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Low-dose naltrexone augmentation of nicotine replacement for smoking cessation with reduced weight gain: A randomized trial☆

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ABSTRACT

Background: Fear of weight gain is a significant obstacle to smoking cessation, preventing some smokers from attempting to quit. Several previous studies of naltrexone yielded promising results for minimization of post-quit weight gain. Given these encouraging findings, we endeavored to test whether minimization of weight gain might translate to better quit outcomes for a population that is particularly concerned about gaining weight upon quitting.

Methods: Smokers ($N = 172$) in this investigation were prospectively randomized to receive either 25 mg naltrexone or placebo for 27 weeks (1 week pre-, 26 weeks post-quit) for minimization of post-quit weight gain and smoking cessation. All participants received open label therapy with the nicotine patch for the first 8 weeks post-quit and behavioral counseling over the 27-week treatment. The 2 pre-specified primary outcomes were change in weight for continuously abstinent participants and biologically verified end-of-treatment 7-day point-prevalence abstinence at 26 weeks after the quit date.

Results: The difference in weight at 26 weeks post-quit between the naltrexone and placebo groups (naltrexone: 6.8 lbs ± 8.94 vs placebo: 9.7 lbs ± 9.19, $p = 0.45$) was not statistically different. Seven-day point-prevalence smoking abstinence rates at 26 weeks post-quit was not significantly different between the 2 groups (naltrexone: 22% vs placebo: 27%, $p = 0.43$).

Conclusions: For smokers high in weight concern, the relatively small reduction in weight gain with low-dose naltrexone is not worth the potential for somewhat lower rates of smoking abstinence.

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1. Introduction

Fear of weight gain is a significant obstacle to smoking cessation, preventing some smokers from attempting to quit (Pomerleau et al., 2001). The effects of pharmacotherapy on minimizing post-quit weight gain have been mixed (Fiore et al., 2008). For instance, nicotine replacement therapy (NRT) is fairly effective in enhancing smoking cessation success rates (Silagy et al., 2004). However, transdermal nicotine therapy does not reduce hunger or weight gain significantly (Abelin et al., 1989b; Cooper et al., 2005; Rose et al., 1990). The effects of nicotine gum on delaying weight gain are stronger than nicotine patch, but the size of this difference, although significant, is modest (Doherty et al., 1996). Sustained-release (SR) bupropion hydrochloride has proven effective in increasing smoking cessation success rates (Ahluwalia et al., 2002; Hurt et al., 1997; Jorenby et al., 1999; Swan et al., 2003), and this treatment is moderately successful in helping participants reduce weight gain upon quitting. Varenicline is also an efficacious smoking cessation medication, but it does not significantly reduce post-quit weight gain (Gonzales et al., 2006; Jorenby et al., 2006). Thus, current pharmacological treatments for smoking cessation are modestly successful in assisting smokers to quit, but only nicotine gum and bupropion significantly attenuate post-cessation weight gain. A medication associated with less weight gain upon quitting could address one of the most important barriers to smoking cessation (Ahluwalia et al., 2002; Hurt et al., 1997).

Clearly, further research is needed to develop medications that address concern about gaining weight after smoking cessation (Pomerleau et al., 2001). Not only does concern about weight gain prevent smokers from trying to quit, weight-concerned smokers may also be less successful in achieving abstinence from smoking because the effort required to control food intake may undermine efforts to avoid smoking (Hall et al., 1986). In fact, attempts to integrate weight control and smoking cessation efforts have sometimes

☆ A CONSORT checklist is available as supplementary material with the online version of this article.

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resulted in poorer smoking cessation outcomes (Hall et al., 1992). Thus, a successful intervention that minimizes post-quit weight gain may be attractive to people who are reluctant to quit or find it difficult to maintain abstinence due to weight gain.

