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Characterization of the effect of naltrexone/bupropion on body composition

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Abstract

Aims: Oral treatment extended-release naltrexone/bupropion (NB) leads to significant weight loss, but its effect on body composition remains unclear. We investigated changes in body composition with dual-energy x-ray absorptiometry after treatment with NB or placebo in a subgroup of participants from a randomized control phase 3 study (COR-I).

Materials and Methods: Observed changes from baseline to week 52 were estimated for total, lean, and fat mass. Changes in body composition were evaluated using linear regression and adjusted for baseline covariates.

Results: The analysis included 82 participants (placebo, $n = 26$; NB, $n = 56$) with comparable baseline characteristics (age, BMI, sex). The NB group experienced a significant −7.8% change of total mass (−12.9% change in fat mass and −4.1% in lean mass), compared with a −2.8% change of total mass (−4.8% change in fat mass and −1.4% in lean mass) in the placebo group. The adjusted changes in lean-to-fat mass ratio of 0.069 in the NB group and −0.056 in the placebo group were significantly different ($p < 0.05$).

Conclusions: NB-induced weight loss is associated with significant reductions in total percent fat mass, increase in total percent lean mass, and change in lean-to-fat mass ratio, in comparison to placebo. Larger studies are needed to further elucidate the clinical significance of these changes and impact of a potentially healthier metabolism.

KEYWORDS
body composition, naltrexone/bupropion, obesity, overweight, weight loss

1 | INTRODUCTION

Obesity and overweight are highly prevalent globally, with a substantial negative impact across multiple health parameters (e.g. cardiovascular, metabolic).[1,2] Intentional weight loss of 5% to 10% among people with obesity is associated with a number of health benefits, including improvements in cardiometabolic risk factors (e.g. hyperglycaemia, hypertension, and dyslipidaemia), reduction in cardiovascular and all-cause mortality, and improvements in quality of life (e.g. improvement in mood and body image, mechanical improvement for arthritis).[3–9]

The changes that occur during weight loss among people with obesity include decreased overall body fat, abdominal fat, and hepatic

fat.[3] These changes are thought to be the key drivers of weight loss–related improvements in health, as the accumulation of adipose tissue in the upper body, particularly abdominal fat, is associated with the development of obesity-related comorbidities and increased cardiometabolic risk.[10,11]

Understanding the impact of weight loss interventions on body composition is therefore important to our overall understanding of the associated health impacts. Most studies, however, focus on overall body weight changes or changes in body mass index (BMI), without considering body composition (i.e. the ratio of lean mass to fat mass) or adiposity.[10] Since weight loss can lead to a reduction in fat-free mass, and consequently loss of skeletal muscle mass,[12] the focus on BMI is even more problematic in certain subgroups of people with obesity, such as individuals with comorbid obesity and sarcopenia.[11] For such individuals, it is particularly important to ensure that the greatest proportion of weight loss occurring with a particular intervention is derived from adipose tissue, as loss of skeletal muscle is associated with reductions in overall health and function.[11]

Extended-release naltrexone/bupropion (NB) is a medication approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in several countries or regions, including the United States, United Kingdom, EU, and Canada. Use of NB in its clinical trial program led to significant reductions in weight compared with placebo (reduced-calorie diet and increased physical activity).[13–18] However, there are limited published data on the effects of NB on body composition. A subset analysis of 80 participants from a phase 2 trial showed, by dual-energy x-ray absorptiometry (DEXA), that NB was associated with a significantly greater reduction in body fat than placebo (−14.0% vs. −4.0%), without a greater relative reduction in lean mass.[19] The reduction in visceral adipose tissue (VAT) mass was also significantly greater with NB than placebo (−15.0% vs. −4.6%).

Body composition can be determined using DEXA, a two-dimensional, non-invasive, rapid imaging method that transmits high- and low-energy x-rays through the body.[11] It is most commonly used to measure bone mineral density for individuals with various conditions, but it is also capable of measuring regional and whole-body fat and lean mass using low radiation exposure.[20,21] For a DEXA scan, the subject is prone and the x-ray beams, which are attenuated differently depending on the tissues (i.e. fat, lean tissue, bone), pass through the body from anterior to posterior.

