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Brief Report

Combination Lorcaserin and Nicotine Patch for Smoking Cessation Without Weight Gain

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Abstract

Introduction: This study explored the efficacy of combination lorcaserin and nicotine patch for smoking cessation treatment and prevention of postsmoking cessation weight gain.
Methods: We conducted a trial in which 61 adult daily smokers were asked to quit smoking using a combination of lorcaserin and nicotine patch. During the first 2 weeks of treatment prior to the quit day, participants were randomized to receive either lorcaserin (10 mg twice daily) plus nicotine patch (21 mg) or placebo plus nicotine patch (21 mg). Following this 2-week period, participants received both medications for 12 weeks. Outcomes included 4-week continuous smoking abstinence at the end of treatment (weeks 7–10 postquit attempt), weight change, ad libitum smoking, withdrawal symptoms, and ratings of cigarette reward.
Results: Biochemically confirmed continuous smoking abstinence from 7 to 10 weeks postquit attempt was 31.1% (90% confidence interval, 21.4%–40.8%). Participants who quit smoking showed no weight gain; in fact, mean weight change was minus 0.16 kg (SD = 3.27) over the study period. There was an unexpected but strong association ($p = .006$) between a decrease in sensory enjoyment of smoking and successful quit outcome on this regimen. During the prequit randomization period, lorcaserin versus placebo reduced the impact of smoking to relieve craving for cigarettes as well as the sensory enjoyment of smoking ($p = .005$). Adherence and tolerability to lorcaserin and nicotine patch was good.
Conclusions: The combination of lorcaserin and nicotine patch was well tolerated, associated with a relatively high smoking abstinence rate, and effectively prevented weight gain associated with quitting smoking.
Implications: This report provides an important contribution to the literature because it details evidence of a medication combination—lorcaserin and nicotine—that is effective for smoking cessation and for ameliorating weight gain associated with smoking cessation. For many smokers, postcessation weight gain is a major obstacle to quitting, and this medication combination provides a suitable treatment option for these smokers.
Clinical Trial Registration: NCT02906644

Introduction

The effectiveness of smoking cessation treatment may be advanced by tailoring treatments to the needs of smoking subgroups with unique challenges. An important subgroup of smokers are those concerned about postcessation weight gain. People who quit smoking gain an average of 5–15 pounds[1]; however, approximately one third of all smokers gain over 20 pounds.[2–5] Postquit weight gain of over 10 pounds is associated with smoking relapse, with higher weight gain being associated with a return to smoking.[6,7] The primary mechanism of postquit weight gain appears to be increased caloric consumption in the first weeks and months after quitting.[8] Thus far,

pharmacologic treatments and behavioral therapies have been found to be ineffective at attenuating postsmoking cessation weight gain.[8,9]

Lorcaserin hydrochloride, marketed as Belviq, is a serotonin receptor (5HT2C) agonist that has been approved by the FDA for weight loss.[10] Lorcaserin has been found to reduce nicotine self-administration in rats.[11] More recently, a Phase 2 clinical trial showed that lorcaserin 10 mg twice daily (standard dose) nearly tripled smoking abstinence rates when compared with placebo (15.3% vs. 5.6% abstinence, respectively) at 7–10 weeks postquit date (p = .0027).[12] Although the effect size over placebo was large, the absolute smoking cessation rate of 15.3% for lorcaserin alone was modest; critically, however, this trial showed that lorcaserin prevented postquit weight gain, with smoking-abstinent subjects showing a weight *loss* of 0.41 kg in the lorcaserin group versus a weight gain of 0.73 kg (p = .004) in the placebo group.[12]

We reasoned that the modest absolute success rates in the previous trial may have been due to the absence of a treatment that adequately addressed nicotine withdrawal. Therefore, the present study was designed evaluate the combination of lorcaserin and nicotine patch for smoking cessation and prevention of postquit weight gain. Nicotine patch treatment has been shown to decrease nicotine withdrawal.[13] As a relatively small exploratory study, we sought to conduct an open-label trial to assess the smoking abstinence rate and weight change during 12 weeks of lorcaserin administration in combination with nicotine patch. Study treatment began with a 2-week prequit treatment period in which participants were randomly assigned to lorcaserin and nicotine patch versus placebo and nicotine patch. This prequit randomization period was used to explore potential mechanisms of action and to determine the effects of lorcaserin on ad libitum smoking prior to the quit date.

