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ORIGINAL ARTICLE

Varenicline and Lorcaserin for Smoking Cessation and Weight Gain Prevention: A Randomized Clinical Trial

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Abstract

Objective: To evaluate the safety and effectiveness of combination varenicline with lorcaserin in preventing post-cessation weight gain.

Participants and Methods: We conducted a randomized (varenicline for 12 weeks + lorcaserin for 24 weeks vs varenicline for 12 weeks + placebo for 24 weeks) phase II clinical study to obtain preliminary data on the safety and effectiveness of combination varenicline and lorcaserin in preventing post-cessation weight gain in overweight and obese smokers. Eighty-four overweight and obese (body mass index [BMI], 27-40 kg/m^2) cigarette smokers were randomized before study termination (lorcaserin: n=40; placebo: n=44). The primary outcomes were weight and waist circumference (WC) changes at 12 and 24 weeks in smokers meeting criteria for prolonged smoking abstinence.

Results: Thirty-nine participants met criteria for prolonged smoking abstinence at 12 weeks (46%) and 21 at 24 weeks (25%). No significant treatment effect was observed at 12 weeks with lorcaserin compared with placebo (weight difference, −0.7 kg; 90% CI, −2.6 to 1.1 kg; *P*=.51; WC difference, −1.9 cm; 90% CI, −4.2 to 0.5 cm; *P*=.18; or BMI difference, −0.4 kg/m^2; 90% CI, −1.1 to 0.3 kg/m^2; *P*=.33). No significant treatment effect was observed between lorcaserin at 24 weeks compared with placebo (weight, 1.4 kg; 90% CI, −3.8 to 6.7 kg; *P*=.65; WC, −0.9 cm; 90% CI, −5.8 to 4.0 cm; *P*=.75; or BMI 0.29 kg/m^2; 90% CI, −1.5 to 2.12 kg/m^2; *P*=.79).

Conclusion: Weight gain and WC increases after prolonged smoking abstinence were not reduced using combination varenicline and lorcaserin. The results do not support further research in the obese and weight-concerned smoking population using lorcaserin or similar drugs.

Trial Registration: clinicaltrials.gov Identifier: NCT02412631

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Some smokers believe that smoking helps control body weight.[1,2] Smokers gain an average of 5 to 10 lb in the months after smoking abstinence,[3,4] with heavier and more dependent smokers gaining more weight.[5,6] The mean weight gain may be as much as 13 lb at 1 year[7] and 21 lb over 5 years.[8] Post-cessation weight gain (PCWG) has been associated with smoking relapse.[9] In a large population-based study, 52% of women and 32% of men with a previous quit attempt reported that weight gain was one of the reasons for relapse to smoking.[10] In a prior study of a large sample of smokers, 47% of female smokers and 22% of male smokers were classified as having weight concerns.[11] A need exists for the development of smoking cessation pharmacological treatments that will increase smoking abstinence. Drugs that have the ability to modulate PCWG, a major reason for relapse, should have the potential to have a large impact.

Activation of the serotonin 5-Hydroxytryptamine (5-HT) receptor 2 (5-HT$_2$) has been associated with satiety, hypophagia, and modulation of the effects of psychostimulant addiction.[12,13] Lorcaserin is a selective 5-HT$_{2C}$ receptor agonist with a 100-fold selectivity of 5-HT$_{2C}$ compared

