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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

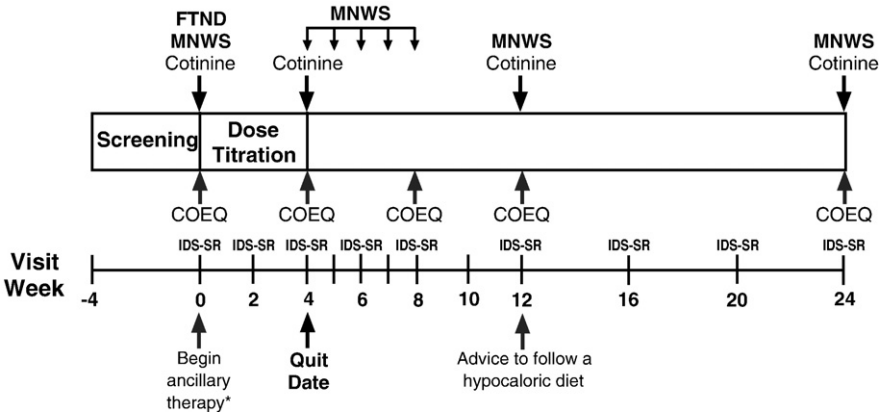

Fig. 1. Study design showing study assessments and interventions. Expired CO, body weight, and vital signs were measured at each visit. *Ancillary therapy: The Mayo Clinic's "Smoke Free and Living It" program, was begun at baseline and continued at every visit through Week 24. Subjects were also given 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.

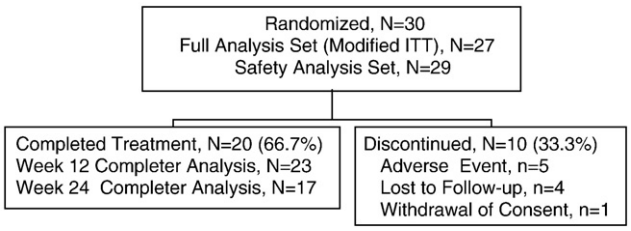

Fig. 2. Subject disposition.

tobacco use diary; change from baseline in nicotine withdrawal and craving measured by the Hughes and Hatsukami Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes & Hatsukami, 1986); effects of smoking cessation and treatment on mood and depressive symptoms measured by the IDS-SR; and changes from baseline in food craving measured by the Control of Eating questionnaire (COEQ) at 12 and 24 weeks; as well as evaluation of safety and tolerability.

2.5. Questionnaires

The Fagerström Test for Nicotine Dependence (FTND) is an 8-item subject-rated instrument A total score ≥7 indicates high nicotine dependence. The MNWS is a subject-rated instrument used to assess symptoms of nicotine withdrawal. This instrument consists of 15 items that are rated from 0 (none) to 4 (severe). The total score is the sum of the 15 items and ranges from 0 to 60. High total scores indicate greater withdrawal symptoms. To facilitate comparison with recent studies on pharmacological smoking cessation aids (Gonzales et al., 2006; Jorenby et al., 2006), post hoc analyses for nicotine craving and appetite were assessed with the "Desire or craving to smoke" and "Increased appetite, hungry, weight gain" items of the MNWS.

The Control of Eating Questionnaire (COEQ) is a 21-item questionnaire based on the Food Craving Record (Hill, Rogers, & Blundell, 1995) (Hill personal communication). It consists of a series of 100 mm visual analog scales that assess hunger, fullness, desire to eat different types of food, mood and alertness, food cravings, and ability to resist urges to eat. It is set within the context of hunger motivation and mood because these factors are known to influence craving. The COEQ is not a traditional questionnaire, in that items are not averaged to yield a single score. Rather, it captures features across several dimensions of eating control. Research using the COEQ in this form has not been previously published.

The IDS-SR is a subject-rated instrument used to assess the severity of depressive symptoms. This instrument consists of 30 items that are rated on a 4-point scale (0 to 3) (Rush et al., 2000). Higher scores indicate greater severity of depressive symptoms. The IDS-SR was scored by summing responses to 28 of the 30 items to obtain a total score ranging from 0 to 84. Higher scores indicated greater severity of depressive symptoms.