Methods

The study was a randomized, double-blind, parallel-arm, controlled clinical trial to ascertain whether combination lorcaserin and nicotine patch would be effective for smoking cessation and amelioration of postcessation weight gain. Subjects were recruited from a metropolitan area via advertisements targeting smokers who were concerned about gaining weight after quitting smoking. Lorcaserin tablets were purchased from a licensed pharmacy and were overencapsulated by a commercial compounding pharmacy, which also supplied placebo capsules. The treatment period of 14 weeks began 4 weeks prior to the target quit day and ended 10 weeks after the target quit day. The two randomized groups received different treatments (lorcaserin plus nicotine patch vs. placebo plus nicotine patch) for the first 2 weeks of the prequit period and then received identical treatment (lorcaserin plus nicotine patch) for 12 weeks, beginning 2 weeks prior to the target quit day and ending 10 weeks after the quit day. Treatment concluded with discontinuation of lorcaserin and a 2-week nicotine taper (1 week of 14-mg patches and 1 week of 7-mg patches). Figure 1 depicts the randomization groups and study flow.

Behavioral treatment was composed of 30 minutes of smoking cessation counseling including discussion of health benefits, quit day planning, and instructions on medication use, but did not include recommendations on weight management strategies. Participants were discouraged from participation in a structured behavioral weight management plan to decrease the chance that behavioral strategies would influence postcessation weight change.

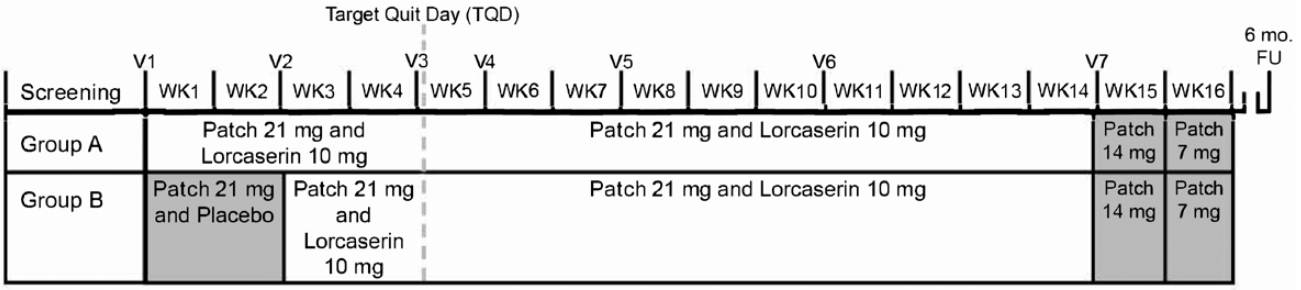
Assessments were conducted at a screening visit, a baseline visit, a laboratory visit, a visit 1 day prior to the target quit date, 4 postquit visits, and a 6-month follow-up visit for participants reporting 7-day abstinence. Ad libitum smoking was assessed weekly via daily diary recordings of cigarettes smoked per day as well as the objective index of expired air carbon monoxide (CO) levels measured at the study visits.