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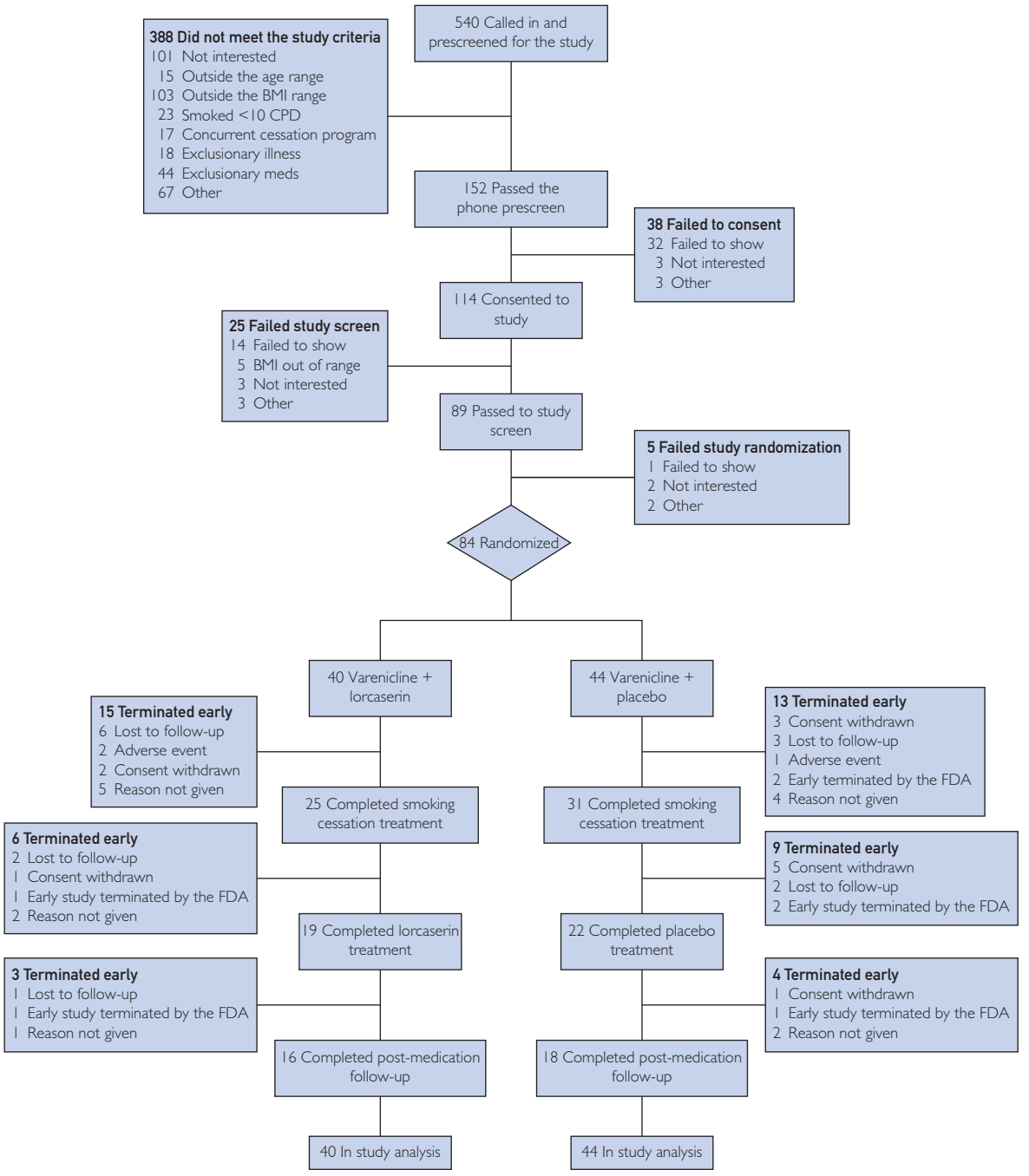

FIGURE. Participant flow in the study. CPD, cigarette per day; FDA, Food and Drug Administration.

with the 5-HT_{2A} receptor subtype. Activation of the 5-HT_{2C} receptor subtype in the hypothalamus increases pro-opiomelanocortin neuron activity, leading to weight loss through hypophagia and satiety. In 3 large phase III studies, there has been no valvular heart disease associated with lorcaserin.

