Pharmacotherapy III: Naltrexone/Bupropion(Contrave®) for Chronic Weight Management

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COI

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- Relationships with commercial interests:
  - Grants/Research Support: N/A
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  - Consulting Fees: Novo Nordisk, Shire, Valeant

Objectives:

Pathophysiology: hunger, satiety, control of eating

Mechanism of action

Efficacy: Phase 3 Clinical Trials

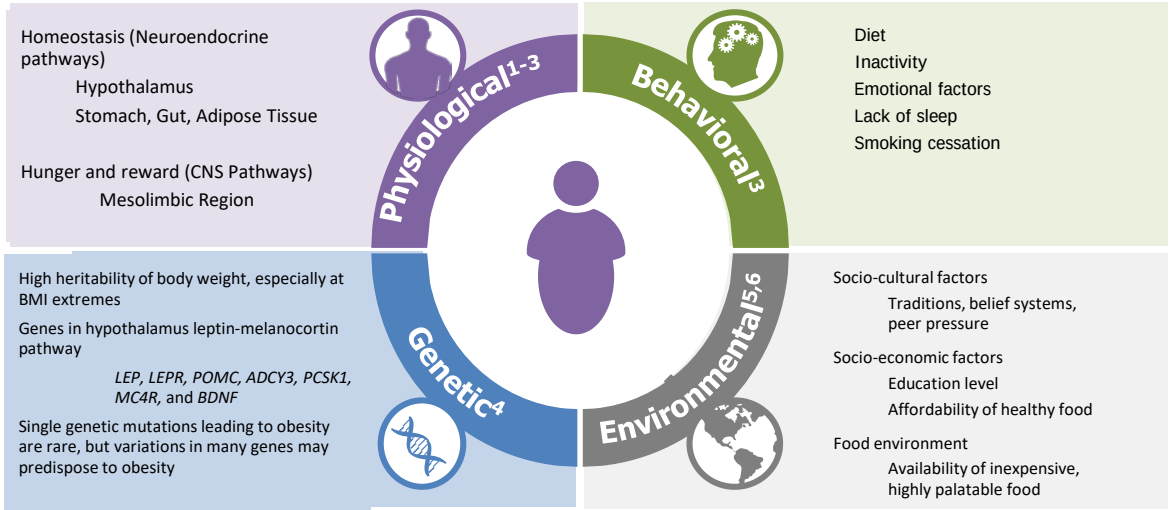
Clinical use of Naltrexone/Bupropion in weight management:

- Indications
- Contraindications
- Side effects
- Dosing schedule

The 10 minute office visit : Rx and counseling

What determines body weight?

There are both modifiable and non-modifiable factors that affect body weight…



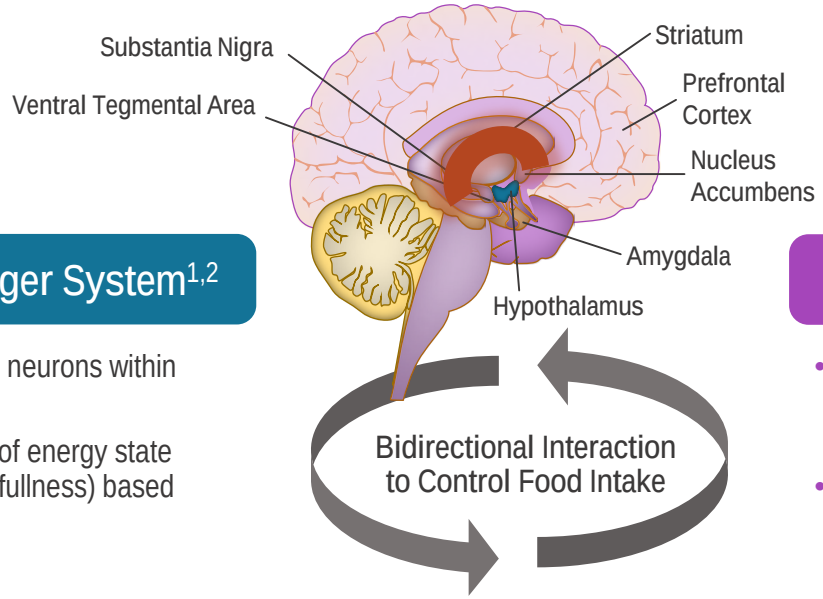
Other factors:
- Microbiome
- Some medications

ADCY3=adenylate cyclase 3; **BDNF**=brain-derived neurotrophic factor; **BMI=body** mass index; **CNS**=central nervous system; **GLP-1**= glucagon-like peptide-1; **LEP**= leptin; **LEPR**= leptin receptor; **MC4R**=melanocortin receptor 4; **POMC**=proopiomelanocortin; **PCSK1**=proprotein convertase subtilisin/kexin type 1.