After the first 2 weeks, participants attended a study visit to assess smoking withdrawal symptoms and undergo a simulated 60-minute smoking lapse paradigm validated by McKee et al.[14] In this paradigm smokers were offered time-based monetary incentives to delay smoking; the amount of each incentive payment decreased over time during the session. The outcome measure was time-to-lapse, which has been found to increase during the use of smoking cessation medications such as varenicline and bupropion.[15]

Results

Subjects

The study sample comprised 61 smokers, 75.4% female, 65.6% Caucasian, 32.8% African American, and 1.6% multiple race; participants had a mean age of 45.5 (SD = 11.3); smoked an average of 16.3 (SD = 6.0) cigarettes/day, and had a baseline expired air CO reading of 20.4 ppm (SD = 6.8). Mean baseline body weight was



Group A: *Nicotine patch 21 mg once daily and lorcaserin 10 mg twice daily for 14 weeks (four weeks pre-TQD and 10 weeks post-TQD), then nicotine patch alone for two weeks (14 mg for one week and 7 mg for one week).*

Group B: *Nicotine patch 21 mg once daily and placebo twice daily for the first two weeks, then nicotine patch 21 mg once daily and lorcaserin 10 mg twice daily for 12 weeks (two weeks pre-TQD and 10 weeks post-TQD), then nicotine patch alone for two weeks (14 mg for one week and 7 mg for one week).*

Figure 1. Randomization groups and study flow.

88.2 kg (SD = 14.5) and body mass index (BMI) was 30.9 (SD = 6.6). The mean Fagerström Test for Nicotine Dependence (FTND) score was 5.3 (SD = 2.1), corresponding to a moderate level of dependence. There were no significant differences between groups for any of these variables.

Key Outcomes

Four-week continuous smoking abstinence for weeks 7–10 postquit was 31.1% overall (90% confidence interval, 21.4%–40.8%); there were no differences between the groups receiving 12 versus 14 total weeks of combination treatment (31.1% vs. 29.0%, respectively). At 6 months, 14.8% reported 7-day smoking abstinence (confirmed by expired air CO ≤ 10 ppm).

Weight change among smoking-abstinent participants after 12 weeks of treatment on lorcaserin and nicotine patch was –0.16 kg (SD = 3.27). For nonabstinent participants, the mean weight change was –0.20 kg (SD = 3.46). In the analysis, we separated participants who were abstinent at 9–12 weeks into two groups—those who remained smoking-abstinent at 6 months and those who had relapsed at 6 months. Participants who had relapsed back to smoking after treatment ended had lost weight during the 12 weeks of treatment (mean change –0.79 kg [SD = 3.25]). Participants who remained abstinent at 6 months showed an average weight gain of 1.65 kg (SD = 2.94) at the end of 12 weeks of treatment and an average of 3.84 kg (SD = 4.76) at 6 months postquit attempt. The weight gain for subjects who remained abstinent at 6 months was positively correlated with the reduction in their sensory enjoyment of smoking the first cigarette of the day at week 2 ($r(8) = .79$, $p = .01$).

Two-Week Prequit Double-Blind Phase

Only six participants lapsed during the 60-minute smoking lapse paradigm, and thus a decision was made early in the study (while blind to subjects' condition assignment) to use withdrawal symptoms as the primary assessment of lorcaserin efficacy. A composite withdrawal measure was used, consisting of mean ratings of the craving, negative mood, arousal, and appetite scales from a modified Shiffman–Jarvik withdrawal questionnaire.[16] Smoking was assessed by daily diaries, and expired air CO was measured at each session.

No significant effects of lorcaserin versus placebo were noted on smoking withdrawal symptoms, changes in ad libitum smoking (via expired air CO) at the end of the first 2 weeks, or on time-to-lapse in the laboratory lapse model. Mean time-to-lapse was 52.0 minutes (SD = 18.3) in the lorcaserin condition versus 56.4 minutes (SD = 12.5) in the placebo condition.