In addition to the effects on satiety and weight loss, serotonin activation appears to be involved with nicotine effects.[14,15]

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Ketanserin, a 5-HT_{2A} and 5-HT_{2C} antagonist, significantly reduced nicotine self-administration in rats.[15] Lorcaserin has been found to reduce nicotine self-administration in 2 animal studies. The first study used self-administered subcutaneous doses of nicotine (0.03 mg/kg per infusion) with fixed doses of lorcaserin (0.3125-20 mg/kg) in rats for 2 weeks.[15] Nicotine self-administration was reduced in all doses of lorcaserin compared with placebo. The second study used self-administered subcutaneous doses of nicotine, and all doses of lorcaserin reduced self-administration.[14] Furthermore, lorcaserin produced a dose-dependent reduction of nicotine-induced hyperactivity.[14] These studies support the hypothesis that lorcaserin could potentially aid in smoking cessation in addition to attenuating PCWG.

Combining pharmacological treatments for tobacco dependence may increase smoking abstinence rates. In a meta-analysis of 267 studies (N=101,804), varenicline was more effective than single categories of nicotine replacement therapy (NRT) but not combination NRT (odds ratio [OR], 1.06; 95% CI, 0.75 to 1.48). Combination NRT increased the odds of quitting as compared with single formulations of NRT. In a recent multicenter randomized clinical trial, combination varenicline and NRT patch was associated with a 55.4% continuously abstinent rate at 12 weeks compared with 40.9% in varenicline and placebo patch (OR, 1.85; 95% CI, 1.19 to 2.89; *P*=.007). At 24 weeks, the continuous abstinence rate for combination was 49% in varenicline and NRT combination vs 32.6% in varenicline and placebo combination (OR, 1.98; 95% CI, 1.25 to 3.14; *P*=.004). We have observed that the combination of bupropion SR and varenicline increases long-term smoking abstinence as compared with varenicline and placebo in heavier smokers.[13] Combination pharmacological treatment holds promise for treating the more dependent smoker, but to date we have only 2 Food and Drug Administration (FDA)—approved medications in addition to NRT. We have a need for the development of new pharmacological treatments of smoking cessation that increase smoking abstinence rates alone or in combination with other smoking cessations and can decrease PCWG.

The purpose of the present study was to evaluate the safety and effectiveness of varenicline combined with lorcaserin in preventing PCWG and treating tobacco dependence in overweight and obese smokers.

PARTICIPANTS AND METHODS

Study Overview

The present study was randomized, placebo-controlled, parallel-group clinical trial. Study participants were randomized to (1) lorcaserin for 24 weeks in combination with varenicline for 12 weeks or (2) placebo for 24 weeks in combination with varenicline for 12 weeks. This study was approved by the Mayo Clinic Institutional Review Board, and written informed consent was obtained for all study participants. This study was registered in ClinicalTrials.gov (NCT02412631).

Setting

In accordance with the Declaration of Helsinki, this study was reviewed (21 CFR Part 56) and approved (ID 15-005230) by the Mayo Clinic Institutional Review Board. The Mayo Clinic Institutional Review Board—approved written informed consent (21CFR Part 50) was obtained for all study participants before study participation. Potential participants were recruited from the local community of Rochester, Minnesota, between June 17, 2016, and February 14, 2020. This report is based on all participants who consented to study, passed study criteria, and were randomized to study. All study visits and treatments took place in the Rochester campus of Mayo Clinic. The study adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines on reporting clinical trials[16] as depicted in the CONSORT diagram presented in the Figure.

Participants

All interested individuals called a central number and underwent a 10-minute phone prescreen. If they passed the telephone prescreen, they were invited to attend an in-person consent visit.

After participants consented to participation, they signed a written informed consent form and were screened for study eligibility. They were excluded if they did not meet the

study entry criteria: age 18 years or older; smoking 10 cigarettes/d or more (for the past 6 months); body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) of 27 to 34.9 kg/m^2; consenting to study; not on any concurrent weight loss program; no recent weight fluctuation of 20 lb or more; no medical unstable condition; no current depression or suicide ideation; no lifetime history of psychosis, bipolar disorder, or schizophrenia; a negative pregnancy test result; no current abuse of or dependence on any substance other than tobacco; no current use of any selective serotonin reuptake inhibitor; no current uncontrolled hypertension; or having any other condition that could have hindered participation or adherence to study procedures. If they passed the postconsent screening procedures, they were invited to participate and randomized to 1 of 2 study medication groups (see below). The study medication was provided to the participant at the next visit, which was the baseline visit. Participants were asked to return once every 4 weeks for 24 weeks while taking study medication with 1 phone visit at week 13 and 4 additional visits in the subsequent 6 months postmedication phase. The follow-up postmedication visits consisted of 1 safety phone visit 1 week after the last of the medication (25 weeks) and 1 phone visit at week 39, along with 2 in-person visits at weeks 26 and 52.