Naltrexone hydrochloride is a medication that has shown promise in reducing post-cessation weight gain and may therefore address weight concerns (King et al., 2006; Krishnan-Sarin et al., 2003; O'Malley et al., 2006; Toll et al., 2008). Several reasons have been suggested for why naltrexone may be effective in minimizing post-quit weight gain. Animal models have implicated opioid antagonists in decreased body weight and food intake (Bodnar et al., 2003), and μ opioid receptor knockout mice have shown resistance to obesity (Tabarin et al., 2005).

Several randomized controlled studies have shown that naltrexone significantly reduces post-quit weight gain. A small preliminary study in 32 smokers found that naltrexone in combination with nicotine patch suppressed weight gain compared to placebo alone (Krishnan-Sarin et al., 2003). Subsequently, King et al. (2006) conducted an 8-week placebo-controlled study of naltrexone (50 mg/day) combined with the nicotine patch with 110 subjects and found that participants in the naltrexone group gained significantly less weight (1.5 pounds) as compared to those in the placebo + nicotine patch group (4.2 pounds). The largest clinical trial conducted to date was a dose ranging study of naltrexone (placebo, 25 mg, 50 mg, or 100 mg – taken daily) in combination with transdermal nicotine patch in 400 participants (O'Malley et al., 2006). The highest dose showed promise for promoting smoking abstinence, but effects on weight were not significant. In contrast, low-dose (25 mg/day) naltrexone significantly reduced post-cessation weight gain over 6 weeks, with participants showing an average weight gain of 1.5 pounds on this dose compared to 4.2 pounds for those taking placebo, although it did not increase smoking abstinence. Based on the weight gain findings, Toll et al. (2008) treated 20 weight-concerned smokers combining 25 mg naltrexone with 300 mg bupropion SR, and showed that continuously abstinent participants in the naltrexone + bupropion group gained less weight (1.67 pounds) than those in a matched group of patients who received bupropion only (3.17 pounds; $p = 0.35$; Cohen's $d = 0.56$) (Toll et al., 2008). Consistent with these findings, a recent review concluded that naltrexone showed promise as a potential drug treatment for preventing post smoking cessation weight gain (Parsons et al., 2009).

Although naltrexone appears to reduce weight gain after quitting, effects on smoking cessation have been inconclusive. Several studies showed that naltrexone did not help participants quit smoking or were mixed (Ahmadi et al., 2003; King et al., 2006; Toll et al., 2008; Wong et al., 1999), whereas other studies showed that naltrexone may be beneficial for smoking cessation (Covey et al., 1999; Krishnan-Sarin et al., 2003; O'Malley et al., 2006). Only the small pilot study by Toll et al. (2008) selected weight-concerned smokers. Prior studies tested short-term treatment from 4 to 8 weeks; whereas most smokers continue to gain weight over the first 6-months following smoking cessation (Hall et al., 1986; Klesges et al., 1997; Pirie et al., 1992).

In the present study, we tested the hypothesis that minimization of weight gain with low-dose naltrexone might translate to better quit outcomes for a population of weight-concerned smokers who believe that smoking helps control their weight. The study design was a double-blind placebo-controlled trial of 25 mg of naltrexone or placebo administered for 1 week pre-quit and for 26 weeks post-quit, the major period of risk for weight gain following smoking cessation. In addition, all subjects received transdermal nicotine replacement for 8 weeks following their quit date and brief smoking cessation counseling throughout the entire treatment period. We hypothesized that participants who received naltrexone would report higher rates of abstinence from cigarette smoking and lower post-quit weight gain compared to participants who received placebo.

2. Methods

2.1. Participants

One hundred seventy-two cigarette smokers were enrolled. Recruitment was via advertisements placed in local media outlets, mailings (to past participants, potential participants, and health care professionals), fliers, fax referrals from healthcare providers, press releases, and websites.

