Naltrexone Reduction of Long-Term Smoking Cessation Weight Gain in Women But Not Men: A Randomized Controlled Trial

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Background: The opioid antagonist naltrexone has shown promise to reduce weight gain during active treatment, but longer-term studies have not been conducted. The goal was to examine effects of naltrexone on weight gain over long-term follow-up in men and women who quit smoking.

Methods: Weight was examined at baseline and 6- and 12-month follow-up in the two largest randomized, double-blind, placebo-controlled trials of naltrexone in nicotine dependence. For 6–12 weeks after the quit date, participants were randomly assigned to receive naltrexone or placebo. Behavioral counseling and open-label nicotine patch were also included for the first 4–6 weeks. Of the 700 participants in the combined intent-to-treat sample, there were 159 (77 women) biochemically verified abstinent smokers at 6 months, and 115 (57 women) of them remained abstinent at 12 months. Changes in weight (in kilograms or in percentage) and body mass index from baseline to the follow-ups were assessed for these participants.

Results: Weight gain was significantly lower for women treated with naltrexone compared with placebo (6 months, 3.3 vs. 5.5 kg; 12 months, 5.9 vs. 7.4 kg, respectively). Increases in body mass index and percentage body weight gain were also significantly lower in women treated with naltrexone versus placebo. These effects were not observed in men.

Conclusion: The results provide evidence for naltrexone as the first pharmacotherapy to reduce postsmoking cessation weight gain among women.

Key Words: Naltrexone, nicotine dependence, opioid antagonist, sex differences, smoking cessation, weight gain

Most adults in the US currently are either overweight (34.4%) or obese (33.8%), and rates continue to increase steadily (1). Obesity is second only to tobacco use as the leading cause of preventable death in our country (2). Ironically, the most common adverse effect of smoking cessation is weight gain, which is observed in more than 80% of persons who are successful in quitting smoking (3). The average weight gain 6 months after the quit date is usually between 2.3 and 4.5 kg (4), but a sizeable portion of smoking abstainers (10%–25%) gain more than 6.8 kg (5). On average, women gain more weight than men (5) and experience greater concern and distress about gaining weight (6), which might deter them from attempting or continuing with a quit attempt (7).

To date, numerous approaches have been examined for reducing weight gain in the treatment of tobacco dependence. The recent 2012 Cochrane Report evaluating interventions to prevent weight gain after smoking cessation concluded that, although some exercise behavioral management strategies and approved pharmacotherapy approaches such as varenicline, nicotine gum, and bupropion might delay weight gain, none were effective 6 or more months after cessation or evidence was insufficient to support them for clinical recommendations in prevention of cessation weight gain (4).

Of the novel pharmacological treatments studied thus far to reduce postcessation weight gain, the Cochrane Report concluded that the most promising results have been obtained with the μ opioid receptor antagonist naltrexone. However, they noted that evidence was lacking on long-term weight gain effects of naltrexone after the medication is stopped. During treatment intervals ranging from 4 to 12 weeks, naltrexone has been shown to significantly reduce weight gain on average by 1 to 1.5 kg relative to placebo (8–11), and effects might be stronger in women compared with men (9,12). The only published study of longer-term weight gain examined low-dose naltrexone (25 mgdaily) for 6 months in weight-concerned smokers; results showed that naltrexone reduced weight gain (3.1 vs. 4.4 kg with placebo), but this difference was not statistically significant (13). This might have been due to the recruitment of a particularly treatment-resistant smoker subgroup with little tolerance for weight gain, high attrition with only 34% completing treatment, and the low dosage, which might not have produced adequate inhibition of μ opioid receptors, as has been shown with 50 mg (14).

The mechanisms underlying weight gain post cessation in smokers are complex but most likely the result of heightened food reward (15) and increased intake of palatable food with high sugar and fat content (16), because changes in metabolic rate likely play a lesser role (17). The endogenous opioid system might represent a good biological target, because it is involved in food hedonics and eating behaviors (18–20). A competitive opioid antagonist such as naltrexone might affect opioidergic pathways and their connections to midbrain dopamine circuitries involved in the motivational and hedonic aspects of feeding behavior (21,22). Effects of naltrexone on weight gain over time is plausible even after the drug is discontinued, because greater food reward

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and high calorie food intake during the first few weeks of cessation predict longer-term weight gain, particularly in women (16). Alteration of opioid-mediated neurobiological processes involved in excess calorie intake during this early period might be crucial in reducing weight gain over time.

The purpose of this study was to compare weight gain at 6- and 12-month follow-up in women and men smoking abstainers who were randomized to naltrexone or placebo for up to 3 months of smoking cessation treatment. Participants were extracted from a combined sample of the two largest randomized, placebo-controlled clinical trials to date examining the efficacy of naltrexone (9,11). Briefly, both studies showed some support for naltrexone to increase quit rates and reduce smoking urge during acute treatment of 6–12 weeks (9,11). Both studies also demonstrated that naltrexone reduced weight gain during active treatment. Less than one-quarter of the participants in either study remained biochemically confirmed as abstinent at the follow-ups, as observed in most smoking cessation trials (23). Therefore, analysis of the longer-term effects of naltrexone on weight gain, particularly examination of potential sex differences in this response, was not possible in the individual trials. By combining these studies, we herein provide the first examination of naltrexone on long-term cessation weight gain. Abstainers were the primary focus to avoid heterogeneity with nonabstainers who usually do not gain weight or lose the weight they had gained during initial abstinence (4). We predicted that naltrexone compared with placebo would significantly reduce the amount of weight gained as well as the increase in body mass index (BMI), percentage increase in body weight, and incidence of clinically significant weight gain defined as 7% baseline body weight gain. This latter criterion is reported as an adverse event in product labeling approved by the U.S. Food and Drug Administration and is a widely used index for measuring unwanted weight gain from use of psychiatric medications (24–26). We also predicted that these effects would be more pronounced in women than in men.