Randomization

Study participants were randomized to 1 of 2 study groups: (1) lorcaserin for 24 weeks in combination with varenicline for 12 weeks or (2) placebo for 24 weeks in combination with varenicline for 12 weeks. To ensure balance, a computerized dynamic allocation randomization program was used with participant stratified on the basis of sex (male, female) and BMI (between 27 and 34.9 kg/m^2). The randomization information was available only to the study pharmacist who used the randomization program to determine the appropriate treatment assignment and prepared the study medications accordingly. Patients, investigators, and study coordinators were all blinded to the study assignments.

Interventions

Study Medication. Participants were randomized to receive either (1) active lorcaserin for 24 weeks simultaneously with active varenicline or (2) placebo lorcaserin for 24 weeks simultaneously with active varenicline. Everyone received 12 weeks of varenicline (weeks 1-12) and 24 weeks of active or placebo lorcaserin (weeks 1-24). Varenicline dosage was 0.5 mg once daily for 3 days, 0.5 mg twice daily for days 4 to 7, and 1 mg twice daily for the remaining 11 weeks of treatment (a total of 12 weeks of treatment). The target quit date for study participants was day 8 of varenicline initiation. Lorcaserin dosage was 10 mg twice daily. The placebo was encapsuled to visullay appear the same as lorcaserin by the Mayo Clinic pharmacy, which also conducted study medication dispensing and instructions for its use.

Behavioral Intervention. During weeks 1 to 12, study assistants completed a brief (10-minute) individual behavioral intervention at each visit focusing on stopping smoking by using the patient self-help manual "Smoke-Free and Living It" (http://mayoweb.mayo.edu/sp-forms/mc2000-mc2099/mc2065-77.pdf). During weeks 13 to 24, study staff completed a brief (10-minute) individual behavioral intervention at each visit focusing on healthy weight by using the patient self-help manual "My Weight Solution" (http://mayoweb.mayo.edu/sp-forms/mc7500-mc7599/mc7587.pdf).

Statistical Analyses

The demographic characteristics for the entire cohort were described using count (percentage) for categorical variables and mean, SD, maximum, and minimum for continuous variables. The same variables are also described for those who completed week 12 and maintained prolonged abstinence. *Prolonged abstinence* was defined as not having used tobacco at least 1 day in each of 2 consecutive weeks for 14 days after the target quit date.

To analyze the average differences between the treatments at week 12 and week 24 for weight outcomes, linear regression models were used. The anthropomorphic measures of interest were weight (in kilograms), BMI

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TABLE 1. Demographic Characteristics of Participants[a,b]

Characteristic	Placebo (n=44)	Treatment (n=40)	Total (N=84)
Age (y)			
Mean ± SD	41.3±9.05	43.4±11.0	42.3±10.0
Median	41.3	42.9	42.1
Range	23.5-61.2	24.9-64.9	23.5-64.9
Sex			
Female	30 (68.2)	25 (62.5)	55 (65.5)
Male	14 (31.8)	15 (37.5)	29 (34.5)
Ethnicity			
Non-Hispanic nor Latino	42 (95.5)	40 (100.0)	82 (97.6)
Hispanic or Latino	2 (4.5)	0 (0.0)	2 (2.4)
Race			
Asian	0 (0.0)	2 (5.0)	2 (2.4
White	41 (93.2)	37 (92.5)	78 (92.9)
≥1 Race	3 (6.8)	1 (2.5)	4 (4.8)
Marital status			
Never married	12 (27.3)	7 (17.5)	19 (22.6)
Separated/divorced	13 (29.5)	10 (25.0)	23 (27.4)
Widowed	0 (0.0)	1 (2.5)	1 (1.2)
Married	17 (38.6)	20 (50.0)	37 (44.0)
Living as married	2 (4.5)	2 (5.0)	4 (4.8)
Education			
Some high school	1 (2.3)	2 (5.0)	3 (3.6)
Graduated high school	12 (27.3)	3 (7.5)	15 (17.9)
GED or ABE certificate	1 (2.3)	0 (0.0)	1 (1.2)
Some college - technical - vocational school (AA, LPN, etc)	22 (50.0)	27 (67.5)	49 (58.3)
4-Y college degree	6 (13.6)	6 (15.0)	12 (14.3)
Graduate or professional degree	2 (4.5)	2 (5.0)	4 (4.8)