The purpose of this study was, therefore, to investigate the effect of NB on body composition by examining changes in the fraction of fat and lean mass among a subgroup of participants who had undergone DEXA in a randomized, placebo-controlled clinical trial (COR-I; NCT00532779).[13]

2 | MATERIALS AND METHODS

2.1 | COR-I participants

This sub-study analysed data from a subgroup of participants from the COR-I trial (Figure S1), whose study design and methods are described elsewhere.[13] Briefly, the phase 3, multi-centre, double-blind, placebo-controlled, 56-week COR-I study included 1742 men and women aged 18 to 65 years either with a BMI of 30 to 45 kg/m^2 and un-complicated obesity, or with a BMI of at least 27 kg/m^2 and controlled hypertension, dyslipidaemia, or both. Exclusion criteria were as follows: obesity of known endocrine origin; type 1 or type 2 diabetes; cerebrovascular, cardiovascular, hepatic, or renal disease; previous surgical or device intervention to treat obesity; a gain or loss of 4 kg or more in the last 3 months before randomization; a history of seizures or serious psychiatric illness; treatment with naltrexone or bupropion in the 12 months prior to the trial; and a history of drug or alcohol abuse or dependence in the 12 months prior to the trial. Women of childbearing age were required to use effective contraception, and no additional weight-loss drugs were allowed during the trial.

Participants enrolled in COR-I provided written informed consent. The protocol was approved by each participating institution, and the study was conducted according to the guidelines and principles of Good Clinical Practices standards and the Declaration of Helsinki.[13] An independent data safety monitoring committee undertook a prespecified interim safety review after 50% of the study population had completed 20 weeks of treatment.[13]

2.2 | COR-I study procedures

Participants in the parent COR-I study were randomized in a 1:1:1 ratio to either receive a fixed dose of extended-release 32 mg naltrexone per day with 360 mg bupropion per day (NB32 group), given as two 8/90-mg tablets twice daily; extended-release 16 mg naltrexone per day with 360 mg bupropion per day (NB16 group), given as two 4/90-mg tablets twice daily; or a matching placebo twice daily (placebo group).[13]

Subjects in the active treatment arms were initiated at one quarter of the target dose and titrated weekly to reach target dose at week 4. All participants were instructed to follow a hypocaloric diet (500 kcal deficit per day) and were given advice on lifestyle modification and increased physical activity. Instructions were given at baseline and on weeks 4, 12, 24, 36, and 48. However, data for compliance with the instructions were not collected.

2.3 | COR-I sub-study procedures

COR-I subjects who had undergone a DEXA scan at baseline and week 52 were included in this sub-study. A sample size of approximately 80 participants was determined to be necessary to reach 99% chance of detecting a statistically significant difference between the pooled NB treatment compared with placebo.

To be eligible for a DEXA scan, COR-I participants of childbearing potential needed a negative urine pregnancy test within 48 h prior to the scan. Exclusion criteria were body weight exceeding table weight limits at the site performing the DEXA scan, a history of claustrophobia or intolerance to DEXA scanning procedures, or the presence of surgically implanted devices that would interfere with the measurement of body or visceral fat. Participants who had upper/lower gastrointestinal

series, or an abdominal computed tomography scan, with barium were required to wait 2 weeks before undergoing the DEXA scan.

DEXA measurement of total fat mass, total lean mass, and body fat percentage was performed as an outpatient assessment using Hologic DEXA technology prior to randomization in the COR-I study (i.e. baseline) and at week 52. Data were acquired by DEXA technologists who had completed training/certification with a body composition reading centre research associate. Measurements were not retaken if the participant discontinued their assigned COR-I treatment prior to week 12. Measurements were taken at an early termination visit if the participant discontinued their assigned COR-I treatment between weeks 12 and 52.

2.4 | COR-I sub-study outcome measures

The primary objective of this sub-study was to evaluate the absolute change in total fat mass from baseline to week 52 between pooled NB doses and placebo. Secondary objectives included the evaluation of the percent change in total fat mass from baseline to week 52 and change in total lean mass from baseline to week 52.