1. Sharma AM, et al. *Obes Rev*. 2010;11:362-370. 2. Chesi A, et al. *Trends Endocrinol Metab*. 2015;26:711-721.

Pathophysiology and the role of the brain in obesity

Satiety, Hunger and Craving



Hypothalamic Hunger System[1,2]

- Primarily driven by POMC neurons within the hypothalamus
- Detection and integration of energy state information (e.g., hunger, fullness) based on peripheral signals
- Altered function in obesity (e.g., leptin resistance)

Mesolimbic Reward System[3]

- Center of the brain that mediates motivation, reward, and desire associated with activities needed for survival
- Dopamine and opioid signaling known to play important roles

Mesolimbic Reward System can typically override the Hypothalamic Hunger System, increasing the consumption of highly palatable foods[4]

CNS = central nervous system; POMC = proopiomelanocortin.
Figure adapted from Billes et al.,© 2014, with permission from Elsevier.
1. Billes SK et al. *Pharmacol Res*. 2014;84:1-11. 2. Yu JH et al. *Diabetes Metab J*. 2012;36:391-398 3. Morton GJ et al. *Nature*. 2006;443(7109):289-295 . 4. Volkow ND et al. *Obes Rev*. 2013;14:2-18.

CONTRAVE®: Naltrexone/Bupropion

CONTRAVE® Is a Combination of Two Compounds: Naltrexone and Bupropion

Naltrexone HCl[1,2]

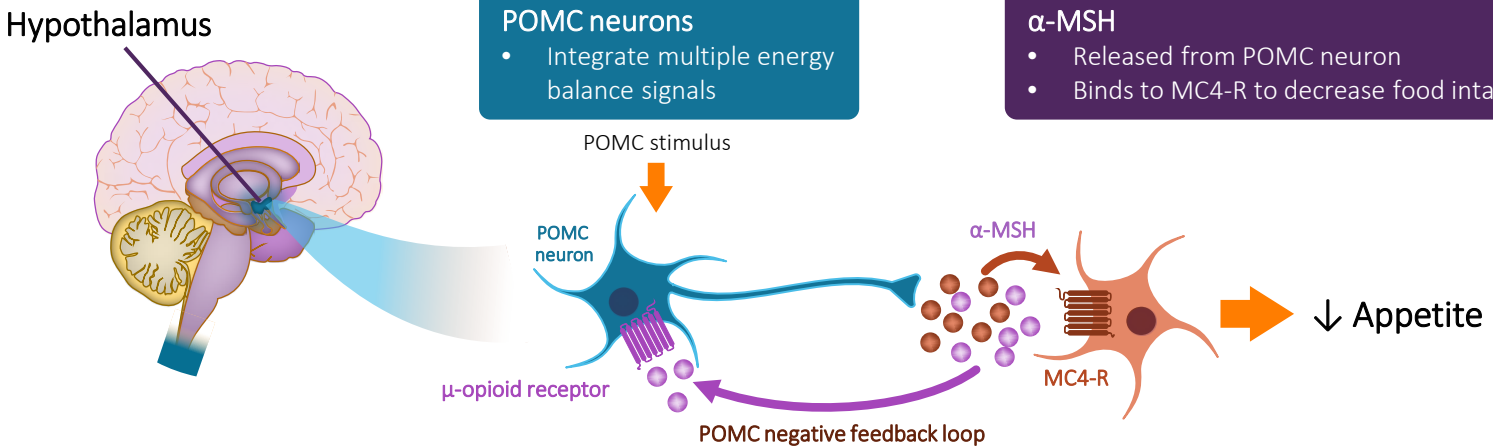
- An opioid receptor antagonist
- Indications: treatment of **alcohol dependence** and prevention of relapse to **opioid dependence**
- More than 20 years of use

Bupropion HCl[1,3]

- A dopamine and norepinephrine reuptake inhibitor
- Indications: **major depressive disorder** and as an aid to **smoking cessation**
- More than 20 years of use

1. CONTRAVE [product monograph], February 12, 2018, Valeant Canada LP; Laval, QC.; 2.. Naltrexone product information; 3. Wellbutrin SR Product Information.