[a]AA, associate of arts; ABE, adult basic education certificate; GED, general equivalency diploma; LPN, licensed practical nurse.
[b]Data are presented as No. (percentage) unless indicated otherwise.

(in kilograms per meters squared), waist circumference (WC; in centimeters), and fat mass (in kilograms). Outcomes were measured as the week 12 or week 24 result minus the baseline measurement. These models were run for both those who met prolonged abstinence and those who met point prevalence abstinence. *Point prevalence abstinence* was defined as those who have not used any tobacco products in the past 7 days. Point estimates and 90% CIs were reported for the treatment effect at both week 12 and week 24 for all linear models. Data were managed using the REDCap (Research Electronic Data Capture) tool hosted at Mayo Clinic,[17] and analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc, Cary, NC).[18]

The sample size for this study was determined for the primary end point of weight change from baseline to week 24 in participants who met criteria for prolonged abstinence. Under the assumption that 30% of participants would meet criteria for prolonged abstinence and a difference in weight gain between groups of 2.0 kg would be clinically meaningful, it was determined that a total sample size of 100 would be required to provide statistical power of more than 80% to conclude that future studies assessing the combination of varenicline and lorcaserin to prevent PCWG were warranted.

RESULTS

A total of 84 participants had been randomized when the study was terminated prematurely on February 14, 2020, a day after the drug lorcaserin was unexpectedly removed from the market by the FDA. Most patients randomized to the study at that point were

TABLE 2. Smoking Abstinence Outcomes[a]

Variable	Placebo	Treatment	*P* value[b]
Week 12	n=42[c]	n=40	
Prolonged abstinence	21 (50.0)	18 (45.0)	.65
Point prevalence abstinence	23 (54.8)	20 (50.0)	.67
Week 24	n=41[d]	n=39[d]	
Prolonged abstinence	13 (49.1)	8 (20.5)	.26
Point prevalence abstinence	15 (36.6)	11 (28.2)	.42

[a]Data are presented as No. (percentage) unless indicated otherwise.
[b]Chi-square test.
[c]Two participants assigned to placebo were still receiving treatment when the study was terminated; lorcaserin was pulled from the market and the study had to be terminated; therefore, they were not included in this analysis.
[d]Three participants assigned to placebo and 1 to treatment and were still receiving lorcaserin/placebo when the study was terminated; lorcaserin was pulled from the market and the study had to be terminated; therefore, they were not included in this analysis.

White (92.9%) and female (65.5%) with a mean age of 42.3±10.0 years (Table 1). The average cigarettes smoked per day was 17.5 (range, 10-35), and the average Fagerström Test for Nicotine Dependence score was 4.9 (range, 1-10) (Supplemental Table 1, available online at http://www.mcpiqojournal.org).

Smoking abstinence by treatment group for week 12 and week 24 is reported in Table 2. Two placebo participants were not included in the overall total to calculate smoking abstinence for week 12 and 4 patients (3 placebo assigned patients and 1 treatment assigned patient) for week 24 owing to the study being terminated because lorcaserin was removed from the market.

