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Naltrexone and Bupropion Combination: A New Promising Therapy for Long Term Weight Loss

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Naltrexone and Bupropion Combination: A New Promising Therapy for Long Term Weight Loss

Abstract

Background: Being overweight or obese is a growing health concern not just in the United States, but worldwide. In 2009-2010, 2 out of 3 adults are considered overweight or obese, and 1 out of 3 adults are considered obese in the U.S. Overweight and obesity acts as a major risk in cardiovascular diseases, diabetes, cancer, and arthritis, and carries an overwhelming economic burden. With a 5-10% weight loss, patients can benefit from reduced metabolic and cardiovascular risks; however, this is a challenging goal to achieve and maintain. Naltrexone is a medication commonly used for opioid addiction and alcohol dependence, and bupropion is commonly used for depression. Separately, these two medications have been shown to reduce weight weakly; this review aims to evaluate the benefits of naltrexone and bupropion used in combination for weight loss.

Method: An exhaustive literature search using the search engines Medline-OVID, CINAHL, and Web of Science combining keywords naltrexone, bupropion, and weight loss was conducted. Eligible criteria include research with naltrexone and bupropion combination therapy comparing to mono-therapy, other weight loss therapy, or placebo. Only randomized controlled trials (RTC) were selected for maximum validity. Excluded from this analysis were articles with animal subjects or other languages except English. Selected articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: Three articles met the criteria and were included in this systematic review. In Greenway et al, enrolled were 419 participants in this randomized, placebo and monotherapy controlled, double blind trial. In general, at week 24, participants in most combination drug groups showed statistically significant weight loss compared to monotherapy and placebo. In the COR-I study, 1742 participants enrolled in this randomized, double blind, placebo controlled phase 3 trial. At week 56, mean change in body weight was statistically significant in combination drug groups compared to placebo. In the COR-II study, a randomized, double blind, placebo controlled study of 1,496 participants, the combination drug group achieved and maintained weight loss at a more pronounced rate than placebo group at the completion of the 28 week trial.

Conclusion: Naltrexone and bupropion combination therapy shows promising evidence as a drug therapy for long-term weight loss as evidenced by these studies. While this combination therapy is a safe alternative, further research is needed to assess naltrexone and bupropion combination therapy against other current FDA approved weight loss therapy and its effects on patients with complicated obesity.

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**Naltrexone and Bupropion Combination: A New Promising
Therapy for Long Term Weight Loss**



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School of Physician Assistant Studies

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BIOGRAPHY

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ABSTRACT

Background: Being overweight or obese is a growing health concern not just in the United States, but worldwide. In 2009-2010, 2 out of 3 adults are considered overweight or obese, and 1 out of 3 adults are considered obese in the U.S. Overweight and obesity acts as a major risk in cardiovascular diseases, diabetes, cancer, and arthritis, and carries an overwhelming economic burden. With a 5-10% weight loss, patients can benefit from reduced metabolic and cardiovascular risks; however, this is a challenging goal to achieve and maintain. Naltrexone is a medication commonly used for opioid addiction and alcohol dependence, and bupropion is commonly used for depression. Separately, these two medications have been shown to reduce weight weakly; this review aims to evaluate the benefits of naltrexone and bupropion used in combination for weight loss.

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Conclusion: Naltrexone and bupropion combination therapy is a promising new drug therapy for long-term weight loss with tolerable side effects.

Keywords: naltrexone, bupropion, weight loss

TABLE OF CONTENTS

Biography	2
List of Tables.....	5
List of Abbreviations	5
Naltrexone and Bupropion Combination: A New Promising Therapy for Long Term Weight Loss	Error! Bookmark not defined.
BACKGROUND.....	6
METHODS.....	8
RESULTS	8
DISCUSSION	15
CONCLUSION	17
References.....	18
Table I. Characteristics of Reviewed Studies	20
Table II. Summary of Findings	20

