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A Preliminary Investigation of Naltrexone Augmentation of Bupropion to Stop Smoking With Less Weight Gain

Benjamin A. Toll^{*,1}, Vanessa Leary¹, Ran Wu¹, Peter Salovey², Boris Meandzija¹, and Stephanie S. O'Malley¹

¹Yale University School of Medicine, Department of Psychiatry

²Yale University, Department of Psychology

Abstract

Certain barriers prevent some cigarette smokers from attempting to quit, particularly the fear of post-cessation weight gain. This investigation was an open label study of naltrexone hydrochloride (25 mg/day) in combination with sustained-release (SR) bupropion hydrochloride (300 mg/day) for smoking cessation and minimization of post-quit weight gain in weight concerned smokers. The study sample ($n = 20$) was compared to matched controls ($n = 20$) who received an identical psychosocial intervention and bupropion SR treatment regimen. The primary outcomes analyzed were: (a) biochemically verified continuous abstinence from smoking over the 6-week treatment, (b) point prevalence abstinence in the last 7 days of treatment, and (c) weight gain from baseline. Neither adherence to the combination pharmacotherapy nor the percentage of patients reporting adverse events differed significantly between the two groups nor were there differences in either continuous or point prevalence abstinence from smoking. Although not statistically significant in this small sample, continuously abstinent participants in the naltrexone + bupropion group gained less weight ($M = 1.67$ pounds) than those in the bupropion only group ($M = 3.17$ pounds; $p = .35$; Cohen's $d = 0.56$). The results of this preliminary study suggest that combining naltrexone and bupropion may help minimize post-cessation weight gain, but does not result in higher smoking cessation rates compared to bupropion alone. The effect size for the difference in weight gain among continuously abstinent participants was in the moderate range, suggesting that this treatment deserves further study in an appropriately powered clinical trial as an adjunct for weight concerned smokers, who may value the weight suppressant effect of naltrexone.

Keywords

naltrexone; bupropion; weight; smoking cessation

Fear of weight gain is a significant obstacle to smoking cessation, preventing some smokers from attempting to quit (Pomerleau, Zucker, & Stewart, 2001). Although pharmacotherapy has been moderately successful in treating nicotine dependence (Fiore et al., 2000), the effects on minimizing post-quit weight gain have been mixed, and further research is needed to develop

*Correspondence concerning this article should be addressed to Benjamin A. Toll, Ph.D., Yale University School of Medicine, Department of Psychiatry, 1 Long Wharf Drive – Box 18, New Haven, CT 06511, USA; telephone: (203) 974-5767; fax: (203) 974-5790; email: benjamin.toll@yale.edu.

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medications that address concern about gaining weight after smoking cessation (Pomerleau, Zucker, & Stewart, 2001).

Naltrexone hydrochloride is a medication that has shown promise in reducing post-cessation weight gain and may therefore address weight concerns. Several randomized controlled studies have shown that naltrexone significantly minimizes post-quit weight gain. In these studies, participants in the naltrexone group gained no more than 1.5 pounds on average, whereas those in the placebo group gained an average of between 2.4 and 4.2 pounds (King et al., 2006; Krishnan-Sarin, Meandzija, & O'Malley, 2003; O'Malley et al., 2006). Although naltrexone appears to reduce weight gain after quitting, effects on smoking cessation have been inconclusive, with some negative (e.g., King et al., 2006; Wong et al., 1999) and some positive (e.g., Covey, Glassman, & Stetner, 1999; O'Malley et al., 2006) findings.

In the present study, we tested a combination of low dose naltrexone and bupropion SR in a sample of weight concerned smokers and compared them to a matched group of weight concerned smokers receiving only bupropion SR. We hypothesized that participants who received naltrexone would exhibit less post-quit weight gain. Given that post-cessation weight gain can lead to smoking relapse in weight concerned smokers (Pomerleau, Zucker, & Stewart, 2001), we also hypothesized that the group receiving naltrexone would have higher rates of abstinence from smoking. The purpose of this study was to develop effect size estimates for smoking cessation and weight gain. The study was not powered to detect statistically significant differences between the study groups.