Differences in anthropomorphic measures among patients meeting criteria for prolonged smoking abstinence are presented in Table 3. The average change in each outcome at week 12 and week 24 is recorded. No significant differences were observed between treatment arms for weight (*P*=.51), BMI (*P*=.33), WC (*P*=.18), or fat mass (*P*=.56). The results of the treatment effect for those who maintained at least point prevalence abstinence are reported in Table 4 for the difference from baseline to weeks 12 and 24. The average difference between baseline and week 12 for the treatment group was not significantly different from the average difference between baseline and week 12 for any of the 4 outcomes. No significant differences were observed between the 2 groups when analyzing baseline to week 24.

No serious adverse effects related to either medication was observed. The 3 most common nonserious adverse events were sleep

TABLE 3. Linear Regression Comparing Mean Differences in Anthropomorphic Measures at Weeks 12 and 24 for Participants Meeting Criteria for Prolonged Smoking Abstinence[a,b]

Variable	Placebo[c]	Treatment[c]	Point estimate (90% CI)	*P* value
Week 12	n=21	n=18		
Weight (kg)	1.9±4.1	1.1±2.6	−0.7 (−2.6 to 1.1)	.51
Waist circumference (cm)	1.3±4.7	−0.6±3.9	−1.9 (−4.2 to 0.5)	.18
BMI (kg/m^2)	0.8±1.4	0.4±0.9	−0.4 (−1.1 to 0.3)	.33
Fat mass (kg)	1.7±3.6	1.1±2.4	−0.6 (−2.3 to 1.1)	.56
Week 24	n=13	n=8		
Weight (kg)	0.7±8.4	2.2±2.1	1.4 (−3.8 to 6.7)	.65
Waist circumference (cm)	0.8±7.6	−0.1±3.0	−0.9 (−5.8 to 4.0)	.75
BMI (kg/m^2)	0.5±2.9	0.8±0.7	0.29 (−1.5 to 2.12)	.79
Fat mass (kg)	0.4±7.1	2.2±2.7	1.9 (−2.7 to 6.5)	.49

[a]BMI, body mass index.
[b]Data are presented as Δmean ± SD unless indicated otherwise.
[c]Average change between baseline and week 12 or week 24.

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TABLE 4. Linear Regression to Compare Mean Differences at Weeks 12 and 24 for Point Prevalence Abstinence[a,b]

Variable	Placebo[c]	Treatment[c]	Point estimate (90% CI)	*P* value
Week 12	n=23	n=20		
Weight (kg)	2.5±4.3	1.5±2.5	−1.0 (−2.8 to 0.9)	.39
Waist circumference (cm)	2.0±5.4	−0.1±3.7	−2.1 (−4.5 to 0.3)	.15
BMI (kg/m^2)	0.9±1.5	0.5±0.9	−0.4 (−1.0 to 0.2)	.29
Fat mass (kg)	1.8±3.4	1.4±2.2	−0.4 (−1.9 to 1.1)	.67
Week 24	n=15	n=11		
Weight (kg)	2.5±9.1	1.4±2.7	−1.2 (−6.0 to 3.7)	.69
Waist circumference (cm)	2.9±8.9	−1.5±4.2	−4.4 (−9.4 to 0.5)	.14
BMI (kg/m^2)	1.1±3.2	0.5±1.0	−0.6 (−2.3 to 1.1)	.55
Fat mass (kg)	1.9±7.8	1.5±3.0	−0.5 (−4.8 to 3.8)	.85

[a]BMI, body mass index.
[b]Data are presented as Δmean ± SD unless indicated otherwise.
[c]Average change between baseline and week 12 or week 24.

disorders (placebo: n=9 [20%] and treatment: n=7 [18%]), nausea (placebo: n=8 [18%] and treatment: n=5 [13%]), and gastrointestinal problems (placebo: n=5 [11%] and treatment: n=4 [10%]).

DISCUSSION

We observed no significant differences in PCWG, WC, or smoking abstinence outcomes in overweight and obese smokers receiving combination varenicline and lorcaserin compared with varenicline and placebo. Combination therapy was well tolerated with few adverse effects. One of the main challenges in interpreting the data is the removal of lorcaserin from the market on February 13, 2020, because of a small increase in the number of cancer cases in the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients − Thrombolysis in Myocardial Infarction (CAMELLIA-TIMI) 61 trial.[19] The present study was terminated immediately (February 14, 2020) after this recommendation, with 16 participants short of a target of 100 for recruitment.

