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Naltrexone Augments the Effects of Nicotine Replacement Therapy in Female Smokers

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Naltrexone Augments the Effects of Nicotine Replacement Therapy in Female Smokers

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ABSTRACT. Background. There is increased recognition that gender differences may influence outcomes and may modify vulnerability to tobacco addiction, severity of course and response to different treatments. We hypothesized that naltrexone, which has been used to successfully treat opioid and alcohol dependence, when combined with nicotine replacement therapy (NRT) and psychosocial therapy (PT) may enhance smoking cessation rates in women.

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Methods. Forty-four adult female smokers meeting DSM-IV criteria for nicotine dependence with expired carbon monoxide content of $\geq$ 15 ppm were randomly assigned in a double blind placebo controlled clinical trial of naltrexone 50 mg + NRT patch + psychosocial therapy (N + NRT + PT) (N = 12) or placebo + NRT patch + psychosocial therapy (P + N + PT) (N = 12) for 12 weeks.

Results. Twelve weeks of treatment was completed by 54.5%. Smoking cessation among females who completed the 12 weeks for N + NRT + PT was 91.7% (11/12) and for P + NRT + PT was 50% (6/12).

Conclusion. Naltrexone combined with NRT and psychosocial therapy appears to have a positive cessation effect on women and may be a new treatment option for recidivist female smokers. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress. com>*

KEYWORDS. Gender differences, smoking cessation, women, NRT

INTRODUCTION

Since 1980, 3 million women in the US alone have died from smoking-related causes.[1] While men have historically been much more likely to smoke than women, since the 1960s, male smoking rates have declined while those of women have remained constant.[1] In the general US population, fewer females than males currently smoke (23% vs. 27.1%); however, among adolescents aged 12 to 17, smoking is slightly more prevalent in females than males (13.6% vs. 12.3%).[2] Although many women worry more about breast cancer, lung cancer is now the leading cause of cancer death for both men and women.[1]

Although smoking is obviously unhealthy for everyone, female smokers face particular problems. Recent research indicates that female smokers are twice as likely to develop lung cancer as male smokers; women who smoke also face increased risks for cervical cancer and possibly osteoporosis.[3-6] Women who smoke and use oral contraceptives are more likely to experience serious cardiovascular conditions such as myocardial infarction and deep venous thrombosis.[7] On the positive side, women who quit smoking may experience greater improvements in lung function than their male counterparts.[8] Approximately 1 in 8 pregnant women report smoking cigarettes during the past month, an alarming statistic as women who smoke are more likely to experi-

ence serious obstetrical complications and poorer pregnancy outcomes, such as miscarriage, preterm delivery, intrauterine growth restriction, stillbirth, and neonatal death.[9,10]

Although smoking among women poses a significant public health problem, until recently most research has focused on male smokers. However, there is now increased recognition that gender differences may influence outcomes and may modify vulnerability to tobacco addiction, severity of course and response to different treatments. It is important to examine female smokers as a distinct group, and develop interventions targeted to them.

Male and female smokers do not engage in the same patterns of tobacco use, with female smokers less likely to smoke heavily.[11-13] Women may also tend to smoke cigarettes with lower nicotine content.[14] The ratio of former smokers to ever smokers, an indication of smoking cessation rates, is higher in men than in women (52% vs. 47%).[15] This disparity holds true across various age groups, as smoking prevalence curves within comparable birth cohorts show lower rates of quitting in women.[16] Although trends in U.S. smoking cessation over the past several decades show a decline in male smoking rates from 52% to 28%, female smoking has declined much less rapidly.[15]

Women tend to smoke for different reasons than men, with factors other than physical dependence on nicotine being more significant in female smokers than in males.[17,18] Women are more likely than men to smoke for stimulation, to help control their weight, to deal with negative affect, and to relax.[19-21] Smoking behavior and attitudes towards smoking of parents and friends, cigarette offers, other substance use, and family conflict exert a stronger influence on tobacco use in adolescent girls than in adolescent boys.[22] The subjective effects of nicotine may be more important in nicotine discrimination in women than in men, suggesting a gender difference in sensitivity to this reinforcing property.[23]

While about one-third of smokers attempt to quit each year, very few–only 2.5%–experience long-term success.[24] Unfortunately, there is no one single ideal treatment for the highly nicotine dependent patient. NRT alone has variable long-term success, ranging from 10% to 30%; the long-term success of non-nicotine pharmacological treatments ranges from 5%-35.5%.[25,26] Pharmacological treatments are increasingly being used to supplement behavioral therapy, which remains the core of any program; these combined approaches have higher cessation rates than any single method.[24] However, smoking cessation remains a clinical challenge, as the majority of quit attempts fail.

