoking assessment. *Thorax*. 1986; 41: 886 – 887.
- Tilashalski K, Rodu B, Cole P. A pilot study of smokeless tobacco in smoking cessation. Am J Med 1998; 104: 456 – 458. Available from: URL: http://www.sciencedirect.com/science/article/pii/ S0002934398000850. (Accessed 2011 August 20).
- Benowitz NL, Jacob P, Ahijevych K, Jarvis MF, Hall S, LeHouezec J, et al. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res.* 2002; 4: 149 – 159.
- Kauffman RM, Ferketich AK, Murray DM, Bellair PE, Wewers ME. Measuring tobacco use in a prison population. *Nicotine Tob Res*. 2010; 12: 582 – 588.
- Bolliger CT, Zellweger JP, Danielsson T, Van BX, Robidou A, Westin A, et al. Smoking reduction with oral nicotine inhalers: Double blind randomized clinical trial of efficacy and safety. BMJ. 2000; 321: 329 333. Available from: URL: http://www.bmj.com/content/321/7257/329.full. (Accessed 2011 August 20).

- Wennike P, Danielsson T, Landfeldt B, Westin A, Tonnesen P. Smoking reduction promotes smoking cessation: Results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction*. 2003; 98: 1395 1402. Available from URL: http://www.ncbi.nlm.nih.gov/pubmed/14519176. (Accessed 2011 August 20).
- Batra, A., Klingler, K., Landfeldt, B., Friederich, H.M., Westin, A. and Danielsson, T. (2005) Smoking reduction treatment with 4-mg nicotine gum: A double-blind, randomized, placebo-controlled study. Clinical Pharmacology & Therapeutics, 78, 689 696. doi:10.1016/j. clpt.2005.08.019 (Accessed 2011 August 20).
- Rennard SI, Glover ED, Leischow S, Daughton DM, Glover PN, Muramoto M, et al. Efficacy of the nicotine inhaler in smoking reduction: A double-blind, randomized trial. *Nicotine Tob Res.* 2006;
 555 – 564. Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed/16920653. (Accessed 2011 August 20).
- Hatsukami D, Mooney M, Murphy S, LeSage M, Babb D. Effects of high dose transdermal nicotine replacement in cigarette smokers. *Pharmacol Biochem Behav.* 2007; 86: 132 – 139. DOI:10.1016/j. pbb.2006.12.017.
- Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database* Syst Rev. 2008 Jan 23;(1):CD000146. DOI: 10.1002/14651858.CD000146.pub3
- Kralikova E, Kozak JT, Rasmussen T, Gustavsson G, Le Houezec J. Smoking cessation or reduction with nicotine replace. DOI: 10.1186/1471-2458-9-433.
- Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D. Cut down to quit' with nicotine replacement therapies in smoking cessation: A systematic review of effectiveness and economic analysis. *Journal of Technology Assessment in Health Care.* 2008; 12: 1 – 135. DOI: 10.3310/hta12020.



Mohtasham Garden in Rasht, Gilan Province - Iran, founded during Nasser al-Din Shah Qajar Period (1848 – 1896) (Photo by M.H. Azizi MD)