2.5 | COR-I sub-study statistical analysis

The NB dosing groups were pooled for the purpose of this analysis, given the primary interest of this sub-study and since there were no meaningful differences in characteristics between participants randomized to NB16 or NB32 in the COR-I trial. Observed mean absolute and percent changes from baseline to week 52 were estimated using available data for each variable, total body mass, total lean mass, total fat mass, with total body mass (or body 'weight') equals to total lean mass plus total fat mass. A general linear model was used to determine the expected change in body composition parameters based on observed changes in total lean mass and fat mass measured from baseline to 52 weeks in participants who received placebo or NB. A general linear model was also used to adjust observed data for covariates such as race, sex, age, BMI, and presence of metabolic syndrome at baseline in the parent study. Differences between distributions were assessed using a Kolmogorov–Smirnov test. Treatment arm comparisons for baseline characteristics and observed data were performed using a Student's *t*-test or chi-square. Differences were considered significant with $\alpha = 0.05$. SAS 9.4 running on Windows platform was used to carry out the calculations.

3 | RESULTS

3.1 | Characteristics of COR-I sub-study participants

The analysis included 82 participants from the COR-I trial: 26 in the placebo group and 56 in the NB group. Most participants were female (84.1%), with a numerically higher proportion of females in the NB group. The participants had a mean (SD) age of 45.6 (10.2) years, a mean (SD) BMI of 35.1 (4.1) kg/m^2, and 19.5% had metabolic syndrome (e.g. hypertension, dyslipidaemia). Total body mass was lower in participants randomized to NB (94.8 kg) than to placebo (100.3 kg); however, percent lean mass, percent fat mass, and lean-to-fat mass ratio were similar between treatment groups at baseline (Table 1).

3.2 | Observed change in total body mass, lean mass, and fat mass

By week 52, the NB group experienced a clinically and statistically significant mean reduction in total body mass of 7.2 kg (95% CI −9.3, −5.2) compared with the placebo group, which only experienced a mean reduction of 2.8 kg (95% CI −4.9, −0.7, Table 2). The changes in the NB group consisted of a −5.0 kg (95% CI −6.5, −3.4) change in total fat mass and a −2.3 kg (95% CI −2.9, −1.6) change in total lean mass. In comparison, the placebo group experienced a smaller −2.0 kg (95% CI −3.4, −0.5) change in total fat mass and a smaller −0.8 kg (95% CI −1.6, 0.0) change in total body lean mass (Table 2).

These changes corresponded to a 7.8% loss of body mass for the NB group and 2.8% loss of body mass for the placebo group (Table 2). In the NB group, this loss consisted of −12.9% (95% CI −16.8, −9.1) change in fat mass and a −4.1% (95% CI −5.3, −2.9) change in lean mass, significantly higher than the loss in the placebo group, which consisted of −4.8% (95% CI −8.2, −1.4) change in fat mass and −1.4% (95% CI −2.7, 0) change in lean mass.

3.3 | Observed change in body composition

At week 52, mean body composition as measured by lean-to-fat mass ratio was 1.54 in the placebo group and 1.64 in the NB group (Table 2), indicating a higher proportion of lean mass in the body composition of the NB group.

The loss of total body mass combined with a higher loss of fat than lean mass resulted in a shift in body composition that was more pronounced in the NB group. In this group, the proportion of lean mass increased by 2.6% (95% CI 1.6, 3.6), which was approximately 3 times the 0.9% (95% CI 0.2, 1.6) increase observed in the placebo group (Table 2). Conversely, the proportion of fat mass decreased by 2.6% in the NB group and by 0.9% in the placebo group.

Based on the linear regression, a fat mass change of 66.8% in the placebo group and a 74.4% in the NB group is expected per change in total body mass (Figure S2A,B). This corresponded to a lean mass change of 33.2% in the placebo group and 25.6% in the NB group, per change in total body mass for NB. Percent change in fat mass vs. lean mass showed a greater number of participants in the NB group than in the placebo group falling along the line of 25% change in lean mass/75% change in fat mass (Figure 1). In individuals who lost both lean and fat mass, the distribution of lean and fat mass change peaked at a composition of 25% lean/75% fat mass for NB, and a composition of 45% lean/55% fat mass in the placebo group (Figure S3). However, there were no significant differences between both subgroups.

TABLE 1 Baseline characteristics.