2.6. Safety and tolerability

Safety assessments included incidence and severity of treatment-emergent adverse events. Other safety parameters included evaluation of concomitant medications, physical examination findings, vital signs, electrocardiograms, and clinical laboratory measures.

2.7. Statistical analysis

The full analysis cohort (modified intent-to-treat [ITT] population) included all subjects who received study drug, had a baseline measurement, and had at least one post-baseline measurement while continuing on study drug ($N=27$; Fig. 2). Safety and tolerability were analyzed for all subjects who were administered at least one tablet of study drug and had at least one investigator assessment at any time after the start of study treatment, regardless of whether or not they discontinued the study ($N=29$). The completer cohort included all subjects who continued on study drug to Week 12 or 24 and who had a baseline measurement and a post-baseline measurement at Week 12 or 24 while on study drug ±1 day from clinic visit ($N=23$ and 17, respectively).

Endpoints were defined as the Week 12 or 24 measurement or the last non-missing measurement prior to Week 12 or 24 (last observation-carried-forward: LOCF). There were no adjustments for covariates. For categorical variables, descriptive statistics included the number and percentage of subjects for each category. Percentages were calculated based upon subjects with non-missing data as the denominator. For continuous variables, Student's *t*-tests were used to determine whether the change (or percentage change) from baseline was statistically significantly different from zero. All inferential statistical tests were conducted at a significance level of 0.05 (2-sided). Data are reported as mean ± SD unless otherwise indicated. Statistical analyses were performed using SAS Version 9.1 (Cary, NC).

3. Results

3.1. Study population

Thirty overweight or obese smokers, mean age 42.5 years, 53.3% male, predominantly White (93.3%), and BMI (body mass index) of 32.6 kg/m^2 were enrolled in this study. Demographics and baseline characteristics are shown in Table 1. Twenty-seven subjects had at least one post-baseline evaluation and were included in the ITT cohort, with 85% completing 12 weeks and 63% completing 24 weeks (Fig. 2).

3.2. Smoking cessation and body weight

During Weeks 4–12, 48.1% of subjects in the ITT cohort reported continuous abstinence and 77.8% achieved a CO ≤10 ppm at Week 12. Expired CO decreased to 6.7 ± 7.8 ppm at Week 12 (-19.7 ± 16.9 ppm; $p<0.001$; Fig. 3A). Serum cotinine decreased from 180 ± 120 to 48 ± 68 μg/L over the same period (-137 ± 119 μg/L; $p<0.001$; Fig. 3B). Tobacco use decreased to 14 ± 27 cigarettes/week (-115 ± 48 cigarettes/week; $p<0.001$; Fig. 3C), while body weight was unchanged in the entire population (-0.1 ± 2.8%; $p=0.826$) and in continuous abstainers (0.1 ± 3.4%; $p=0.981$). In the completer cohort, 52.2% reported continuous abstinence during Weeks 4–12.

During Weeks 4–24, 40.7% of subjects in the ITT cohort reported continuous abstinence and 66.7% achieved a CO ≤10 ppm at Week 24. Expired CO decreased to 8.6 ± 10.1 ppm at Week 24 (-17.9 ± 17.0 ppm; $p<0.001$; Fig. 3A). Serum cotinine decreased to 61 ± 76 μg/L (-125 ±

Table 1
Demographics and baseline characteristics.

	Randomized $N=30$
Age (y)	42.5 ± 11.3
BMI (kg/m^2)	32.6 ± 4.8
Weight (kg)	94.3 ± 15.2
Gender (% male)	53.3
Race (% White)	93.3
Smoking history (y)	22.6 ± 12.5
Tobacco use (cigarettes/week)	129 ± 40
Expired CO (ppm)	26.5 ± 17.2
Serum cotinine (μg/L)	198 ± 124
FTND score[a]	9.2 ± 2.2
MNWS total score	9.4 ± 4.5
IDS-SR total score	4.1 ± 4.5

Data are mean ± SD.
[a] FTND score >6 indicates high nicotine dependence.