LIST OF TABLES

Table I: GRADE QUALITY OF ASSESSMENT AND SUMMARY FINDINGS

Table II: SUMMARY OF FINDINGS

List of Abbreviations

Nal	Naltrexone	GABA	Gama-aminobutyric acid
Bup	Bupropion	FDA	Food and Drug Administration
NB	Naltrexone/bupropion	POMC	Pro-opiomelanocortin
SR	Sustained release	HDL	High density lipoprotein
IR	Immediate release	LDL	Low density lipoprotein
GRADE	Grading of recommendations, assessment, development, and evaluation	TSH	Thyroid stimulating hormone
COR-I	Effect of Naltrexone Plus Bupropion on Weight Loss in Overweight and Obese Adults	SBP	Systolic blood pressure
COR-II	A randomized, Phase 3 Trial of Naltrexone SR/Bupropion SR on Weight and Obesity-related Risk Factors	DBP	Diastolic blood pressure
BMI	Body mass index	hsCRP	High sensitive C-Reactive protein
ADR	Adverse drug reaction	ITT	Intent to treat

Naltrexone and Bupropion Combination: A New Promising Therapy for Long Term Weight Loss

BACKGROUND

Being overweight is defined as a body mass index (BMI) of 25.0-29.9, and being obese is defined as 30.0 and above. This is a worldwide concern as its prevalence is rising, and it is a known risk factor that leads to increase morbidity and mortality. Statistics from 2009-2010 National Center for Health Statistics indicate that 2 out of 3 adults are considered overweight or obese, and 1 out of 3 adults are considered obese, which is an increase since the last decades.¹ More importantly, overweight and obesity is associated with significant health risks such as diabetes, hypertension, high cholesterol, stroke, heart disease, certain cancers, and arthritis.¹ Due to its associations with chronic health diseases, overweight and obesity is a great economic burden. Obesity is accountable for the substantial amount of \$345.9 million annually.²

Causes of overweight and obesity are many, relating to the environment, genetic makeup, metabolism, lifestyle behavior, and many more. Nonetheless, lifestyle modification is the first line treatment for obesity and overweight due to its low cost and low risk profile; however, this method is often ineffective due to low compliance rates and patients often need more than one intervention to reach and maintain a healthier weight. Adjunct to lifestyle modifications are medications that can be used long-term; these include orlistat, lorcaserin, and phentermine-topiramate combination. Orlistat is an inhibitor of pancreatic and intestinal lipases, which prevents the breakdown of ingested triglycerides into absorbable fatty acids and monoacylglycerol and reduces the absorption of fat.³ Lorcaserin,

is a 2C serotonin receptor activated in the hypothalamus to reduce food intake.⁴ Lastly, phentermine acts to reduce appetite through increasing norepinephrine in the hypothalamus, while topiramate affect gamma-aminobutyric acid (GABA) receptors, which induce appetite-reducing mechanism that is not thoroughly understood.⁴ While these drugs have been shown to be effective, some of its side effects are intolerable. For example, orlistat may cause stomach pain, has diarrhea, leakage of oily stools; locaserin may trigger headaches, dizziness, constipation, and cannot be taken with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitor (MAOI); lastly phentermine-topiramate may cause tingling of hands and feet, dizziness, taste alterations, insomnia, and may lead to birth defects.

Recently, the Food and Drug Administration (FDA) approved another weight loss medication, naltrexone/bupropion (NB) combination, also marketed with brand name Contrave. NB individually has been in the market for over 20 years. Naltrexone is an opioid receptor antagonist marketed in the U.S. for the treatment of narcotic and alcohol dependency, while bupropion is a dopamine and norepinephrine reuptake inhibitor prescribed as an antidepressant and smoking cessation aid.⁵ Separately, these two drugs are weak weight loss interventions; however, together they have synergistic effects in the CNS that reduce food intake by stimulation of pro-opiomelanocortin (POMC) neuronal firing and modulate food cravings through an effect on the mesolimbic reward pathways at the same time.^{5,6} Research on central nervous system (CNS) pathways that regulate food intake and bodyweight has identified the hypothalamic melanocortin system and the mesolimbic reward system as the two main key systems. The hypothalamic melanocortin

system integrates input related to energy balance and produces anorexigenic signaling while the mesolimbic modulates reward value and goal-oriented behavior.⁷ NB was thought to play an important role into these complex systems, which makes this drug a promising means for weight loss. Moreover, naltrexone and bupropion has been used by providers for over 20 years, and their ADRs profiles are typically mild, which also make is drug a valuable drug loss regimen as it gives providers more prescribing powers and patients more conservative options for weight loss. This review aims to evaluate the benefits of NB in treating patients who are overweight or obese.