Characteristics		Placebo ($n = 26$)	NB ($n = 56$)	p value
Age	Mean (SD)	44.7 (10.3)	46.1 (10.3)	0.569
Sex, *n* (%)				
Female		20 (76.9%)	49 (87.5%)	0.222
Male		6 (23.1%)	7 (12.5%)	
Race, *n* (%)				
White/Caucasian		19 (73.1%)	41 (73.2%)	0.783
Black or African American		7 (26.9%)	14 (25.0%)	
Other or unknown		0	1 (1.8%)	
Metabolic syndrome, *n* (%)	Yes	6 (23.1%)	10 (17.9%)	0.579
BMI, kg/m^2		36.0 (4.8)	34.7 (3.7)	0.224
Total body mass, kg		100.3 (13.3)	94.8 (14.5)	0.098
Lean mass				
Total, kg		58.5 (10.1)	55.7 (11.4)	0.266
Proportion of body mass, %		58.4 (6.7)	58.6 (5.0)	0.911
Fat mass				
Total, kg		41.7 (9.0)	39.1 (6.7)	0.192
Proportion of body mass, %		41.6 (6.6)	41.4 (5.0)	0.912
Lean-to-fat mass ratio		1.47 (0.46)	1.46 (0.35)	0.858

Note: Data are expressed as mean (SD) unless otherwise stated.
Abbreviations: BMI, body mass index; NB, extended-release naltrexone/bupropion 16/360 or 32/360 mg; SD, standard deviation.

TABLE 2 Observed change from baseline body mass composition.

	Placebo ($n = 26$)			NB ($n = 56$)			Treatment difference	
	Mean at week 52 (SD)	Mean change from baseline (95% CI)	% change from baseline (95% CI)	Mean at week 52 (SD)	Mean change from baseline (95% CI)	% change from baseline (95% CI)	% change (95% CI)	p value
Total body mass, kg								
Total mass	97.5 (13.8)	−2.8 (−4.9, −0.7)	−2.8 (−4.8, −0.8)	87.6 (16.8)	−7.2 (−9.3, −5.2)	−7.8 (−10.0, −5.6)	−5.1 (−8.0, −2.1)	<0.001
Lean mass	57.7 (10.0)	−0.8 (−1.6, 0.0)	−1.4 (−2.7, 0.0)	53.5 (11.5)	−2.3 (−2.9, −1.6)	−4.1 (−5.3, −2.9)	−2.7 (−4.5, −1.0)	0.003
Fat mass	39.7 (9.6)	−2.0 (−3.4, −0.5)	−4.8 (−8.2, −1.4)	34.1 (8.7)	−5.0 (−6.5, −3.4)	−12.9 (−16.8, −9.1)	−8.1 (−13.2, −3.1)	0.002
Proportion of total body mass, %								
Lean mass	59.3 (7.0)	0.9 (0.2, 1.6)	-	61.2 (5.8)	2.6 (1.6, 3.6)	-	-	-
Fat mass	40.7 (7.0)	−0.9 (−1.6, −0.2)	-	38.8 (5.8)	−2.6 (−3.6, −1.6)	-	-	-
Body composition, ratio								
Lean-to-fat mass ratio	1.54 (0.49)	0.06 (0.02, 0.11)	-	1.64 (0.44)	0.18 (0.12, 0.25)	-	-	-

Abbreviations: CI, confidence interval; NB, extended-release naltrexone/bupropion 16/360 or 32/360 mg; SD, standard deviation.

3.4 | Adjusted change in total body mass, lean mass, and fat mass, and body composition

Similar changes in total body mass, lean mass, and fat mass from baseline to week 52 were seen after adjusting for sex, race, age, presence of hypertension, presence of metabolic syndromes, and baseline mass covariates (Figure 2, Table 3, Table S1). An adjusted treatment difference in favour of NB was observed for the change in total body mass (−5.0%, $p < 0.001$), lean mass (−2.6%, $p < 0.05$), fat mass (−7.8%, $p < 0.05$), and change in lean-to-fat mass ratio (0.125, $p < 0.05$; Table 3). The 0.069 change in ratio in the NB group was indicative of a relative gain in lean mass, while the −0.056 change in ratio in the placebo group was indicative of a relative loss of lean mass.