Female smokers appear even less likely to quit successfully than male smokers.[27] Women are three times less likely to succeed in an unaided quit attempt; they also achieve less success with transdermal nicotine replacement therapy (NRT).[19,28] Government interventions designed to reduce smoking, such as antismoking laws and cigarette taxes, are a less useful intervention in female than male smokers.[18] Smoking cessation programs and the drug buproprion may be equally efficacious in men and women.[14,29,30]

A mixture of biopsychosocial factors may contribute to the gender differences in response to smoking cessation interventions. Hormonal factors influence smoking cessation in women; females who quit during the follicular phase of the menstrual cycle may experience fewer withdrawal symptoms than women who quit in the luteal phase.[31] Attitudes towards smoking cessation differ between male and female smokers, and may impact the effectiveness of particular interventions. The thought of quitting may be more daunting for women than for men, as female smokers express less confidence in their ability to quit, and believe that quitting is more difficult than their male counterparts.[13,14] However, women who perceive quitting as less difficult may experience higher rates of relapse, an effect not seen in male smokers.[19] The degree of motivation to quit may play a more significant role in determining relapse in female than male smokers.[28] The cognitive and psychological factors underlying smoking maintenance in women may explain why smoking cessation programs improve quit rates for women more than other methods, but are no more or less effective than other methods for men.[14,29] Buproprion, an atypical antidepressant, is also particularly effective in female smokers, possibly because women are more likely to smoke for mood regulation.[30]

As compared to male smokers, female smokers experience more sensitivity to the subjective effects of smoking, with physical dependence playing a lesser role.[17,18] NRT targets physical dependence on nicotine, and not the subjective pleasurable effects of smoking, which may explain its lesser efficacy in female smokers. The importance of subjective reinforcing effects in female smoking maintenance suggests that blunting these effects with a drug such as naltrexone may improve smoking cessation rates in women.

The opioid antagonist naltrexone, long used in the treatment of alcohol and opioid dependence, is being investigated as a therapy for smoking cessation.[32-36] Early results from a placebo-controlled trial of naltrexone in smoking cessation indicate that the use of this medication, in conjunction with nicotine transdermal replacement, diminished the positive

subjective effects of smoking and improved the rate of abstinence at one month after quitting.[37] Another recent study has shown a gender-specific response to naltrexone in smoking cessation, with only female smokers benefiting significantly.[35]

Our current study investigates the hypothesis that naltrexone therapy, used in conjunction with nicotine replacement therapy (NRT) and psychosocial therapy (PT), will improve smoking cessation rates in female smokers.

METHODS

Design

This was a double-blind, placebo-controlled trial with random assignment to twelve weeks of treatment with either naltrexone 50 mg per day or placebo. Subjects in both groups received psychosocial therapy (PT) and Nicotine Replacement Therapy (NRT) transdermal patches for the duration of the study.

Sites

This study was conducted at the University of Florida (UF) Health Sciences Center. The project was reviewed and approved by the University of Florida Institutional Review Board IRB-01.

Subjects

Participants were recruited through advertisements and from our outpatient clinics. Informed consent was obtained prior to study entry. Inclusion criteria were that participants had to be between the ages of 18 and 65, able to read and able to provide informed consent, must currently want to attempt to quit smoking and must have had one or more unsuccessful quit attempts in the past. Other inclusion criteria included current diagnosis of nicotine dependence. Persons were excluded if they were unable to provide informed consent, if they were pregnant or nursing, if they had past allergic reaction to natrexone, if they were taking certain medications, if they had psychiatric disorders including major depression and alcohol or drug dependence and if they had a history of significant liver, renal, metabolic or gastrointestinal disease or can-

cer. They were also excluded if they were currently using other therapies to stop smoking. Additional exclusion criteria are listed in Table 1.