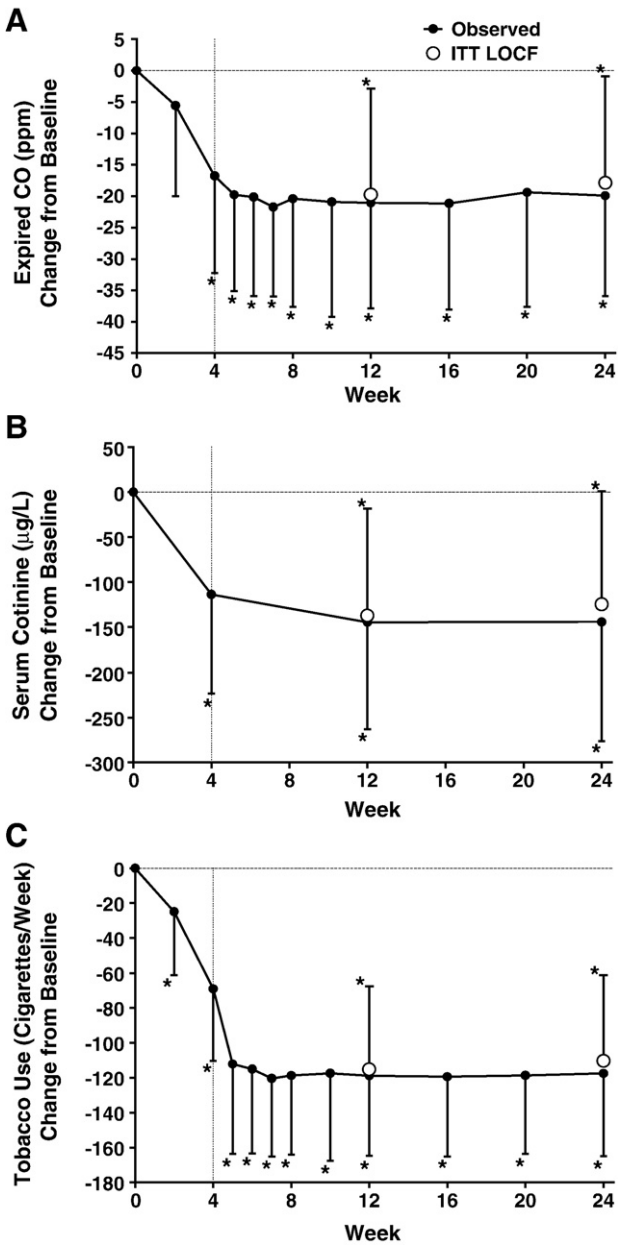

Fig. 3. (A) Expired CO change from baseline over time. (B) Serum cotinine change from baseline over time. (C) Tobacco use change from baseline over time. Mean ± SEM. Data are for the ITT population ($N = 27$). Dashed line indicates quit date. *$p < 0.001$ vs. baseline.

126 µg/L; $p < 0.001$; Fig. 3B). Tobacco use decreased to 18 ± 31 cigarettes/week (-110 ± 49 cigarettes/week; $p < 0.001$; Fig. 3C). Body weight did not significantly change in the entire population (+0.4 ± 3.0%; $p = 0.555$), but increased slightly in continuous abstainers (1.3 ± 3.3%; $p = 0.148$). In the completer cohort, 58.8% reported continuous abstinence during Weeks 4–24.

3.3. Questionnaires

In the ITT cohort, MNWS total scores did not change from baseline at Week 12 or 24 ($p > 0.05$). The only significant change over the course of the study was a small increase at the Week 5 visit (+4.9 ± 9.5, $p = 0.018$). Craving, as assessed by the "Desire or craving to smoke" MNWS item, was significantly reduced from the baseline item score of 2.93 ± 1.27 at Week 12 (−1.48 ± 1.63; $p < 0.001$) and Week 24 (−1.41 ± 1.69; $p < 0.001$). Appetite, as assessed by the "Increased appetite, hungry, weight gain" MNWS item, was not changed at any time point.

There were no clinically-relevant changes in mean IDS-SR total score. At Week 12, the mean IDS-SR total score increased modestly from 4.2 ± 4.7 at baseline to 7.0 ± 6.9 (+2.8 ± 6.3; $p = 0.031$; IDS-SR total score <14 indicates no depression), primarily due to one outlier experiencing insomnia. At Week 24, the mean IDS-SR of 5.5 ± 1.1 was not significantly different from baseline (+1.3 ± 5.8; $p = 0.242$). Median IDS-SR scores remained unchanged throughout the study.