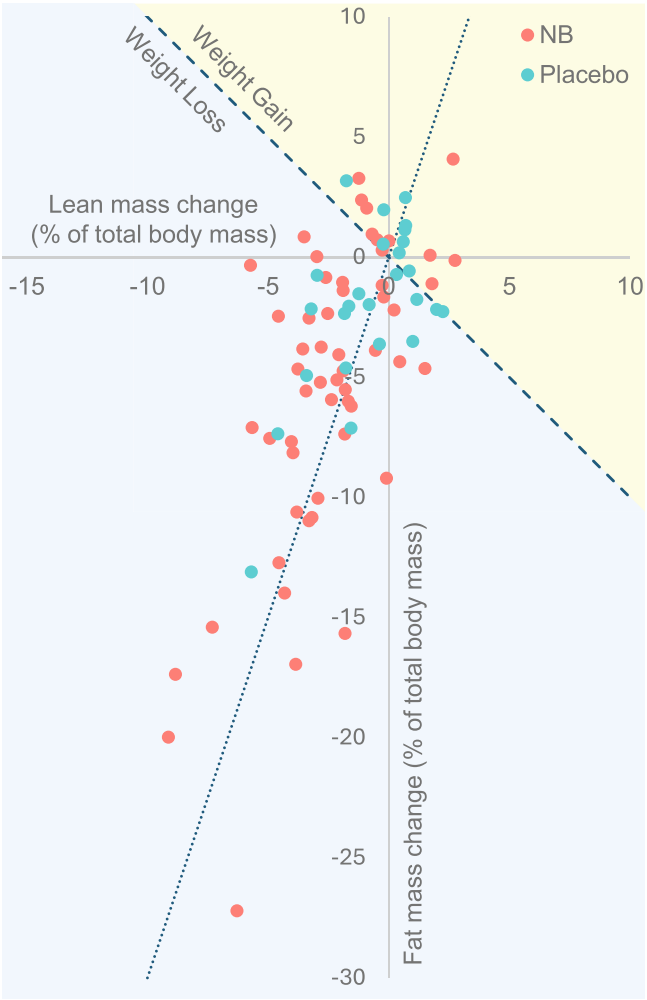

FIGURE 1 Linear regression analysis of observed change in body composition parameters. Linear regression of observed change in body composition parameters from baseline to week 52. Each dot represents an individual participant (NB, $n = 56$; placebo, $n = 26$). Values that fall above/below the dashed line (representing no change in body mass) signify a gain/loss of body mass. The dotted line represents a 25% change in lean mass and 75% change in fat mass. NB, extended-release naltrexone/bupropion 16/360 or 32/360 mg.

4 | DISCUSSION

The changes in body composition observed in this analysis suggest that weight loss (i.e. mass loss) with NB is associated with a beneficial shift in body composition. Overall, participants experienced reductions in both total fat mass and total body lean mass. However, the reduction in total fat mass was considerably greater for participants in the NB group than participants in the placebo group, leading to an overall favourable shift in the ratio of lean mass to fat mass.

The weight-reducing properties of NB had been previously established in multiple randomized clinical trials,[13–16] and the magnitude of overall weight loss among the subjects in this analysis (7.8% for NB vs. 2.8% with placebo) were consistent with previous findings. The observation that the NB-related weight loss is predominantly due to loss of fat mass rather than lean mass is a welcome finding and is hypothesis-generating for future research with this medication. This may help further clarify the mechanism of action resulting from the combined effect of naltrexone and bupropion. The current hypothesis suggests that bupropion mediates the anorectic effect of pro-opiomelanocortin-producing neurons in the hypothalamus and that naltrexone blocks the auto-inhibition of these neurons, allowing the anorectic effect to persist.[22]

The extent of weight loss due to loss of lean mass ranges in the literature from 11% to 25% depending on the dietary restrictions and exercise programs prescribed.[23] While diets high in protein can mitigate lean mass loss, some degree of lean mass loss is to be expected with any regimen.[12,23] Several participants in the NB group in our study experienced a ratio of approximately 25% lean mass loss to 75% fat mass loss (Figure 1). Although the ideal range of lean-to-fat mass loss is unknown, the observations in our study align with the body composition changes observed with dietary restriction and/or exercise, as published in the literature.[23]