METHODS

An exhaustive literature search using the search engines Medline-OVID, CINAHL, and Web of Science combining keywords naltrexone, bupropion, and weight loss was conducted. Eligible criteria include research with naltrexone and bupropion combination therapy comparing to mono-therapy, other weight loss therapy, or placebo. Only randomized controlled trials (RTC) were selected for maximum precision. Excluded from this analysis were articles without randomization, animal subjects, and other languages except English. Articles were scanned for relevance and its attached references were also further scanned for related researches. Finally, the selected articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

RESULTS

Initial search combining all 3 key terms yield 17, 13, and 54 in Medline-OVID, CINAHL, and Web of Science respectively. After screening the articles according to the eligible criteria, 3 articles⁶⁻⁸ met the requirements for this systematic review. See Table I.

Greenway et al 2009

This randomized, placebo and mono-therapy controlled, double blind, dose finding trial⁸ took place between August 2005 and December 2006 in seven U.S. outpatient clinics. Included were 419 participants with uncomplicated obesity, defined as BMI 30-40kg/m², nonsmokers, 18-60 years old, normotensive, low density lipoprotein (LDL) <190mg/dl, triglyceride < 400mg/dl, fasting glucose < 140 mg/dl, no significant abnormalities on complete blood count, urinalysis, or thyroid stimulating hormone (TSH), and scored lower than 11 on their the depression or anxiety components of the Hospital Anxiety and Depression Scale (HADS).⁸

Subjects were randomized by site and gender. All seven sites, subjects, and the study team were blinded to the study drug throughout except in emergency situations. The study was carried out with two cohorts. In cohort 1, participants were randomized into five groups in a 1:1:1:1:1 ratio: bupropion SR 400mg/d plus naltrexone IR 48mg/d (NB48); bupropion SR 400mg/d plus naltrexone 16mg/d (NB16); bupropion SR 400mg/d plus naltrexone placebo (Bup); naltrexone IR 48mg/d plus bupropion placebo (nal48); bupropion placebo plus naltrexone placebo (placebo). In cohort 2, participants were randomized in a 1:3 ratio: bupropion placebo and naltrexone placebo (placebo); bupropion SR 400mg/d plus naltrexone IR 32mg/d (NB32). Drugs were gradually titrated up weekly and reached

maximum dose at week 4. All groups were prognostically balanced at the start of the trial; however, there was a female and Caucasian dominance.⁸

In addition, participants were advised to follow a hypo-caloric diet of 500kcal below maintenance diet plus 30 min walking exercise most days of week. Subjects were evaluated at screening, baseline, and every 4 weeks through week 48. Primary endpoint was difference in body weight. Secondary endpoint was absolute change in body weight, waist circumference, triglycerides, glucose, insulin, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, blood pressure, and pulse. Exploratory endpoints include food craving (assessed by the Yale Brown Obsessive Compulsive Scale).⁸

At 24 week, placebo subtracted weight loss in the intent to treat population (ITT) was -4.62kg for NB16 (95% CI, -6.24 to -2.99, $p < 0.001$), -4.65kg for NB32 (95% CI, -6.20 to -3.09, $p < 0.001$), and -3.53kg for NB48 (95% CI, -5.19 to -1.90, $p < 0.001$). At 48 weeks, placebo-subtracted weight loss was -6.45kg (95% CI, -8.46 to -4.43, $P < 0.001$) for NB16, -5.92kg (95% CI, -7.82 to -4.02, $P < 0.001$) for NB32, and -6.39kg (95% CI, -8.69 to -4.09, $P < 0.001$) for NB48. Weight loss was significant in NB combinations compared to monotherapy except with NB48 ($p = 0.0684$). A greater than 10% Weight loss was 4.89 times more likely in the NB combination groups compared to placebo and monotherapy. This comparison also resulted in a number needed to treat (NNT) of 8 (see Table II). However, there is some loss of significance when looking at the NB48 group. Weight loss continued after 24 weeks, and the study was stopped as planned at 48 weeks. Researchers also found that NB32 was associated with improvements in cardiometabolic markers (waist circumference, fasting insulin, fasting glucose, triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol,

systolic blood pressure (SBP), and diastolic blood pressure (DBP) compare to other doses, monotherapy, and placebo. The Yale Brown Obsessive and Compulsive Assessment II scores between study baseline and completion showed no significant difference in NB combination drugs, monotherapy, or placebo.⁸