The Modified Cigarette Evaluation Questionnaire[17] revealed treatment-related differences with "craving reduction" item, and ratings were significantly lower in the lorcaserin versus placebo group; for the first cigarette in the morning (of a priori interest given its prominent role in the FTND dependence questionnaire), the mean was 4.3 (SD = 2.0) for lorcaserin versus 5.6 (SD = 1.4) for placebo, $F(1, 55) = 8.40$, $p = .005$. The same was true for the "enjoy the sensations of the smoke in your throat and chest" item: mean = 2.0 (SD = 1.3) for lorcaserin versus 2.9 (SD = 1.8) for placebo, $F(1, 55) = 4.56$, $p = .04$. Ratings for cigarettes throughout the day showed similar effects. These results showed that both craving reduction and enjoyment obtained from cigarettes was significantly decreased in participants using lorcaserin versus placebo.

An unexpected finding was that smoking abstinence was associated with higher baseline sensory enjoyment of smoking and greater prequit decrease in the sensory enjoyment of smoking. The relationship was significant for the first cigarette of the day and strongest for cigarettes smoked throughout the day; for the latter, the mean baseline rating was 4.0 (SD = 1.9) for subjects who went on to achieve abstinence versus 2.0 (SD = 1.5) for those who were nonabstinent, $F(1, 59) = 12.25$, $p = .0009$. Subjects scoring 4 or more on the 7-point rating scale at baseline had a 37.5% (6/16) abstinence rate at 6 months, whereas those scoring less than 4 showed a 6.7% (3/45) abstinence rate ($p = .005$ by logistic regression). The mean change in enjoyment rating at week 2 was –1.1 (SD = 1.9) in abstinent subjects and 0.1 (SD = 1.0) in nonabstinent subjects, $F(1, 55) = 8.35$, $p = .006$.

Tolerability and Adherence

Tolerability/side effects

The treatments were generally well tolerated, with 3.3% of participants withdrawing due to medication-related side effects. One participant was on placebo lorcaserin when experiencing an episode of somnambulism, which was therefore attributed to the nicotine patch. Another participant reported dizziness and low energy when receiving lorcaserin with nicotine patch. The most common side effects reported were dry mouth, fatigue, vivid dreams, and itching at the patch application site. Table 1 details the frequency of reported adverse events.

Adherence

During the 12-week period when participants received combination lorcaserin and nicotine patch, adherence was moderately good, with participants reporting using patches on 90.3% of the assigned days and taking lorcaserin as prescribed on 77.8% of days. Adherence to both medications occurred on 72.1% of days.

Discussion

The results support the hypothesis that combination lorcaserin and nicotine patch may be a useful treatment to promote smoking cessation while preventing postcessation weight gain. The rate of 4-week continuous abstinence at the end of treatment was 31.1% overall (90% confidence interval, 21.4%–40.8% and exceeds the abstinence rate [15.3%] reported at the same time point in the Phase 2 trial on lorcaserin alone).[12] Thus, it is likely that the addition of nicotine patch contributed to the treatment efficacy in the present study. The abstinence rate at the 6-month follow-up (>3 months after termination of treatment) was lower, in keeping with the long-term relapse that is typically observed in smoking cessation trials.[18] Smoking abstinence rates for lorcaserin plus nicotine patch appear to be similar to that of other FDA-approved pharmacotherapies reviewed in large meta-analyses.[18]

The absence of postcessation weight gain in participants taking lorcaserin is consistent with amelioration of postquit weight gain revealed in the previous trial. An important similarity between these two trials is that mean change in weight was of a similar magnitude, with abstinent participants in each trial showing small and nonsignificant weight loss at the end of treatment compared with baseline. The mechanism of postcessation weight loss is uncertain, but central activity on serotonin 2C subtype receptors with a resulting reduction in caloric intake is certainly possible because this appears to be the primary mechanism of weight loss when lorcaserin is used in the nonsmoking population.[19]

