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An open-label study of naltrexone and bupropion combination therapy for smoking cessation in overweight and obese subjects

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ABSTRACT

A combination of sustained release (SR) naltrexone (32 mg/day) and bupropion SR (360 mg/day) plus behavioral counseling was evaluated for the treatment of smoking cessation and mitigation of nicotine withdrawal and weight gain. Thirty overweight or obese nicotine-dependent subjects were enrolled in a 24-week, open-label study; 85% and 63% completed 12 and 24 weeks, respectively. The target quit date was Week 4. Week 4–12 continuous abstinence rate was 48%, 78% of subjects achieved CO ≤ 10 ppm, serum cotinine decreased from 185 to 48 μg/L, and tobacco use decreased from 129 to 14 cigarettes/week. Similar results were seen at Week 24. Body weight was essentially unchanged (Week 12: −0.1%; Week 24: +0.4%). Except for a transient significant increase 1 week after the target quit date ($p<0.05$), nicotine withdrawal scores did not change. The most common adverse events were nausea, insomnia, and constipation. These tended to be transient and mild or moderate in severity. In overweight or obese smokers, naltrexone/bupropion combination therapy with behavioral counseling was associated with decreased nicotine use, limited nicotine withdrawal symptoms, and no significant weight gain.

1. Introduction

In 2006, 45.3 million adults were active cigarette smokers in the U.S. (CDC, 2007). Cigarette smoking is the country's leading preventable cause of premature death, with approximately 50% of all long-term smokers dying prematurely as a result of the adverse effects of their habit. Smoking increases the risk of cancer, respiratory problems, and cardiovascular disease, and the risks of morbidity and mortality are directly proportional to the number of cigarettes smoked (CDC, 2007; Lloyd-Jones et al., 2009). Smoking-related financial costs in the U.S. are estimated to be $167 billion annually as a result of lost productivity and healthcare expenditures (CDC, 2007). Thus, tobacco smoking is widespread, causes significant health issues, and is costly to both employers and healthcare management operations.

Smoking cessation reduces premature deaths and improves prognosis and quality of life (CDC, 2007), however nicotine withdrawal syndrome and weight gain are common deterrents to smoking cessation, and post-cessation weight gain has been associated with relapse (Galanti, 2008; Parsons, Shraim, Inglis, Aveyard, & Hajek, 2009). Smoking cessation is associated with 2–3 kg weight gain at 12 weeks and 4–6 kg weight gain at one year (Parsons et al., 2009). Three pharmacological options are currently approved for smoking cessation in the U.S.: nicotine replacement therapy (NRT: gum, patch, and inhaler), bupropion, and varenicline. Of these, varenicline is the most effective for smoking cessation, followed by bupropion and NRT (Eisenberg et al., 2008). However, these therapies do little to reduce the weight gain that usually accompanies smoking cessation. Bupropion reduces post-cessation weight gain by 0.8 kg, NRT by 0.5 kg, and there is no consistent evidence that varenicline reduces weight gain compared with placebo (Parsons et al., 2009). Consequently, efficacious smoking cessation therapies that do not result in weight gain are needed.

Naltrexone is an opioid antagonist indicated for the treatment of alcohol and opioid dependence. There is conflicting evidence for the effectiveness of naltrexone monotherapy for smoking cessation (David, Lancaster, Stead, & Evins, 2006), however naltrexone increases the effect of NRT on nicotine craving and has also been shown to attenuate post-cessation weight gain (O'Malley et al., 2006). In a small, short-term (7-week), open-label study in non-obese adults, naltrexone/bupropion combination therapy produced smoking cessation rates similar to

Abbreviations: BMI, body mass index; NRT, nicotine replacement therapy; SR, sustained release.

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bupropion, but there was a trend for less weight gain with the combination than with bupropion alone (Toll, Leary, Wu, Salovey, Meandzija, & O'Malley, 2008). In two Phase 2 weight loss studies in overweight and obese adults, naltrexone in combination with bupropion significantly reduced body weight compared with placebo and monotherapy (Greenway, Whitehouse et al., 2009; Greenway, Dunayevitch et al., 2009). Since both smoking and obesity are associated with increased mortality (Whitlock, et al., 2009), the present clinical trial was designed to evaluate naltrexone/bupropion combination therapy on smoking cessation and body weight in overweight or obese smokers.

2. Materials and methods

2.1. Study design

This was an exploratory, 24-week, open-label clinical trial conducted at 3 study sites. An overview of the study design is shown in Fig. 1. The study protocol was approved by the local institutional review board, and each subject provided written informed consent. Implementation of the study was consistent with Good Clinical Practice standards and the Declaration of Helsinki.

2.2. Interventions

The study medication was a combined formulation of naltrexone SR (8 mg)/bupropion SR (90 mg), with final daily doses of 32 mg/day naltrexone SR and 360 mg/day bupropion SR. Study drug was to be taken with food as follows: 1 tablet in the morning during Week 1, 1 tablet in the morning and 1 tablet in the evening during Week 2, 2 tablets in morning and 1 tablet in evening during Week 3, and 2 tablets BID thereafter. Doses of study medications were selected based on previous clinical experience (Anderson et al., 2002; Croghan et al., 2007; Gadde et al., 2001; Greenway, Whitehouse et al., 2009; Hurt et al., 1997; Jain et al., 2002; O'Malley et al., 2006; Simon, Duncan, Carmody, & Hudes, 2004; Tonnesen et al., 2003; Tonstad et al., 2003). Ancillary therapy beginning on Day 1 included exercise instruction and participation in the Mayo Clinic's "Smoke Free and Living It" program administered at regular intervals during the study (Mayo Clinic, 2000). Beginning at Week 12, subjects were instructed to follow a hypocaloric diet (500 kcal/day deficit). The target quit date was the morning of the Week 4 visit.