Baseline Measures

A complete smoking history was collected by questionnaires and the Fagerstrom Nicotine Dependence Questionnaire was used to assess level of dependence.[38]

Women of childbearing age were asked to take a pregnancy test and to use effective methods of contraception throughout the study. All subjects were screened for alcohol and drug dependence, and for depression and other psychiatric conditions. All participants had a medical exam and had their medical history reviewed by a physician to assess for possible exclusions.

Cessation of Smoking and Randomization

Study nurses provided individual counseling to participants prior to smoking cessation and at every visit. Participants were asked to set a quit date prior to randomization into the study. After enrollment, participants were randomized in double blind fashion.

Initiation of Drug Therapy

After randomization, bottles of study medications (naltrexone 50 mg or placebo) were dispensed in addition to NRT patches. Participants were instructed to take one tablet of study medication by mouth daily.

At each visit, a urine sample was collected and radioimmunoassy was used to determine urine cotinine levels. Cotinine levels were then con-

TABLE 1. Additional Exclusion Criteria

• current use of any form of opioid
• injection drug use within six months of treatment
• use of cigars, pipes or smokeless tobacco
• current use of nicotine replacement therapies, antidepressants, antipsychotics, clonidine, SSRIs, benzodiazapines, or lithium
• use of an antidepressant within 2 weeks of screening visit
• use of naltrexone or opioid antagonist within two months of screening visit
• positive urine drug screen for opioids

firmed by gas chromatography/mass spectroscopy. Exhaled carbon monoxide (CO) was also used as a measure of tobacco smoke exposure. Participants were asked to keep a diary which included the number of cigarettes smoked and ratings of their withdrawal symptoms.

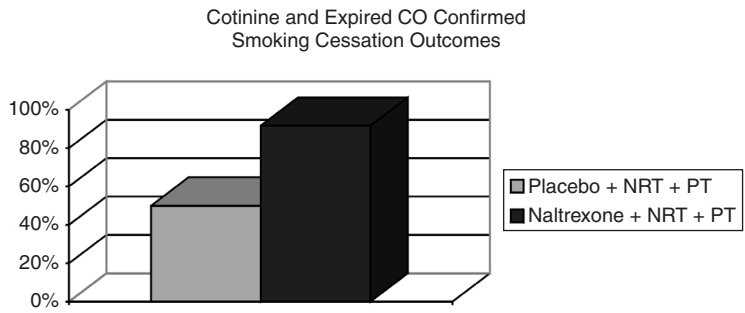
Analysis

As treatment compliance and retention are often correlated with successful outcome, we decided to focus on those who completed the study. Of the forty-four healthy adult female smokers meeting DSM-IV criteria for nicotine dependence with expired carbon monoxide content of $\geq$ 15 ppm that were randomly assigned in this double blind placebo controlled clinical trial of naltrexone 50 mg + NRT patch + psychosocial therapy (N + NRT + PT) or placebo + NRT patch + psychosocial therapy (P + N + PT), 54.5% completed the 12 weeks of treatment. Treatment retention did not differ by study group. Successful outcome was defined as continued abstinence from smoking. Smoking abstinence was confirmed by self reports, urine cotinine and expired CO. Between-group differences in treatment outcomes were analyzed using the exact unconditional test, as described by Suissa and Shuster.[39]

RESULTS

Of the forty-four women who were randomized, twelve women in each group completed the 12-week study. Treatment outcomes are presented in Figure 1.

FIGURE 1



Smoking cessation among females who completed the 12 weeks was 91.7% (11/12) for N + NRT + PT and was 50% (6/12) for P + NRT + PT. While naltrexone did not have an effect on treatment retention, it does appear to have a beneficial effect on smoking cessation in this population of female smokers ($p = .029$).