The COR-I Study

This randomized, double blind, placebo controlled, phase 3 trial took place at 34 health centers in the U.S. from October 2007 to May 2009. Participants included 260 men and 1,742 women aged 18-65 years with BMI of 30-45kg/m² and uncomplicated obesity, or BMI of 27-45kg/m² and controlled hypertension or dyslipidemia, or both. Excluded from study were patients who were pregnant or lactating, obese with known endocrine origin, type 1 or type 2 diabetes; cerebrovascular, hepatic, or renal disease; previous surgical or device intervention for obesity; loss or gain of more than 4 kg within 3 months before randomization; severe psychiatric illness; history of seizures; treatment with bupropion or naltrexone in the previous 12 months; history for alcohol or drug abuse in previous 12 months. Participants were randomized into a 1:1:1 ratio of: naltrexone SR 32mg/day plus bupropion SR 360mg/day (NB32); naltrexone SR 16 mg/day plus bupropion SR 360mg/day (NB16); or placebo. All groups were prognostically balanced at the start of the trial; however, there was a female and Caucasian dominance. Beginning with a quarter of the full dose, each drug was titrated up weekly and reached full dose at week 4. Patients were also advised of a mild hypocaloric diet consisting of 500kcal deficit per day based on WHO algorithm for calculating resting metabolic rate and were advised of lifestyle modification at baseline and at 12, 24, 36, and 48 weeks. All subjects were evaluated at screening and every

4 weeks for 56 weeks total. Drug compliance was assessed during evaluation by pill count. Patients were considered non-compliant if they were found to take medications correctly <70% of the time and were re-educated. Furthermore, non-compliant patients with two consecutive visits or 15 consecutive days were re-evaluated for continuation.⁷

As a result, 870 (50%) participants completed 56 weeks of treatment. Rates of discontinuation were similar across all 3 subgroups. Primary endpoints were change in body weight and proportions of participants with decrease of 5% or more from baseline at end of study. Mean change in body weight was -1.3% in placebo, -5.0% in NB16, and -6.1% in NB32 group. 16% of participants had decrease in bodyweight of 5% or more in placebo, compared to 39% in NB16, and 48% in NB32 (Table 1). Weight loss was statistically significant in both NB32 and NB16 groups compared to placebo, with NB32 with the greatest success in losing bodyweight compared to other 2 subgroups. For example, participants in NB32 groups were 2.66 times more likely to experience $\geq 5\%$ weight loss compared to placebo, 3.01 times more likely to experience $\geq 10\%$ weight loss compared to placebo, 5.26 times more likely experience $\geq 15\%$ weight loss compared to placebo (see Table II). Weight loss was observed as soon as week 4, with peak weight loss between week 28 and 36. Secondary endpoint include proportion of participants with $\geq 10\%$ and $\geq 15\%$, change in cardiometabolic risk factors, patient reported measures of appetite, control of eating and food craving, depressive symptoms, and weight-related quality of life. As a result, participants on NB32 and NB16 also showed significant improvements from baseline to 56 weeks in waist circumference, insulin resistance, and concentrations of HDL cholesterol, triglycerides, high-sensitivity C-reactive protein, and fasting glucose compared to placebo. Control of Eating

Questionnaire (COEQ), a proven reliable method which measure cravings for specific food items shows combined naltrexone and bupropion reduced hunger or desire for sweet, non-sweet, or starchy foods; increased feeling of fullness, reduced incidence and strength of food cravings; reduced eating in response to food cravings; and increased ability to resist food cravings and control eating.⁷

The COR-II Study

This randomized, parallel-arm, double-blind, placebo controlled, phase 3 trial was performed in 36 U.S. private or institutional practices between December 2007 and June 2009 for 56 weeks. Participants included 229 men and 1267 women age 18-65 years old with BMI 30-45kg/m², or BMI 27- 45kg/m² and controlled hypertension and or dyslipidemia. Excluded were patients with diabetes; significant vascular, hepatic, or renal disease; weight change of more than 4 kg within 3 months prior to randomization; history of seizures or serious psychiatric illness. Participants were randomized via interactive voice system in a 2:1 ratio. Patients either received SR Naltrexone 32mg/day plus SR Bupropion 360mg/day (NB32), or SR Naltrexone 16mg/day plus SR Bupropion 360mg/day (NB16), or matching placebo. All groups were prognostically balanced at the start of the trial; however, there was a female and Caucasian dominance. Naltrexone and bupropion was titrated up weekly and reached full dose at week 5. Furthermore, participants in NB32 group with less than 5% weight loss at week 28 were re-randomized, double-blinded to receive either NB32 or NB48 in 1:1 ratio for the remaining of the study. Patients were evaluated at baseline and every 4 weeks. At baseline, 12, 24, 36, and 48 weeks, patients also received instructions to

follow a 500kcal/day deficit hypocaloric diet, increase physical activity, and behavioral modification.⁶