Regulation Of Hunger: Role Of Hypothalamic POMC Neurons



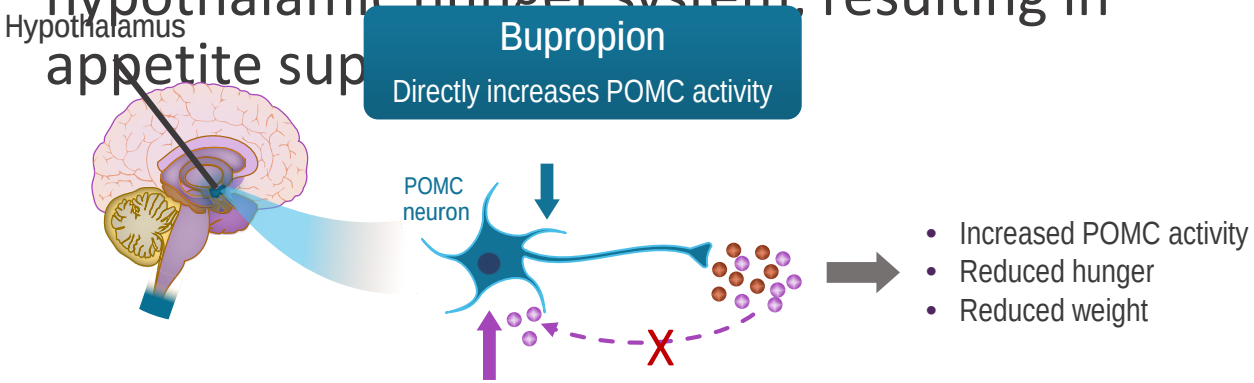
α-MSH=α-melanocyte-stimulating hormone; **MC4-R=**melanocortin-4 receptor; **POMC=**proopiomelanocortin.

1. Billes SK et al. *Pharmacol Res*. 2014;84:1-11.

Figure adapted from Billes et al,[1] © 2014, with permission from Elsevier.

Naltrexone and Bupropion Act Together

Naltrexone and Bupropion act together to activate the POMC neurons in the hypothalamic hunger system, resulting in appetite sup



MSH = melanocyte-stimulating hormone; POMC = pro-opiomelanocortin.
Figure adapted from Billes et al,[1] © 2014, with permission from Elsevier.
1. Billes SK, et al. *Pharmacol Res*. 2014;84:1-11.

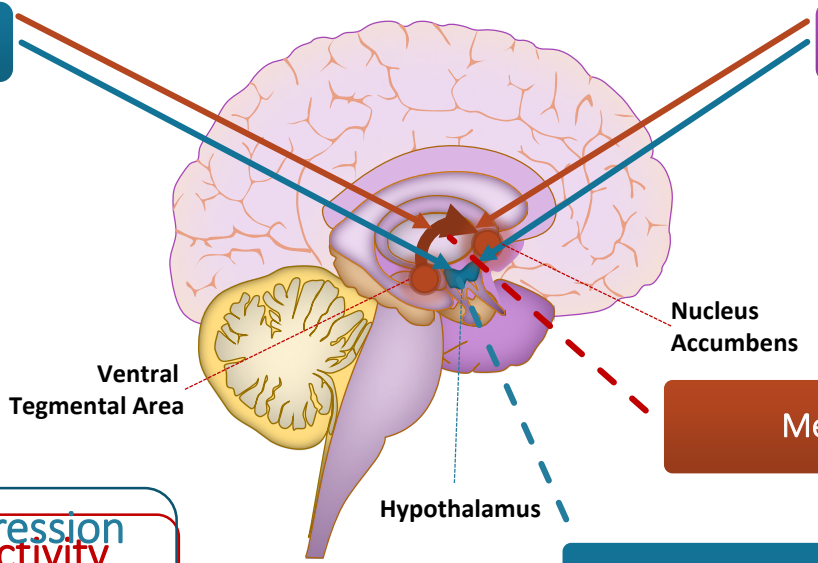
Boosting Effect: the Whole Is Greater Than the Sum of its Parts