DISCUSSION

Naltrexone appears to increase cigarette abstinence rates in female smokers. Our results support the conclusions of Covey et al.; their study examined the efficacy of naltrexone as a smoking cessation aid in a double-blind placebo-controlled randomized trial and indicated the usefulness of naltrexone primarily for female smokers and those with a history of major depression.[35] As the beneficial effect of naltrexone is confined to women, the interaction between naltrexone and brain mechanisms involved in smoking maintenance and cessation may vary with gender.[35]

Although this study had a 49.5% noncompletion rate, the noncompleters were equally divided between the naltrexone and placebo groups, and the overall dropout rate is not out of line with the rates reported in other randomized clinical trials of therapies for smoking cessation. Two recently published, large-scale studies (N = 1818, N = 400) of nicotine replacement therapy reported dropout rates at 12 weeks of 72% and 45%, respectively.[40,41] As quitting smoking is notoriously difficult, even within the structured setting of a research study, it is not surprising that retention rates may be low.

Naltrexone is an opioid antagonist; it attenuates the effects of both exogenous and endogenous opioids primarily by acting on the mu-opioid receptor, the receptor most centrally involved in opioid reward, analgesia, tolerance, and dependence.[42] Naltrexone's ability to enhance smoking cessation rates are likely due to its antagonist properties, as the endogenous opioid system appears to mediate the reward mechanism of nicotine. Nicotine administration increases beta-endorphin release in both humans and animals, increases enkephalin and dynorphin release in animals, and produces pleasurable effects similar to those of opioid drugs, such as anxiolysis, increased pain tolerance, and muscle relaxation.[43] Thus naltrexone diminishes the positive subjective effects of smoking, a finding which not only supports the theory that endogenous opioids are involved in smoking reward, but which also suggests that such antagonists can play a role in smoking cessation treatment.[37,44]

Men and women respond to opioids in different ways. Many studies have demonstrated that women experience greater sensitivity to opioid receptor agonist drugs than do men. This gender difference in sensitivity has been found for a variety of drugs, including both kappa- and mu-opioid agonists. Women experience greater kappa-opioid analgesia and increased potency of the mu-opioid morphine, and self-administer less morphine during recovery from surgery.[45,46]

The different response to opioid drugs in men and women may be related to gender differences in the endogenous opioid system. A recent PET-imaging study examining the in vivo activity of exogenously administered mu-opioids in the human brain demonstrated higher mu-opioid binding in women; at least some of this effect may be hormonally mediated, as binding decreased significantly in post-menopausal women.[47] Another brain-imaging study found that, in response to an equivalent pain challenge, the endogenous mu-opioid system is more active in men than in women during the follicular phase of the menstrual cycle.[48] Women have also been shown to have lower beta-endorphin plasma concentrations, possibly due to the influence of ovarian steroid hormones.[49]

Given these gender differences, the opioid response stimulated by nicotine may play a greater role in smoking reward for women than for men. Since women have lower basal concentrations of beta-endorphin than men, female smokers may experience the boost in this chemical provided by nicotine more strongly than male smokers. Also, women appear to be more sensitive to the effects of opioids than men, so the low dose provided by nicotine may produce more psychoactive effects in women than men.

Gender differences in sensitivity to the opioid effects produced by nicotine may explain why the subjective effects of smoking play a more important role in smoking maintenance in women than in men, and why NRT is less successful in female smokers. If women do experience greater opioid-mediated reward, opioid antagonist drugs such as naltrexone represent a logical addition to smoking cessation therapies targeted towards women.

CONCLUSIONS

Consistent with treatment data reported for other addictions, treatment compliance and retention correlated with successful outcome. N + NRT + PT appears to have a positive cessation effect on women. These

data support previously reported findings that naltrexone may have beneficial effects in female smokers.[35] In general, women appear to have less success in smoking cessation than men, indicating the need for treatments targeted to female smokers. Women and men may smoke for different reasons, with physiological dependence on nicotine more important for men, and the subjective effects of smoking more important for women. These gender differences may be due to differences in the brain's endogenous opioid system, which is activated by nicotine. Adding naltrexone, an opioid antagonist, to NRT and psychosocial therapy may be a new treatment option for recidivist female smokers.

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