The study concluded with 54% completion rate at week 56, with drop out rates similar across study groups. Primary endpoint was percent change in weight and the proportion of participants with $\geq 5\%$ in weight loss and week 28.⁶ As a result, weight loss was most statistically significant with NB32 compared to placebo at week 28 and continues to progress through week 56. Participants on NB32 lost 6.5% of bodyweight compare to 1.9% of participants on placebo (p-value < 0.001). Participants on NB32 also lost more body weight (-6.4%) compared placebo (-1.2%) at week 56 (p-value < 0.001), exemplifying that NB32 is superior to placebo at maintaining weight loss. Risk ratio for NB32 vs placebo at completion of study were 2.96, 1.66, and 5.61 for $\geq 5\%$, 10%, and 15% respectively, exemplifying that patients taking combination drug NB32 were almost two times or more likely to lose weight (see Table II). Secondary endpoints included participants with $\geq 10\%$ and $\geq 15\%$ weight loss, improvements in cardiometabolic parameters such as waist circumference, triglycerides, HDL cholesterol, LDL cholesterol.⁶

Other endpoints were high sensitive C-reactive protein (hsCRP), fasting blood glucose, fasting insulin, homeostatis model assessment of insulin resistance (HOMA-IR), impact of Weight on Quality of Life (IWQOL, quality physical function, self-esteem, and sexual life subscales), Control of Eating Questionnaire (COEQ, indicates control of eating, food craving, frequency of craving, and difficulty in resisting food cravings), systolic blood pressure (SBP), diastolic blood pressure (DBP), and Inventory of Depressive Symptomatology (IDS-SR). Compared to placebo, NB32 participants showed improved

hsCRP, fasting blood glucose, fasting insulin, insulin resistance, and quality of life.

Participants also had reduced food craving, reduced frequency of craving, reduced difficulty in resisting food cravings, and improved control of eating.⁶

Patients on NB32 showed a slight increase in both SBP and DBP compared to placebo; however, the changes were not statistically significant as the mean SBP and DBP remain within approximately 1mmHg of baseline.⁶ Lastly, IDS-SR questionnaire (score range from 0-84, a total score of ≤ 13 suggests no depression) shows no significant changes in depression comparing NB32 with placebo.

DISCUSSION

The three studies⁶⁻⁸ listed above were dissected and consistently shows that combination of naltrexone and bupropion leads to improvement in weight loss, cardiometabolic risk factors, and control in eating habits. First, the Greenway et al⁸ study shows that weight loss was most significant in participants in the NB16 and NB 32 group compared to other interventions and weight loss was sustained over 48 weeks; participants in this subject group lost at least 5% body weight loss compared to placebo and Nal48 (naltrexone-bupropion placebo). See Table II. Adverse effects are consistent with the effects of naltrexone and bupropion profile, with the most common side effects being nausea, headache, dizziness, and insomnia. In addition, NB 32 was associated with statistically significant improvements in cardiometabolic risk factors. Second, in the COR-I study,⁷ participants were three times more likely to lose 5% to 10% of body weight in NB32 groups compared to placebo. Patients on NB32 also showed greater improvements in cardiometabolic risk factors and weight-related quality of life. With mild adverse drug

reactions of nausea, headache, constipation, dizziness, vomiting, and dry mouth, this drug shows favorable results as a means for long-term weight loss of obese or overweight adults. Last, in COR-II study, ⁶ participants in NB32 group were associated with most significant weight loss and great improvement in cardiometabolic markers compared to placebo. Weight loss was maintained in NB32 to completion of study at week 56. Furthermore, NB32 participants were more likely than NB16 and placebo to achieve more than 5%, 10%, and 15% weight loss. See Table II. The adverse drug reactions of naltrexone and bupropion seemed consistent with other trials⁵ and their known profile, with most common side effects being mild to moderate nausea, constipation, and headache.