Methods and Materials

Participants

Participants were extracted from the two randomized, placebo-controlled clinical trials examining the efficacy of naltrexone in general adult smokers seeking treatment for nicotine dependence at the University of Chicago (9) and Yale University (11). The total intent-to-treat sample included 700 smokers, with 315 participants from the Chicago sample and 385 participants from the Yale sample (consort diagram in Supplement 1). At 6-month follow-up, there were 159 smokers (22.7%) who reported being smoke-free over the past 7 days and provided biochemical verification (i.e., ≤10 ppm on an expired air carbon monoxide breath test). These included 82 participants from Chicago (40 in the placebo group, 42 in the naltrexone group [dose: 50 mg]) and 77 participants from Yale (20 in the placebo group, and 57 in the naltrexone group [25 mg, 20 participants; 50 mg, 15 participants; 100 mg, 22 participants]). There were 115 smokers (72% of the 6-month abstainers) who remained biochemically confirmed as abstinent at the 12-month follow-up, with 58 from Chicago (33 placebo, 25 naltrexone) and 57 from Yale (15 placebo, 42 naltrexone group [25 mg, 11 participants; 50 mg, 11 participants; 100 mg, 20 participants]).

Participants were enrolled in the trials from July 2006 to March 2008 (Chicago) and November 2000 to April 2003 (Yale). Recruitment methods were similar between sites and included advertisements by the Internet, radio, and print media as well as posting of flyers and word-of-mouth referrals. At screening, eligible candidates provided informed consent and signed the consent form approved by the institutional review boards at either the University of Chicago or Yale University. Participants all received comprehensive physical and psychological assessment for study inclusion examination (for details, see [9,11]). Eligibility criteria were: age between 18 and 75 years, cigarette smoker of at least 12 cigarettes daily for a minimum of 1 year, fluency in English, stable residence, and desire to quit smoking. Candidates were excluded if they had a past-year history of a major medical or psychiatric disorder, substance dependence (except nicotine), a lifetime diagnosis of opioid abuse or dependence; use of opioid or psychotropic medications; elevated hepatic transaminase concentrations (>2.5× normal range); or, for women, were nursing or pregnant. The only differences in recruitment for these studies were minimum smoking threshold (12 cigarettes/day Chicago vs. 20 Yale) and targeting of minorities (27) (35% African Americans Chicago vs. 7% Yale).

Procedures

The two studies were similar in general procedures, including a double-blinded design, randomization to naltrexone hydrochloride (Mallinckrodt Pharmaceuticals, St. Louis, Missouri) or placebo, and inclusion of standard smoking cessation treatment platform with open-label transdermal nicotine patch (Nicoderm CQ; GlaxoSmithKline, Brentford, Middlesex, United Kingdom) and behavioral counseling. The main differences between studies involved medication dosing and length of treatment. All naltrexone-randomized participants in the Chicago study received 50 mg as the dose for 12 weeks compared with naltrexone randomization to 25-, 50-, or 100-mg doses for 6 weeks at Yale. Participants in the Chicago study took the nicotine patch at 21 mg daily for the first 2 weeks after the quit date, followed by 14 mg during the third week, and 7 mg during the fourth week, compared with 21 mg daily for the 6 weeks at Yale. Finally, behavioral counseling included six 45-min sessions ending at 4 weeks after the quit date at Chicago compared with a 45-min initial session and then five 15-min sessions ending at 6 weeks at Yale. As with most stop-smoking behavioral counseling treatments, the interventions focused mainly on smoking cessation techniques with the inclusion of a brief module to address potential weight gain.

At the first study visit, which was 1 week before the quit date, height and weight were measured on all participants. Also at baseline, participants were administered a Timeline Followback (28) interview to assess past-month cigarette smoking. At follow-up 6 and 12 months after the quit date, participants completed a telephone-delivered Timeline Followback interview and, if they had a 7-day point prevalence of smoking abstinence, were scheduled for an in-person visit to provide a breath test to assure carbon monoxide ≤10 ppm and have weight measured. For weight measurement, participants at both sites were asked to first remove their shoes and coat, as appropriate. Weight was measured by a calibrated digital (Chicago) or beam scale (Yale). Participants were conservatively classified as relapsed if they did not participate in follow-up or provide biochemical confirmation, and therefore they were not included. Percentage increase in body weight was calculated for each follow-up interval, and BMI was calculated as weight divided by height (in kg/m^2), with baseline height used in all calculations, because height changes over time were assumed to be negligible.