Method

Study Design, Screening, and Participants

This investigation was a 7-week open label study of naltrexone hydrochloride (25 mg/day) in combination with bupropion hydrochloride SR (300 mg/day). The study sample ($n = 20$, the naltrexone + bupropion group) was compared to matched controls who received an identical psychosocial intervention and bupropion SR treatment regimen ($n = 20$, the bupropion only group; Toll et al., in press). This study was approved by the Institutional Review Board of the Yale University School of Medicine.

Participants were recruited through advertisements and the Internet. They were screened by telephone and at two subsequent intake appointments. Written informed consent was provided by all participants at the first study visit. To be eligible, all participants needed to report that they were concerned about post-quit weight gain using two questions from Perkins et al. (2001).¹ Participants were excluded for aspartate amino transferase or amino alanine transferase > 3 times normal or elevated bilirubin, current use of opiates, an opiate positive drug screen, pain conditions requiring opiates, history of cirrhosis, Body Mass Index > 35 , or participation in the comparison study. All other inclusion and exclusion criteria matched those of the comparison study (Toll et al., in press).

Participants in the naltrexone + bupropion group ($n = 20$, 70% female) were primarily white (85%), had a mean age of 43.0 ($SD = 11.16$), smoked an average of 19.7 ($SD = 5.67$) cigarettes per day, had smoked an average of 19.7 years ($SD = 11.36$), and had a mean weight of 159.2 pounds ($SD = 29.31$). These characteristics were similar to those in the bupropion only group ($n = 20$, 70% female) who were mostly white (90%), had an average age of 42.3 ($SD = 12.30$), smoked an average of 20.6 ($SD = 7.83$) cigarettes per day, had smoked an average of 16.8 years

¹These items were: "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 the Perkins et al. (2001) criteria, a rating of 50 or higher on a 100 point scale on either question qualified the subject as weight concerned.

($SD = 11.40$), and had a mean weight of 161.5 pounds ($SD = 28.34$). There were no significant differences between the groups on these variables.

Treatment Period

Starting with the baseline visit, all participants received 150 mg of bupropion SR (Zyban, GlaxoSmithKline, Research Triangle Park, NC) once per day for 3 days, then twice per day for the duration of the 7-week treatment period (Hurt et al., 1997). All participants received naltrexone hydrochloride (Depade, Mallinckrodt Pharmaceuticals, Hazelwood, MO) on the sixth day of bupropion treatment, and the initial dose was 12.5 mg, followed by 25 mg daily for the duration of the 7-week treatment. The target quit date for each participant was set for 1 week after starting bupropion, usually on day 8. A nurse practitioner called all participants approximately 3 days after the targeted quit date to assess smoking status and side effects. For 6 weeks after their quit date, participants came to the clinic for research appointments on a weekly basis. Questionnaires were administered, and framed video and print messages encouraging smoking abstinence (see Toll et al., in press) were provided at these appointments. With the exception of the addition of naltrexone, the only other difference between the two studies was that participants in the naltrexone + bupropion group were assessed (vitals, adverse events, weight, & smoking data) more frequently to monitor safety. In contrast to participants in the naltrexone + bupropion group, those in the bupropion only group were not assessed at weeks 1, 3, and 5 post-quit.

Assessments

At intake, participants completed a battery of questionnaires that assessed demographics, smoking history, and potential predictors. Smoking was assessed using Timeline Followback (TLFB) methods at baseline (for 30 days prior to screening) and at each weekly appointment (for the preceding week; Brown et al., 1998). Weight was assessed without footwear. Bupropion SR adherence was monitored with electronic Drug Exposure Monitor (eDEM) caps, which recorded the time and day of pill bottle openings (APREX, Union City, CA). Percent adherence equaled the number of times the bottle was opened divided by 95 (the number of times bupropion should have been taken over the 7-week treatment). Adverse events were obtained using a checklist of commonly reported events for bupropion, rated on a scale from 0 (not present) to 3 (severe). Other concerns were elicited with open-ended questions.