We previously conducted an open label, single-arm, phase II clinical pilot study to obtain preliminary data on the safety and effectiveness of combination varenicline and lorcaserin in preventing PCWG in overweight and obese smokers.[20] The design was similar to the present study, although we provided 12 weeks of lorcaserin vs the current 24 weeks. We had increased the length of lorcaserin given the peak PCWG previously being reported around 6 months. All participants received open label varenicline (1 mg twice a day) and lorcaserin (10 mg twice a day) for 12 weeks with follow-up at 26 weeks. Ten participants met criteria for prolonged smoking abstinence at 12 weeks (n=10 of 20 [50%]) and 6 at 26 weeks (n=6 of 20 [30%]). These rates are similar to the present study at 12 weeks (n=39 of 84 [46.4%]) and 24 weeks (n=21 of 84 [25.0%]).[20] In those achieving prolonged smoking abstinence at 12 weeks, WC was 0.2±6.0 cm (90% CI, −2.9 to 3.4 cm) and weight gain was 1.1±3.9 kg (90% CI, −0.9 to 3.1 kg).[20] During the present study, the change in WC in those receiving varenicline and lorcaserin was −0.6±3.9 cm and the change in weight was 1.1±2.6 kg; however, neither of these measures were found to differ significantly when compared to patients who received varenicline and placebo.

A recently published study explored the efficacy of combination lorcaserin and nicotine patch for smoking cessation treatment and prevention of PCWG.[21] The trial included 61 adult daily smokers who were asked to quit smoking using a combination of lorcaserin and NRT (patch). Before the quit day (set at 2 weeks), participants were randomized to 2 weeks of either (1) lorcaserin (10 mg twice daily) plus NRT (21 mg; transdermal patch)

or (2) placebo plus NRT (21 mg; transdermal patch). After this 2-week period, all participants received both lorcaserin and NRT. At week 14, combination therapy was discontinued and NRT was continued for an additional 2 weeks. The clinical outcomes evaluated included 4-week continuous smoking abstinence at the end of the treatment and weight change from baseline. Biochemically confirmed continuous smoking abstinence from 7 to 10 weeks after the targeted quit date was 31.1% (90% CI, 21.4% to 40.8%). Participants who were successful in quitting had a mean weight change of −0.16±3.27 kg. As with our open label varenicline and lorcaserin pilot, this study suggested that the combination of lorcaserin and NRT could be beneficial in reducing PCWG.

The FDA reported on February 13, 2020, an increased risk of cancer with lorcaserin in follow-up of the CAMELLIA-TIMI 61 trial and requested its removal from the market by the manufacturer.[19,22] As part of a postmarketing study to evaluate cardiovascular safety, the CAMELLIA-TIMI 61 trial randomized 12,000 participants with cardiovascular risk factors to lorcaserin (10 mg twice a day) vs placebo.[19] The primary outcome was not cancer but major cardiovascular events, nor was it listed as a secondary outcome in the article. The median follow-up period was 3.3 years, and there were no significant differences in primary outcome. Major cardiovascular events occurred with 364 participants (n=6000 [6.1%]) in the lorcaserin group and 369 (n=6000 [6.2%]) in the placebo group (hazard ratio, 0.99; 95% CI, 0.85 to 1.14; $P<.001$).[19] Listed in the article was any cancer of special interest, with 215 occurring in lorcaserin vs 210 in placebo participants.[19] The FDA stated that they identified a cancer signal after publication.[22] The FDA continued to follow these patients and attempted to identify, when possible, the cause of death on cancer-related events. They published results suggesting 462 participants reporting cancer with lorcaserin (n=6000 [7.7%]) vs 423 cases with placebo (n=6000 [7.1%]).[22] They stated that after weighing the evidence of excess cancer risk associated with lorcaserin with its benefits of modest weight loss, they recommended removal from the US market. They did recognize the small cancer risk and nowhere did they mention lorcaserin as a potential treatment of addiction and the multiple clinical trials ongoing in cocaine, tobacco, and marijuana abuse disorders.[22]