2.3. Study population

Thirty subjects were enrolled and 27 subjects had at least one post-baseline evaluation (Fig. 2). Inclusion criteria were: 18 to 65 years of age; a body mass index (BMI) $\geq$27 and $\leq$45 kg/m^2; smoking an average of $\geq$10 cigarettes/day in the preceding year with <3 months of total abstinence; an expired CO concentration >10 ppm; self-reported motivation to stop smoking of $\geq$7 on a scale of 1 to 10, with 10 defined as highest motivation; at least moderate concern about gaining weight after quitting smoking (on a scale of 1–10 where a score of 5 indicates moderate concern and weight gain is defined as at least 10 lbs); systolic blood pressure $\leq$140 mmHg; diastolic blood pressure $\leq$90 mmHg (a stable regimen of antihypertensive medications was allowed with the exception of α-adrenergic blockers and clonidine); triglycerides <400 mg/dL (a stable regimen of medications for dyslipidemia was allowed); no clinically significant laboratory or electrocardiogram findings; Inventory of Depressive Symptomatology — Subject Rated (IDS-SR) scores <2 on items 5 (sadness), 6 (irritability), 7 (anxiety/tension) and 18 (suicidality), with an IDS-SR total score at screening and baseline <30 (Rush, Carmody, & Reimitz, 2000). Female subjects of child bearing potential were not pregnant or lactating and agreed to use effective contraception throughout the study period and 30 days after discontinuation of study drug. Exclusion criteria included: a history of treatment with bupropion or naltrexone within the previous 12 months; weight loss or gain >4 kg within the previous 3 months; surgical intervention for obesity; obesity of known endocrine origin; smoking of non-tobacco cigarettes or consumption of other forms of tobacco more than three times within the previous 3 months; a previous smoking quit-attempt of more than 1 day within the previous 3 months; participation in behavioral or motivational counseling, therapy or support group to assist smoking cessation on more than 3 days within the previous month; serious medical conditions or psychiatric illness; a history of drug or alcohol abuse or dependence (except nicotine dependence). Excluded concomitant medications included any psychotropic agents with the exception of low dose benzodiazepine or hypnotic sleep aids; any anorectic or weight loss agents; any over-the-counter dietary supplements or herbs with psychoactive, appetite or weight effects; alpha-adrenergic blockers; dopamine agonists; clonidine; coumadin; theophylline; cimetidine; oral corticosteroids; cholestyramine, cholesterol; any smoking cessation agents; and regular use of opioid or opioid-like medications.

2.4. Study endpoints

The primary endpoint was the rate of smoking cessation as defined by subject-reported continuous abstinence during Weeks 4–12. Secondary endpoints were: rate of smoking cessation as defined by subject-reported continuous abstinence during Weeks 4–24; changes from baseline (Day 1 of study) in serum cotinine levels, expired CO, and percent change from baseline in body weight; rate of smoking cessation as measured by expired CO <10 ppm; tobacco use as measured by a

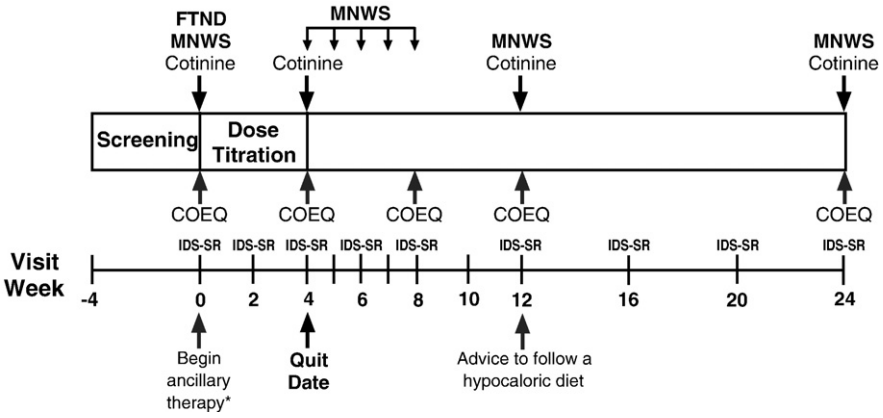

Fig. 1. Study design showing study assessments and interventions. Expired CO, body weight, and vital signs were measured at each visit. *Ancillary therapy: The Mayo Clinic's "Smoke Free and Living It" program, was begun at baseline and continued at every visit through Week 24. Subjects were also given an exercise prescription and dietary behavioral modification advice at baseline. At Week 12, subjects were counseled to follow a hypocaloric diet. MNWS, Hughes and Hatsukami Minnesota Nicotine Withdrawal Scale. COEQ, Control of Eating Questionnaire. IDS-SR, Inventory of Depressive Symptomatology — Subject Rated.