Bupropion HCl

Indicated for the treatment of major depressive disorder and as an aid to smoking cessation

Naltrexone HCl

Indicated for the treatment of alcohol dependence and for prevention of relapse to opioid dependence



Mesolimbic Reward System

+

Hypothalamic Hunger System

Promote appetite suppression
Act on dopaminergic activity neurons (POMC)
↓ food cravings
↓ hunger

1. Billes SK, et al. *Pharmacol Res*. 2014;84:1-11.

Figure adapted from Billes et al,[1] © 2014, with permission from Elsevier.

Efficacy of CONTRAVE® Was Assessed in a Phase 3 Clinical Development Program

The clinical development program consisted of four 56-week, placebo-controlled studies (n = 4536 subjects)

	COR-I[2] n = 1742	COR-II[3] N=1496	COR-BMOD[3] n = 793	COR-DM[4] n = 505
Co-Primary Endpoints	Percent change from weight from baseline Percent of subjects achieving ≥5% weight reduction			
Study Design	56 weeks, placebo controlled, including 4-week dose escalation			
Population	BMI 30-45 kg/m^2 BMI 27–45 kg/m^2 (with comorbidities)			T2DM, BMI 27–45 kg/m^2
Diet and Exercise	Diet and exercise counseling		Intensive BMOD	Diet & exercise counseling
Dose and Randomization	NB16 & NB32 1:1:1	NB32 2:1	NB32 3:1	NB32 2:1

BMI=body mass index; **BMOD**=behavior modification; **NB=**naltrexone/bupropion; **DM=**type 2 diabetes mellitus.

1. Contrave [prescribing information]. La Jolla, CA: Orexigen Therapeutics, Inc.; 2016. 2. Greenway FL, et al. *Lancet*. 2010;376:595-605. 3. Apovian CM, et al. *Obesity*. 2013;21:935-943. 4. Wadden TA, et al. *Obesity*. 2011;19:110-120. 5. Hollander P, et al. *Diabetes Care*. 2013;36:4022-4029.

CONTRAVE® Use in Phase III Clinical Trials

Trial commencement → 52 weeks at full dose: NB 32/360 mg

4 week titration to full dose:

Week 1	1 tablet OD, morning
Week 2	1 tablet BID
Week 3	2 tablets morning + 1 table evening
Week 4	2 tablets BID

CONTRAVE® is available as prolonged release tablets that contain 8 mg naltrexone HCl and 90 mg bupropion HCl each

CONTRAVE [product monograph], February 12, 2018, Valeant Canada LP; Laval, QC.

Phase 3 Clinical Development Program: Baseline Characteristics

Age

- Mean = 46 years

Gender

- Men: 17%
- Women: 83%

Body Mass Index (BMI)