Outcome Measures

Three primary outcomes were examined: (a) continuous 6-week abstinence from the quit date, (b) point prevalence abstinence over the last 7 days of the 6-week post-quit treatment period, and (c) weight gain from baseline. Abstinence from smoking was defined as self-reported abstinence during the specified post-quit treatment period, verified by an exhaled CO level ≤ 10 ppm. The primary weight analysis examined weight gain (week 6 weight minus baseline) in continuously abstinent smokers. A secondary analysis examined weight gain for the entire sample (last weight measurement minus baseline).

Comparisons with Matched Controls and Statistical Analyses

To select matched controls, the sample of participants in the bupropion only group was restricted to those participants who were coded as weight concerned [i.e., unwillingness to permanently gain 10 or more pounds after quitting (Perkins et al., 2001)]. Based on bupropion SR predictors of treatment outcome (Dale et al., 2001; Swan et al., 2003), gender, age (± 5 years), weight (± 5 pounds), and number of cigarettes smoked daily (± 5 cigarettes) were used to match participants. If it was impossible to find a match who met all of these criteria, one or more criteria were relaxed to find the closest match. Matching was done without knowledge of smoking cessation outcome or weight gain.

Between groups differences in the smoking cessation outcomes were analyzed using chi-square statistics. Between groups t-tests were used to compare the two groups on weight gain from baseline. Effect sizes (Cohen's *d* or Phi) were calculated for treatment adherence, smoking and weight outcomes.

Results

Treatment Exposure, Smoking Outcomes, and Weight Gain

As presented in Table 1, rates of adherence to the combination pharmacotherapy were slightly lower than rates with mono-therapy, but none of these differences were significant. There were no differences in either continuous or point prevalence abstinence. Continuously abstinent participants in the naltrexone + bupropion group gained less weight ($M = 1.67$ lbs, $SD = 3.17$) than those in the bupropion only group ($M = 3.17$ lbs, $SD = 2.04$), although this effect was not significant [$t(10) = 0.97$; $p = .35$; Cohen's $d = 0.56$]. When considering the entire sample, those in the naltrexone + bupropion group still gained less weight ($M = 0.28$ lbs, $SD = 3.88$) than participants in the bupropion only group ($M = 1.25$ lbs, $SD = 2.90$), but again this effect was not significant [$t(38) = 0.90$; $p = .37$; Cohen's $d = 0.28$].

Safety

There was one unexpected adverse event involving unresolved alopecia, a rare side effect associated with bupropion SR. Table 2 shows the percent of unique participants who reported non-serious adverse events rated moderate to severe for symptoms with a prevalence of 5% or more. The proportion of participants reporting specific adverse events did not significantly differ between the two groups.

Discussion

This study found that combining naltrexone and bupropion may help minimize post-cessation weight gain, but does not result in higher smoking cessation rates compared to bupropion alone. The effects on weight gain were not statistically significant, likely due to the small study sample. However, the effect size for the difference in weight gain among continuously abstinent participants was in the moderate range (Cohen, 1988), suggesting naltrexone deserves further study as a means to reduce postcessation weight gain in combination with effective pharmacotherapies.

In this study, continuously abstinent participants receiving bupropion and 25 mg naltrexone gained an average of 1.67 pounds, which is comparable to the mean weight gain of 1.54 pounds found by O'Malley et al. (2006) in continuously abstinent participants taking 25 mg naltrexone and nicotine patch. In the full sample, the mean weight gain of 0.28 pounds was somewhat lower than the average 1.50 to 1.76 pound gain found for the entire sample in prior studies of nicotine patch in combination with 25 mg naltrexone (O'Malley et al., 2006) or 50 mg naltrexone (King et al., 2006). With weight concerned smokers receiving behavioral treatment, Perkins et al. (2001) found a mean weight gain of 4.84 pounds after 4 weeks, a value 3 pounds higher than any findings with participants taking naltrexone. Thus, these results suggest that naltrexone may be a promising adjunctive therapy for weight concerned smokers.