Examination of COEQ scores revealed that there are changes in only two questions (Supp Table 1). Items #3 (How strong was your desire to eat sweet foods?) and #5 (How happy have you felt?) were significantly decreased at both 12 and 24 weeks ($p < 0.05$). There was also a trend towards a reduction in the desire to eat non-sweets. There were no significant changes in overall hunger, food craving, or subject-reported eating behavior.

3.4. Safety and tolerability

The combination of naltrexone and bupropion was generally well-tolerated. The most common adverse events were nausea, insomnia, and constipation (Table 2). These events tended to be transient and mild or moderate in severity. Nausea occurred primarily during the first 10 weeks. No serious adverse events occurred. Five subjects withdrew due to adverse events (fatigue, somnolence, insomnia, nausea, and urticaria). No clinically-relevant changes in chemistry laboratory results, blood pressure, or ECG readings occurred.

4. Discussion

In this exploratory, open-label, 24-week clinical trial, naltrexone/bupropion combination therapy plus behavioral intervention was associated with significantly reduced nicotine use and craving from baseline without an increase in nicotine withdrawal symptoms or weight gain. Continuous abstinence rates were consistent with biochemically verified measures of nicotine abstinence and were generally sustained through 24 weeks. There was no significant increase in body weight from baseline at any time point.

Combination therapy with naltrexone and bupropion reduced nicotine use as measured by subject-reported tobacco use and biochemically verified abstinence. Week 4–12 and Week 4–24 subject-reported continuous abstinence rates were 48% and 41% in the ITT cohort, and 52% and 59% in the completer cohort. The rapid and well-maintained reduction in serum cotinine that occurred in this study is in agreement with an equally substantial decrease in self-reported cigarette use and confirms sustained reduction of nicotine use. Nicotine withdrawal scores were slightly higher one week after the quit date and then returned to baseline. Cigarette craving also significantly decreased with treatment.

Naltrexone/bupropion combination therapy was generally well-tolerated. Nausea was the most frequent adverse event and was generally transient; most subjects experiencing nausea were able to

Table 2
Treatment-emergent adverse events with frequency ≥10%.

Adverse event	Incidence (%) ($N = 29$)
Nausea	37.9
Insomnia	24.1
Constipation	20.7
Headache	17.2
Dry mouth	13.8
Dizziness	10.3
Influenza	10.3
Middle insomnia	10.3

continue therapy. Few subjects discontinued therapy due to adverse events.

Varenicline is considered the most effective pharmacotherapy for smoking cessation and generally produces continuous abstinence rates at Week 12 of 30–50% (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006; Oncken et al., 2006). Bupropion commonly produces continuous abstinence rates of 20–40% but is associated with the least post-cessation weight gain (Gonzales et al., 2006; Jorenby et al., 2006, 1999; Nides et al., 2006; Tonnesen et al., 2003). In two trials comparing varenicline with bupropion and placebo, bupropion resulted in 1.9–2.1 kg weight gain in continuous abstainers at 12 weeks, compared with 2.4–2.9 kg for varenicline and 2.9–3.2 kg for placebo (Gonzales et al., 2006; Jorenby et al., 2006). In the current study, continuous abstinence rates were comparable with bupropion and varenicline; however no clinically significant weight gain was observed. It remains to be determined whether naltrexone/bupropion combination produces smoking cessation rates that are clinically different from other smoking cessation treatments.

A previous smoking cessation study that did not specifically target overweight or obese smokers demonstrated similar results with the naltrexone/bupropion combination. This 7-week open-label trial in 20 weight-concerned smokers (baseline weight 72 ± 13 kg), compared the effect of naltrexone (25 mg/day) plus bupropion (300 mg/day) for smoking cessation and body weight with 20 smokers from another study who were administered bupropion monotherapy. Week 1–7 continuous abstinence rates were 30% in each arm (Toll et al., 2008), however, Week 7 weight gain in continuously abstinent subjects trended lower with naltrexone/bupropion combination therapy ($+0.77$ kg) than with bupropion monotherapy ($+1.45$ kg). The attenuation of short-term weight gain in non-obese subjects as reported by Toll et al. is consistent with the results reported in the present study in overweight and obese subjects.