Changes in body composition have also been reported with glucagon-like peptide 1 (GLP-1) receptor agonists. For example, weight loss associated with liraglutide and semaglutide has been reported to be due mainly to reduction in body fat, with a smaller reduction in lean body mass.[24–28] In the STEP 1 phase 3 trial, semaglutide treatment led to reductions in total fat mass and regional visceral fat mass.[28] The proportion of lean body mass relative to total body mass increased in the treatment group, although the absolute lean body mass decreased. In this study, the proportion of lean mass loss to fat mass loss could be estimated at 39% to 61%, although differences between studied populations limit our ability to compare results.[27]

The ratio of lean mass to fat mass loss is important for basal metabolic rate, which may be weight-loss-dependent.[29] and loss of lean mass alone is an important marker of a weight loss regimen.[30] Guidelines for the management of obesity also recognize the importance of the location of body fat for cardiometabolic risk. The 2020 Canadian guidelines, for example, recommend loss of visceral abdominal fat and maintenance of lean mass, even in the absence of overall weight loss.[2] This recommendation is due to the understanding that the location of the adipose tissue, its type and its function, are key determinants of metabolic health.[31] Accumulation of fat in the lower body, for example, is associated with a protective lipid and glucose profile as well as a decrease in cardiovascular and metabolic disease prevalence after adjustment for total body mass.[10] The mechanistic explanation for the protective effect of lower body fat is that it has lower lipid turnover and therefore acts as a metabolic sink, sequestering lipids that would be directed toward non-adipose tissue.[10]

In contrast, abdominal fat, of which VAT is a constituent, is associated with high lipid turnover, and is strongly associated with cardiometabolic risk.[11] Infiltration of VAT with macrophages contribute to chronic inflammation and insulin resistance.[31,32] VAT is also more strongly associated with metabolic risk in women when compared with men.[11,33] Unfortunately, in this study, VAT data were only

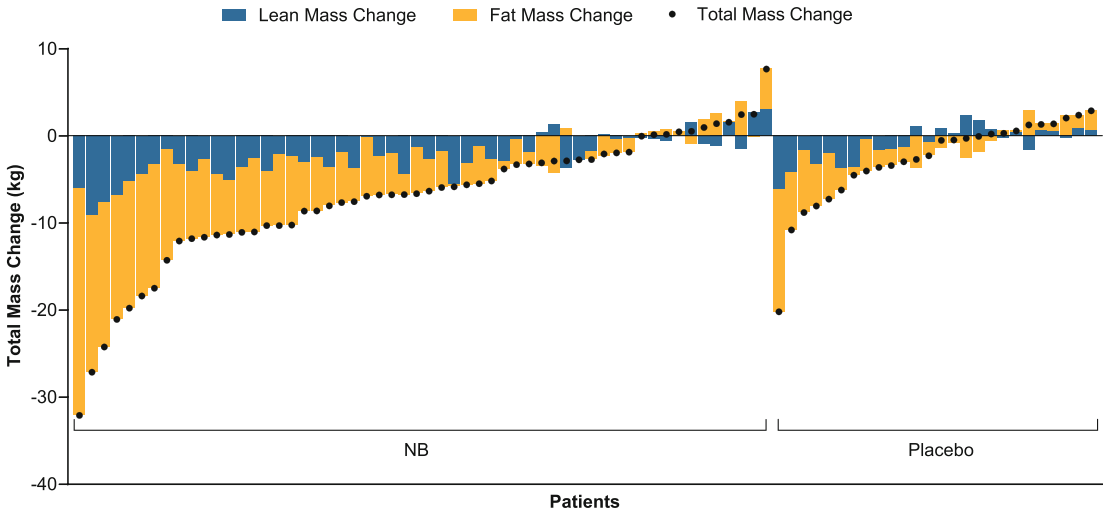

FIGURE 2 Observed changes in fat and lean mass, baseline to week 52. NB, extended-release naltrexone/bupropion 16/360 or 32/360 mg.

TABLE 3 Adjusted percent change from baseline body mass composition.

