Regular article

Twenty-four week maintenance treatment of cigarette smoking with nicotine gum, clonidine and naltrexone

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Abstract

This research study investigated the effect of nicotine gum, clonidine, and naltrexone, in the maintenance treatment of cigarette smoking. In a double blind study, 171 nicotine-dependent male subjects who met DSM-IV criteria for nicotine dependence and smoking 10 cigarettes or more per day, were allocated randomly to three equal groups of 57. Subjects received nicotine gum, clonidine, or naltrexone over a 24-week treatment period. The nicotine gum dose was 2 mg every 1 to 2 h for the first 6 weeks, 2 mg every 2 to 4 h for the next 3 weeks, and 2 mg every 4 to 8 h for the remaining 15 weeks. The clonidine dose was 0.4 mg and the naltrexone dose was 50 mg per day. Continuous abstinence rates were recorded weekly for 24 weeks from the quit date.

The abstinence rates by treatment groups were 36.8% for the nicotine gum group, 19.3% for the clonidine group, and 5.3% for the naltrexone group, and all between groups differences were significant. These results support the efficacy and safety of nicotine gum and clonidine for smoking relapse prevention among Iranian nicotine-dependent patients, but call in question the utility of naltrexone treatment for smoking relapse prevention. © 2003 Elsevier Inc. All rights reserved.

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1. Introduction

Nicotine dependency is regarded as a psychiatric disorder (Diagnostic and Statistical Manual of Disorders, 4th edition [DSM-IV]; American Psychiatric Association, 1994; World Health Organization, 1993). Although cigarette smoking is the greatest source of preventable morbidity and mortality, however, most clinicians dealing with individuals using alcohol and abusing substances do not diagnose or treat this disorder (Hurt, Eberman, & Slade, 1993).

The main reasons clinicians do not treat nicotine dependence is that the majority have had little, if any, training in dealing with nicotine dependence (Bobo & Gilchrist, 1983) and that such dependency is largely socially accepted.

Lifetime prevalence rates of tobacco/nicotine dependence have been reported as 20% to 40% of the total community population in the United States of America (Anthony, Warner, & Kessler, 1994; Breslau, Kilbey, & Andreski, 1991). In a survey in Iran, 26% of men and 3.6% of the women reported being current cigarette smokers (Ahmadi et al., 2001).

Accordingly, it is essential to promote quitting smoking; however, cessation of tobacco smoking is not easy and as Garvey, Bliss, Hitchcock, & Rosner (1992) reported, without treatment most quit attempts (97%) were unsuccessful. Pharmacotherapy and behavior therapy could enhance success rate (Fiore et al., 2000). Although treatment of nicotine dependence is difficult, nicotine replacement therapy with nicotine gum or nicotine patch is fairly effective (Silagy et al., 2000).

The public health impact of treatment of cigarette smoking, i.e., the number of cigarette smokers converted to non-smoking, depends on the effectiveness of treatments in actual use (Shiffman et al., 1997). Use of nicotine replacement therapy is highly influenced by its regulatory status, which may impose limitations on access (Shiffman & Gitchell, 2000). Pharmacotherapy has been shown to help cigarette smokers stop smoking (Blondal et al., 1999; Shiffman et al., 2002). Drugs that do not contain nicotine have special interest for researchers. Naltrexone has been reported to be effective for treatment...
of alcohol dependents (O’Malley, Croop, Wroblewski, Labriola, & Volpicelli, 1995; Volpicelli, Alterman, Hayashida, & O’Brien, 1992). Some researchers have theorized that there could be an interaction between endogenous opiates and the reinforcement of smoking behavior mediated by nicotine. Cigarette smoking enhances the levels of plasma β-endorphin by 30–200%; this enhancement was correlated with plasma level of nicotine (Pomerleau, Fertig, Seyler, & Jaffe, 1983).

The results of various studies involving the use of opioid antagonists in cigarette smokers have been mixed. Some investigators have shown that opioid antagonists such as naltrexone reduce cigarette smoking (Gorelick, Rose, & Jarvik, 1989; Karras & Kane, 1980). However, other investigators have reported that opioid antagonists have no effects on cigarette smoking (Nemeth-Coslett & Griffiths, 1986; Sutherland, Stapleton, Russell, & Feyerabend, 1995; Wong et al., 1999).

Due to the modest success the current approaches have achieved, further research is needed, especially research directed to specific cultures. Therefore, the goal of this study was to evaluate the efficacy and the safety of nicotine replacement therapy compared to clonidine and naltrexone as well among a sample of Iranian smokers seeking treatment.

2. Materials and methods

2.1. Subjects

The present study was a prospective, double blind, randomized trial carried out in an outpatient treatment center in the capital city of Shiraz with a population of 1.5 million. One hundred seventy-one (171) male cigarette smokers (3 groups with 57 patients in each group) seeking treatment were screened for participation in the year of 2002. Men were selected for the study because not only is the rate of nicotine dependence thought to be negligible in women, but also women usually do not refer for treatment. In addition it should be noted that in Iran, women are socially downgraded if they smoke cigarettes.