Table 1. Frequency of reporting adverse effects

	Lorcaserin + patch		Patch (first 2 wk)	
	Affected/at risk (%)	Number of events	Affected/at risk (%)	Number of events
Total	35/56 (62.5)		12/27 (44.44)	
Gastrointestinal disorders				
Constipation	5/56 (8.93)	9	0/27 (0)	0
Nausea	3/56 (5.36)	3	0/27 (0)	0
General disorders				
Coughing	5/56 (8.93)	8	2/27 (7.41)	2
Dizziness/lightheadedness	3/56 (5.36)	3	0/27 (0)	0
Dry mouth	7/56 (12.5)	13	0/27 (0)	0
Fatigue	12/56 (21.43)	14	2/27 (7.41)	2
Insomnia	4/56 (7.14)	5	1/27 (3.7)	1
Vivid dreams	20/56 (35.71)	27	9/27 (33.33)	9
Skin and subcutaneous tissue disorders				
Itching at patch site	13/56 (23.21)	25	4/27 (14.81)	4
Rash at patch site	5/56 (8.93)	11	0/27 (0)	0

The prequit phase sheds light on potential mechanisms of action. Although the smoking lapse procedure did not yield a useful time-to-lapse measure, as many participants achieved the maximum wait duration, craving reduction reported after smoking appeared to be attenuated by lorcaserin. Craving reduction is a measure akin to satisfaction, and it may be speculated that the serotonergic action of lorcaserin to attenuate satiety signals accompanying food intake might generalize to craving for cigarettes. It is uncertain why this did not translate into a significant reduction in craving, but perhaps a longer duration of precessation treatment would allow the reduction in satiation to translate into reduced craving or smoking behavior relative to placebo. Further studies would need to explore this possibility.

An intriguing relationship was observed between smoking abstinence and the effect of lorcaserin on the enjoyment of respiratory tract sensations of smoking (assessed by the change from baseline to week 2). This simple self-report measure could provide clues to mechanism of action as well as potentially be used to identify smokers who would be most responsive to combination lorcaserin/nicotine patch treatment.

Limitations

This trial was relatively small and did not include a control group after the quit smoking date. As such, the study is limited by relatively low power and a lack of placebo control on key outcomes of abstinence and weight change. The use of a design in which all subjects used a single treatment (lorcaserin plus nicotine patch) throughout the primary treatment period allowed for a greater sample size and thus a smaller margin of error to assess the effect of this combination treatment, compared, for example, with a study design in which half of the sample had been randomized to a control condition. A potential limitation is that the sample showed relatively high BMI (30.9). On the other hand, because high BMI is associated with postcessation weight gain, there was a sample bias against the finding of no weight gain, strengthening this finding. In addition, overweight smokers are an important subgroup in need of effective treatments.

The relapse of a substantial fraction of subjects between end of treatment and the 6-month follow-up, 3 months after treatment ended, and the weight gain observed in smoking-abstinent subjects at follow-up, suggest that longer duration treatment or other long-term weight management strategies will be needed to sustain smoking abstinence and forestall long-term weight gain. Postcessation weight gain commonly continues for the first year after quitting,[20] and lorcaserin, when used for weight loss, is often prescribed for a year or more.[21,22] Additional research is needed to assess the extended use of lorcaserin for amelioration of postcessation weight gain over longer periods than the 12-week treatment duration of the present study.

In summary, combination treatment with lorcaserin and nicotine patch appears to provide smokers with a treatment that ameliorates weight gain while offering a success rate comparable to other available cessation treatments.

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Declaration of Interests

J.R. received funding from Philip Morris International, Altria, JUUL Labs. He discloses consulting with Philip Morris International and Revive Therapeutics LLC. He obtained patent purchase agreement in 2011 with Philip Morris International for nicotine inhalation system. J.R.'s privately funded projects are limited to the development and evaluation of reduced-risk tobacco products. J.M.D. received funding from Pfizer Inc. and Axsome Therapeutics Inc. J.M.D. privately funded projects are limited to evaluation of programs or development of drugs designed to treat tobacco use.

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