	Placebo ($n = 26$)	NB ($n = 56$)	Treatment difference	
	% (95% CI)	% (95% CI)	% (95% CI)	*p* value
Adjusted change, baseline to week 52				
Total mass	−1.1 (−7.4, 5.3)	−6.1 (−11.9, −0.3)	−5.0 (−8.6, −1.4)	$p < 0.001$
Lean mass	0 (−3.7, 3.6)	−2.6 (−6, 0.8)	−2.6 (−4.6, −0.6)	$p < 0.05$
Fat mass	−1.4 (−12, 9.2)	−9.2 (−19.0, 0.6)	−7.8 (−14.1, −1.5)	$p < 0.05$
	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	*p* value
Lean-to-fat mass ratio	−0.056 (−0.240, 0.127)	0.069 (−0.104, 0.240)	0.125 (0.021, 0.229)	$p < 0.05$

Note: Adjusted for covariates: race, sex, age, body mass index at baseline, presence of metabolic syndrome, and body composition variable value at baseline.
Abbreviations: CI, confidence interval; NB, extended-release naltrexone/bupropion 16/360 or 32/360 mg.

available for 34 patients of the COR-I sub-study, which is insufficient to perform a meaningful analysis.

Other weight-loss medications result in changes in fat types. In the MAGNA VICTORIA study ($n = 50$ subjects with type 2 diabetes) investigating the impact of liraglutide on left ventricular diastolic and systolic function, liraglutide-treated participants primarily lost subcutaneous fat but not visceral, hepatic, myocardial or epicardial fat.[26] This stands in contrast to prior findings with liraglutide in the LEAD-2 trial,[25] where the mean reductions in tissue area with liraglutide were greater for visceral adipose tissue than abdominal subcutaneous adipose tissue.[24]

4.1 | Limitations

Potential bias may have been introduced in this exploratory study due to its small size and non-ideal randomization of the subset of subjects, even in the absence of significant differences in baseline characteristics between the two study arms. In addition, the use of DEXA, a useful tool to measure total lean and fat mass, presents inherent limitations. For example, in subjects with depleted body protein or bone mineral mass, the results must be interpreted with caution.[11,20,21] DEXA assumes that the amount of fat over bone is the same as the amount of fat over bone-free tissue, which may lead to inaccurate measurement of percent body fat in certain individuals.[20] DEXA calculations also assume constant hydration of lean soft tissue. Hydration is, however, variable with age, disease state, and gender.[20] The mean subject age in this sub-study was about 45 years, which is younger than the populations of subjects studied with other weight loss medications. DEXA is also contraindicated for individuals with extreme BMIs or body weights[21] and may not be able to fully image the entire body,[11] and result accuracy may be device-dependent.[34]

Furthermore, the lack of information regarding the adherence to a hypocaloric diet and increased physical activity in the original COR-I study, even if participants were reminded on numerous occasions, is also a major limitation as the contribution of these interventions cannot be assessed.

Finally, as noted above, the metrics used in this analysis (total body fat and lean mass) are useful markers, but more informative would be to investigate fat deposition in particular areas of the body and in various organs, particularly visceral abdominal fat and liver fat.

4.2 | Future directions

Prospective investigation of the effects of NB (and other weight-loss medications) on body composition in a larger number of subjects, including the assessment of medications on changes in fat mass at specific sites and organs and the changes in bone density, would be a welcome addition to the evidence base. This type of research could give substantial further insight on the effects of weight-loss interventions on overall metabolic health.

5 | CONCLUSION

In this sub-study analysis, NB was associated with a significantly greater reduction in total body mass vs. placebo, in line with previous findings in randomized, controlled trials. More importantly, collecting data based on real-world evidence will offer valuable insights into how NB impacts body composition in a broader and more diverse population, ultimately resulting in improved clinical decision-making. The significant trends toward improvement for NB vs. placebo in body composition parameters will require further confirmation in larger and longer multi-centre studies.

AUTHOR CONTRIBUTIONS

VT and MAT are responsible for conceptualization, design, and for data curation. FC and PY performed the data collection and analyses. VT, MAT, PY, FC, and MB drafted the first version of the manuscript. All coauthors were involved in the critical interpretation of the results, discussed the findings together, critically reviewed the manuscript and approved its final version.

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CONFLICT OF INTEREST STATEMENT

VT has received speaker honoraria from Eli Lilly. MAT has received speaker honoraria from Bausch Health, NovoNordisk, Eli Lilly, and Boehringer-Ingelheim. PY and MB are employees of, and shareholders in, Bausch Health Companies. FC has received consulting fees from Bausch Health, Merck Canada and Janssen Inc.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16235.

DATA AVAILABILITY STATEMENT

Individual participant data are not available. The data used in this study were extracted from an older study and are proprietary, individual participant data are not available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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