Patients were stratified into treatment groups by levels of physical dependence and number of cigarettes per day. Research staff consisted of addiction psychiatrist, general practitioner, and psychologist. At screening, patients were examined by a physician to establish eligibility and to discuss the informed consent. Patients had to meet DSM-IV criteria for nicotine dependence (American Psychiatric Association, 1994). Daily use of 10 cigarettes or more for at least one year was also a requirement. The patients were eligible for inclusion if they were between 17 and 64 years old, and had good health. The patients were excluded if they were using any medications that were a contraindication for the use of nicotine gum, naltrexone, or clonidine. The participants were also excluded if they had substance dependence other than tobacco/nicotine.

2.2. Procedures

After physical examination and biochemical tests, subjects were allocated randomly to one of three treatment groups: nicotine gum (2 mg pieces), oral naltrexone (50 mg), and oral clonidine (0.4 mg). Induction onto nicotine gum was done by administering nicotine gum (2 mg every 1 to 2 h for the first 6 weeks, 2 mg every 2 to 4 h for the next 3 weeks, and 2 mg every 4 to 8 h for the remaining 15 weeks).

Subjects were visited by an outreach worker once a week and were asked to discuss their general health and adjustment, and their smoking within the past week. Induction into clonidine group was done by administering 0.2 and then 0.4 mg over the first 2 study days and then continuing with 0.4 mg daily. The naltrexone group was started on 50 mg naltrexone and then continued with 50 mg daily. All groups were eligible to continue at their assigned dose for up to 24 weeks. Abstinence rates were based on self-report and test verification.

2.3. Statistical analysis

Analysis of data was done on SPSS for Windows. Chi-square analyses were used to test for differences in 24-week...
abstinence rates among the three groups, and two-sided \( t \)-tests were used to test for differences in means. A \( p \)-value of less than .05 was considered significant.

3. Results

3.1. Demographic variables

One hundred seventy-one (171) nicotine-dependent male patients were allocated randomly to receive nicotine gum (57), clonidine (57), and naltrexone (57). The mean age of the total group (171) was 37.68 years (SD = 10.07, range 17–64).

There were no significant differences among the three groups on mean age (\( F = 0.006, DF = 2, p = ns \)). The majority (63.1%) were between 30 and 44 years of age. The mean number of cigarettes per day was 19.93 for the total group and there were no significant differences among groups on mean number of cigarette smoking per day (\( F = 0.04, DF = 2, p = ns \)). One hundred fifty-four (90.1%) had no history of abstinence and only 17 (9.9%) gave history of abstinence before study entry. As Table 1 shows, only 10.5% of the subjects were single and the others (89.5%) were married.

3.2. Effects of nicotine gum, clonidine and naltrexone on smoking

As Table 2 shows, overall 35 (20.5%) subjects were abstinent throughout the 24-week study. Abstinence rates at 24 weeks were 21 (36.8%) for the nicotine gum group, 11 (19.3%) for the clonidine group and 3 (5.3%) for the naltrexone group (\( \chi^2 = 17.53, DF = 2, \text{Significance (2-tailed)} = 0.000 \)). The Kaplan-Meier survival analysis is shown in Fig. 1.

3.3. Safety

Although subjects did not report any severe side effects, some of them complained of minor adverse effects during the study as discussed below.

Nicotine gum: Forty-two percent of nicotine gum users reported experiencing at least one adverse event. The most common reported adverse events were:

![Relapses](image-url)

Fig. 1. Kaplan-Meier survival analysis of relapses.
headache, nausea, mouth and throat irritation, bad taste, and
anxiety, respectively.

**Clonidine:** Approximately 31.6% of clonidine users
reported drowsiness, hypotension, or lethargy.

**Naltrexone:** A majority (84.2%) of naltrexone users
complained of at least one side effect. The most common
side effects reported by the patients were headache, gastro-
intestinal upset, or sleep disturbances.

4. Discussion

The present study examined the efficacy of nicotine gum,
clonidine, and naltrexone in a sample of Iranian cigarette
smokers. Our study did not show any strong evidence that
naltrexone can considerably reduce cigarette smoking. Our
findings (5.3% success rate for naltrexone) are consistent
with previous studies, which showed no effect of naltrexone
on smoking consumption (Palmer & Berens, 1983; Suther-
land et al., 1995).

The current study demonstrated that clonidine was more
effective than naltrexone (19.3% for clonidine vs. 5.3% for
naltrexone, p = .02) in the treatment of nicotine dependence.
Finally, the study showed that nicotine gum could be used
safely and was more effective than clonidine or naltrexone
(36.8% for nicotine gum, 19.3% for clonidine, 5.3% for
naltrexone). Our findings are consistent with previous studies
on nicotine replacement therapy, with nicotine gum (Shiff-
man et al., 2002) or nicotine patch (Fiore, Smith, Jorenby, &

Our study had several positive points which strengthened
our findings: (1) it was a 24-week study; (2) the subjects
were allocated randomly; (3) it was prospective; and (4) it
was the initial study with three large groups in Iran.

5. Conclusions

The results support safety and efficacy of both nicotine
replacement therapy (nicotine gum) and clonidine, but not
naltrexone, for quitting smoking for Iranian nicotine-depen-
dent individuals.

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