While all three studies ⁶⁻⁸ showed consistent results, the limitations of these studies could not be dismissed. First, there were risks of bias, variability across the studies, and important flaws in these studies. Sampling in all three studies consisted of mainly middle aged white females, which limits the generalizability of the results. Most selected participants were voluntary females, which implies that these women were more motivated to lose weight and were more likely to be compliant to the study drugs. Second, completion rates of these studies were low: 63% in the Greenway et al ⁸ study, 50% in the COR-I study, ⁷ and 54% in the COR-II study. ⁶ Participants in the NB groups likely discontinued due to adverse reactions, whereas participants in placebo group discontinued due to unsatisfactory weight loss. Participants who left were even across all groups, and data were logistically equal; however, these low completion rates can risk attrition bias. Third, all three studies ⁶⁻⁸ excluded patients with complicated obesity, such as patients with cardiovascular disease or diabetes, which abandoned the purpose to find a drug that works for these

patients as obesity is an important risk factor. Fourth, two of these studies did not collect participants' adherence to diet and exercise. These missing data are an important variance across patient groups. Fifth, none of the studies compared NB combined therapy with other current FDA approved weight loss therapy. Although data on naltrexone and bupropion combination drug for weight loss is promising, it fails to compare itself to other approved weight loss medications. This results in an overall moderate quality of evidence (see Table I). All in all, more studies is recommended to obtain a larger sample size, more male participants, participants with diabetes or cardiovascular disease, account for lifestyle modification more consistently, and comparison with other current weight loss medications.

CONCLUSION

Naltrexone/bupropion combined therapy has been demonstrated to be effective for long-term management of weight loss in overweight or obese adults. Furthermore, the effective dose of naltrexone and bupropion was also included in the study, with naltrexone SR 32mg/day and Bupropion SR 360-400mg/day as the most effective dose that is tolerable. Naltrexone and bupropion are medications that have been used for over 20 years and their adverse drug reaction profiles are familiar to primary care providers; therefore, providers are more likely to be comfortable to prescribe this medication. Most importantly, adverse drug reactions to naltrexone and bupropion are tolerable, which makes its benefits outweigh its risks. Further research is needed to assess naltrexone and bupropion combined therapy against other current FDA approved weight loss therapy and its effects on patients with complicated obesity.

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Table I. Characteristics of Reviewed Studies

Quality Assessment							Quality	Importance
Downgrade Criteria								
No. of Studies	Design	Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely		
Weight loss >5%								
3	3 RCT	No serious limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	No bias likely	Moderate	Important
Weight loss >10%								
3	3 RCT	No serious limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	No bias likely	Moderate	Important
Weight loss >15%								
2	2 RCT	No serious limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	No bias likely	Moderate	Important

Table II. Summary of Findings

Study	Percent of subjects with weight loss	Number of participants (%) in NB groups	Number of participants (%) in monotherapy/placebo groups	RR ^a	NNT ^a
Greenway et al ⁸	Total in groups ^b	n=171	n=190		
	≥5%	81 (48%)	32 (17%)	2.72	4
	≥10%	29 (17%)	7 (4%)	4.89	8
The COR-I Trial ⁷	Total in groups ^b	n=942	n=511		
	≥5%	412 (44%)	84 (16%)	2.66	4
	≥10%	211 (22%)	38 (7%)	3.01	7
	≥15%	97 (10%)	10 (2%)	5.26	12
The COR-II Trial ⁶	Total in week 28 groups ^b	n=825	n=456		
	≥5% (week 28)	459 (56%)	80 (18%)	3.17	3
	≥10% (week 28)	225 (27%)	32 (7%)	3.89	5
	≥15% (week 28)	84 (10%)	8 (7%)	1.45	32
	Total in week 56 groups ^b	n=702	n=456		
	≥5% (week 56)	355 (51%)	78 (17%)	2.96	3
	≥10% (week 56)	199 (28%)	26 (17%)	1.66	9
≥15% (week 56)	95 (14%)	11 (2%)	5.61	9	

^a RR and NNT were calculated by combining data from all of the NB combination groups and comparing it to combined data from the monotherapy and placebo groups. Greenway et al⁸ groups were placebo, NaI48, Bup, NB16, NB32, NB48; The COR-I trial⁷ groups were placebo, NB16, and NB32; and the COR-II trial⁶ groups were placebo and NB32.

^b Intention to treat analysis or primary analysis data used.