Although the percentage of patients reporting adverse events did not differ significantly between the two groups, some side effects exhibited either a higher (e.g., nausea, nervousness, headache, & constipation) or lower (e.g., insomnia & itching) incidence in the naltrexone + bupropion group. These differences might have been significant with a larger sample size. Of note, this is our second study showing a lower incidence of pruritus in participants taking 25 mg naltrexone (O'Malley et al., 2006).

The lack of a placebo control and randomization are major limitations of this study. Additionally, participants in the naltrexone + bupropion group were monitored more frequently than those in the bupropion only group, which may have influenced study outcomes. Last, the small sample size made it difficult to detect statistically significant differences in outcomes.

Accruing evidence suggests that that naltrexone can reduce weight gain in combination with effective smoking cessation pharmacotherapies. Future studies using naltrexone in combination with varenicline may be of particular interest because varenicline, unlike bupropion, does not significantly suppress post-quit weight gain but results in higher quit rates (e.g., Gonzalez et al., 2006).

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Table 1
Treatment Exposure and Smoking and Weight Outcomes

Characteristic	Naltrexone + Bupropion	Bupropion Only	<i>d</i>	Phi
No. of patients who completed treatment (No., %)	12/20 (60)	14/20 (70)	-----	.11
No. of weeks of treatment attended (<i>M, SD</i>)	5.25 (2.55)	5.60 (2.35)	.14	-----
No. weeks using bupropion SR (<i>M, SD</i>)	4.20 (3.08)	5.35 (2.21)	.43	-----
No. weeks using naltrexone (<i>M, SD</i>)	3.90 (3.01)	-----	-----	-----
Percent days bupropion SR taken (<i>M, SD</i>)	54.74 (38.51)	66.37 (33.78)	.33	-----
No. of patients reporting continuous abstinence over 6 weeks (No., %)	6/20 (30)	6/20 (30)	-----	0
No. of patients reporting point prevalence abstinence over last 7 days (No., %)	8/20 (40)	8/20 (40)	-----	0
Weight gain for continuously abstinent participants in pounds (<i>M, SD</i>)	1.67 (3.17)	3.17 (2.04)	.56	-----
Weight gain for the entire sample in pounds (<i>M, SD</i>)	0.28 (3.88)	1.25 (2.90)	.28	-----

Note. N = 20 per group, except for weight gain for continuously abstinent participants, for which n = 6 per group. Effect size estimates are expressed as *d* for Cohen's *d* and Phi. No differences were significant at $p < .05$.

Table 2
Moderate and Severe Events Reported During Treatment by Group

Adverse Event	Bupropion only group n (%)	Bupropion + naltrexone group n (%)
Nausea	1 (5.0)	5 (25.0)
Vomiting	1 (5.0)	1 (5.0)
Diarrhea	1 (5.0)	0 (0.0)
Headache	0 (0.0)	2 (10.0)
Dizziness	0 (0.0)	1 (5.0)
Fatigue	0 (0.0)	1 (5.0)
Nervousness/anxiety	2 (10.0)	4 (20.0)
Insomnia	5 (25.0)	3 (15.0)
Pruritus	2 (10.0)	0 (0.0)
Dry mouth	4 (20.0)	4 (20.0)
Irritability	2 (10.0)	2 (10.0)
Constipation	0 (0.0)	2 (10.0)
Sweating	1 (5.0)	2 (10.0)
Ringing in ears	0 (0.0)	1 (5.0)
Alopecia	0 (0.0)	1 (5.0)

Note. N = 20 per group. Data are expressed as number (percentage) of participants. There were no statistically significant differences at $p < .05$.