It has been suggested that several mechanisms, such as decreased energy expenditure and increased appetite, contribute to weight gain during smoking cessation (Chiolero, Faeh, Paccaud, & Cornuz, 2008; Filozof, Fernandez Pinilla & Fernandez-Cruz, 2004). Energy expenditure was not measured in this study, and although there was a reduction in the desire to eat sweets and a trend for reduced desire for non-sweets, there were no changes in overall hunger or appetite, food craving, or subject-reported eating behavior. The finding that the naltrexone/bupropion combination was not associated with an increase in various measures of appetite, hunger, or eating behavior, is consistent with the absence of significant weight gain.

In this study, baseline FTND scores were 2–4 points higher than what has been reported in other studies discussed here (Gonzales et al., 2006; Jorenby et al., 2006; Tonnesen et al., 2003). A higher FTND score is indicative of greater nicotine addiction. Whether or not nicotine cessation rates would be different in subjects with lower nicotine dependence remains to be determined.

There were several limitations to this study. First, the extent of the contributions of the ancillary therapy to the study outcome is unknown. Similar to other smoking cessation trials, this study included a behavioral intervention component designed to facilitate smoking cessation and minimize weight gain ("Smoke free and Living it"). Additional ancillary therapy was administered to assist subjects in maintaining their weight and could have impacted study outcome. At baseline, subjects were advised to increase exercise; however advice to follow a hypocaloric diet was begun at Week 12 and would have not affected the primary outcome. Furthermore, the LOCF method for imputation of missing subjects may have overestimated treatment efficacy compared to larger studies where dropouts are assumed to be smokers. Additional limitations are related to the exploratory nature of the study design (open-label, small sample size, and the absence of a placebo or active therapy comparator), which does not allow for direct efficacy comparisons with current pharmacotherapies for smoking cessation.

In summary, open-label combination therapy with naltrexone SR and bupropion SR plus behavioral therapy for 24 weeks in overweight and obese smokers was associated with nicotine abstinence rates comparable to those of leading smoking cessation aids. Furthermore, naltrexone/bupropion combination therapy was not associated with the weight gain that sometimes accompanies smoking cessation. Smoking and obesity are associated with excess risk of mortality and their combined effects are roughly additive (Whitlock, et al., 2009). Thus, the potential effects of naltrexone/bupropion combination therapy for smoking cessation may be especially relevant in overweight and obese smokers or for subjects where concerns about weight gain are an obstacle to nicotine cessation. Further investigation of the efficacy and safety of the naltrexone/bupropion combination in the treatment of nicotine dependence is warranted.

Role of Funding Sources

Orexigen Therapeutics, Inc. participated in discussions regarding study design and protocol development, in cooperation with the authors, and provided logistical support during the trial. The sponsor and the authors participated in collection, analysis or interpretation of the data. The first draft of the manuscript was prepared by Loretta L. Nielsen, PhD in cooperation with the corresponding author and the sponsor. The sponsor was permitted to review the manuscript and suggest changes. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Contributors

Dr. Wilcox, Dr. Oskooilar, Ms. Katz, Dr. Dunayevich and Dr. Erickson, designed the study. Dr Wilcox, Dr. Dunayevich and Dr. Erickson wrote the protocol. Dr. Wilcox, Ms. Katz, Dr. Dunayevich, and Dr. Billes conducted literature searches and provided summaries of previous research studies. Dr. Wilcox and Dr. Oskooilar were study investigators. Dr. Erickson and Dr. Wilcox participated in statistical analysis. The manuscript was prepared by Loretta L. Nielsen, PhD and Dr. Billes in cooperation with the corresponding author. Dr. Wilcox, Dr. Dunayevich, Dr. Erickson and Dr. Billes participated in data interpretation and revised the manuscript in collaboration with all authors. All authors have approved the final manuscript.

Conflict of Interest

Dr. Wilcox, Dr. Oskooilar, and Ms. Katz received research support from Orexigen. Dr. Dunayevich and Dr. Billes are employees of Orexigen. Dr Erickson is a former employee of Orexigen. Dr. Dunayevich holds stock in Orexigen.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.addbeh.2009.10.017.

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