To be eligible, all smokers needed to be classified as weight-concerned smokers based on 2 criteria. Concern about gaining weight after quitting was assessed using the questions Perkins et al. (2001) used to define weight concern in their clinical trial of CBT. These included "How concerned are you about gaining weight after quitting?" and "How concerned would you be if quitting smoking caused you to permanently gain 10 lbs?" Consistent with their criteria, a rating of 50 or higher on a 100 mm scale on either question qualified the subject on this criterion. Smoking to manage weight was assessed with the weight control subscale of the Smoking Consequences Questionnaire [SCQ] (Copeland et al., 1995) on which participants rate their expectations about the consequences of smoking a cigarette on a scale of 0-9 with 1 being "completely unlikely" and 9 being "completely likely". Five items make up this subscale (alpha = 0.96) and include "smoking keeps my weight down", "cigarettes keep me from eating more than I should", "smoking helps me control my weight', "cigarettes keep me from overeating", and "smoking controls my appetite". A mean rating of 6 or above ("somewhat likely") qualified participants on this criterion.

Other inclusion and exclusion criteria were age 18 and older, willingness and ability to give written consent, smoking greater than 10 cigarettes per day for at least 1 year, at least 1 prior attempt to stop smoking, baseline expired carbon monoxide (CO) level of at least 10 ppm, weight of at least 100 lbs, English speaking, and only 1 participant per household. Exclusion criteria included pregnant or nursing women or women attempting to conceive, unstable cardiac disease, history of dermatoses, current alcohol or drug dependence other than nicotine dependence, serious current neurologic, psychiatric, suicidal risk or medical illness, chronic pain conditions necessitating opioid treatment, history of cirrhosis or of significant hepatocellular injury, current use of smokeless tobacco, pipes, cigars, nicotine gum, patch, lozenge, inhaler, or nasal spray, patients requiring concomitant therapy with any psychotropic drug or on any drug with a psychotropic component [except those who were on a stable dose of an Selective Serotonin Reuptake Inhibitor for at least 2 months for the indications of Major Depressive Disorder, Premenstrual Syndrome or Premenstrual Dysphoric Disorder], subjects with a positive opioid urine drug screen, current use of opioids, or currently on a medically prescribed diet. The institutional review board of the Yale University School of Medicine approved this study.

2.2. Procedures

Following written informed consent, patients completed baseline assessments, a physical examination, and laboratory testing. Eligible participants were randomized to conditions, with blocked stratified (for gender) randomization due to the fact that weight-concerned samples are usually mostly female (Perkins et al., 2001). Random sequence was provided by one of the authors (RW) to the pharmacist who assigned participants; all others were blind to treatment assignment. All participants were seen at a community mental health center. Participants were randomized between February 3, 2005 and September 25, 2008, and the last treatment appointment was completed on April 27, 2009.

2.3. Medication conditions

Participants received placebo or 25-mg naltrexone daily beginning the week before quitting. Naltrexone (Depade, Mallinckrodt Pharmaceuticals) was titrated for the first 2 days (i.e., 12.5-mg for 1 day, then 25-mg thereafter) then taken for a total of 27 weeks (1 week pre- and 26 weeks post-quit). Naltrexone medication in opaque capsules was dispensed in bottles, with the first dose in an individual glassine envelope within the bottle. Participants received 21 mg transdermal nicotine patches (Nicoderm CQ, GlaxoSmithKline) for 6 weeks, then 14 mg patches for 2 weeks, beginning on their quit date. Participants were instructed to take their naltrexone and replace their patch at the same time. Based on tolerability, dose reductions or discontinuation were permitted with the option to continue the nicotine patch and counseling.

2.4. Counseling

The counseling was adapted from the cognitive-behavioral therapy (CBT) protocol for weight-concerned smokers created by Perkins et al. (2001) and the treatment manual was developed in collaboration with Dr. Michele Levine, who assisted in implementation and development of the source CBT protocol. The first session with the nurse lasted 45 min and subsequent weekly sessions with a research assistant supervised by an investigator (BAT) lasted 5–15 min, with longer sessions occurring in earlier meetings. Counseling occurred weekly for the first 4 weeks, bi-weekly twice, then monthly. Handouts described the benefits of quitting smoking and

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