A recent systematic review and meta-analysis further examined the risk of cancer with lorcaserin and asked the central question whether lorcaserin is associated with a higher incidence of cancer.[23] The authors used MEDLINE, Embase, and Cochrane Central Register of Controlled Trials including randomized controlled trials that compared lorcaserin with other interventions or no treatment in adults and identified 11 trials (N=21,299 participants).[23] There were 476 cases of cancer (n=10,342 [4.60%]) in participants receiving lorcaserin and 438 cases in those receiving placebo (n=9429 [4.65%]) (relative risk, 1.08; 95% CI, 0.96 to 1.23).[23] The authors point out that the results were heavily influenced by the CAMELLIA-TIMI 61 trial, which, as stated previously, found that the lorcaserin group had a higher risk of lung and pancreatic cancer but not colon cancer.[23] The meta-analysis did not support conclusion of increased risk of cancer with lorcaserin, but the authors suggested a trend with a potential higher incidence of lung and pancreatic cancer.[23]

Although lorcaserin has been pulled from the market, the concept of preventing PCWG in obese smokers is one that deserves further consideration. Glucagon like peptide-1 receptor agonists (GLP-1 RAs) are a class of medications that are currently FDA approved for the treatment of diabetes mellitus (DM) and obesity. In addition to obesity and DM, there has been some basic science work that has examined the role of GLP-1 in addiction. Animal data have indicated that GLP-1 RAs may decrease the reinforcing properties of cocaine through dopamine pathways.[24] Recent animal data indicated that GLP-1 and ghrelin modulate the mesolimbic reward pathways and decreased ethanol uptake.[25] A recent randomized clinical trial examined the role of GLP-1 RAs (exenatide) and NRT in PCWG and smoking cessation in 84 pre-DM or overweight smokers.[26] Participants were randomized to 2 mg of exenatide vs placebo with all receiving NRT (21 mg patches) and brief counseling for 6 weeks with pilot aims of

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7-day point prevalence abstinence and PCWG. Exenatide improved smoking abstinence compared with placebo (46% vs 27%), and post-cessation body weight was 5.6 lb lower in those who met abstinence criteria. When clinicians have obese patients and/or patients with DM who smoke, considering GLP-1 RA therapy for weight and DM management may have the added benefit of smoking cessation. Larger trials should be conducted to determine whether GLP-1 RAs can lead to prolonged smoking cessation.

There are a number of limitations of the present study that need to be acknowledged. This was a small single-center randomized controlled trial that was terminated before reaching the target enrollment of 100 participants. The study was terminated because of lorcaserin removal from the market owing to a small increased cancer risk of prolonged use. Our study may be underpowered for the outcomes of interest. The results from this study should be interpreted within the context of these limitations.

CONCLUSION

Post-cessation weight gain is a concern among overweight and obese smokers. Prior studies using combinations of varenicline, lorcaserin, and NRT found potential benefit in preventing or attenuating weight gain. The present study did not confirm these earlier studies, but the results should be interpreted with caution given the early termination of our study owing to the removal of lorcaserin from the market and the possibility that we were underpowered for the present analysis.

POTENTIAL COMPETING INTERESTS

Dr Hurt reports financial support from the National Institutes of Health and reports receiving equipment, drugs, or supplies from Pfizer; he is a consultant for Nestlé Nutrition for research activities unrelated to the content of this article. The other authors report no competing interests.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and acronyms: **BMI,** body mass index; **CAMELLIA-TIMI 61 trial,** Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients — Thrombolysis in Myocardial Infarction 61, trial; **DM,** diabetes mellitus; **FDA,** Food and Drug Administration; **GLP-1 RA,** glucagon like peptide-1 receptor agonist; **NRT,** nicotine replacement therapy; **OR,** odds ratio; **PCWG,** post-cessation weight gain; **WC,** waist circumference

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