- Baseline mean = 36 kg/m^2

Waist Circumference

- Baseline mean = 110 cm

Ethnicities

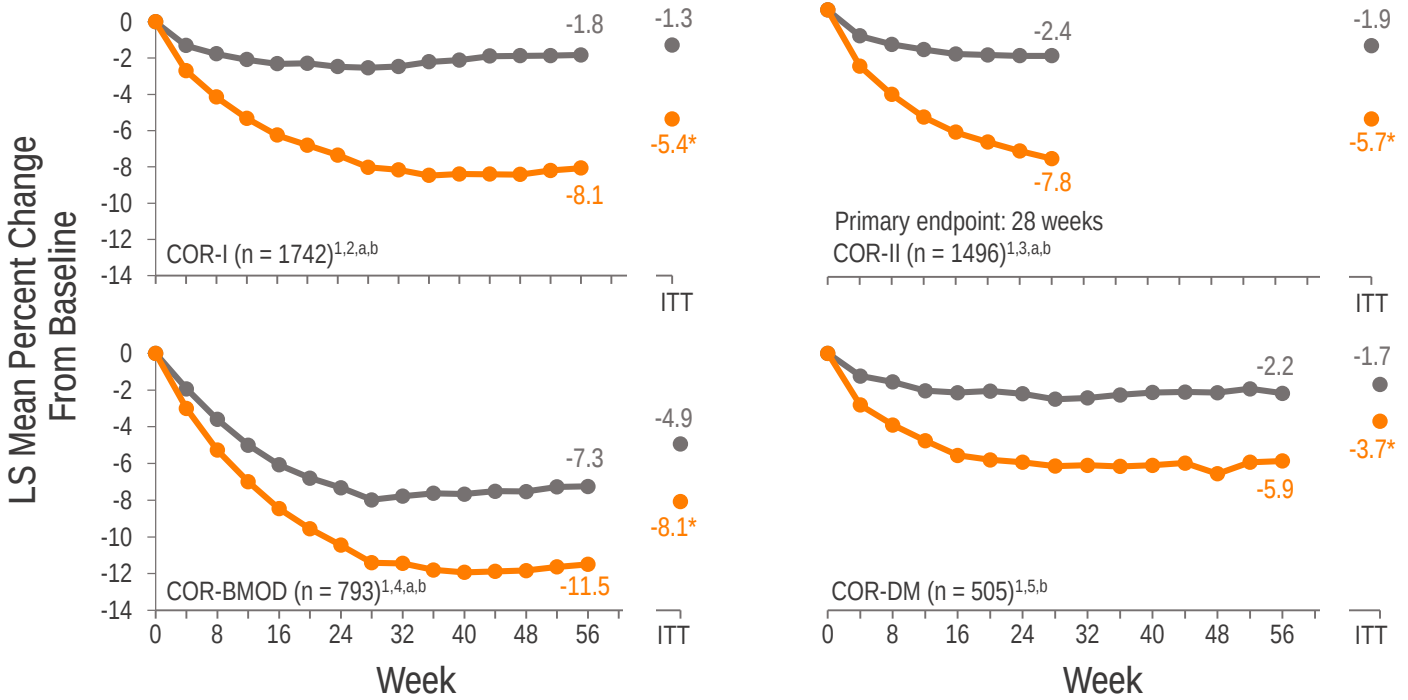
- White: 77%
- Black: 18%
- Other: 5%

Comorbidities

- Hypertension: 25%
- Dyslipidemia: 54%
- Prediabetes: 33% (defined FPG ≥5.7 mmol/L)
- Type 2 diabetes: 11%

1. CONTRAVE [product monograph], February 12, 2018, Valeant Canada LP; Laval, QC.; 2. Greenway FL, et al. *Lancet*. 2010;376:595-605;
3. Apovian CM, et al. *Obesity*..13;21:935-943.; 4. Wadden TA, et al. *Obesity*. 2011;19:110-120;. 5. Hollander P, et al. *Diabetes Care*. 2013;36:4022-4029.

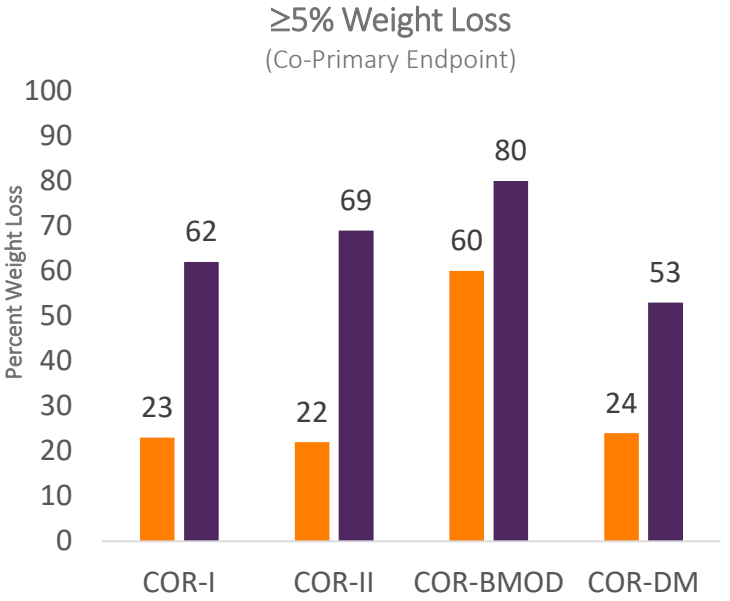
CONTRAVE® Was Significantly More Efficacious than Placebo in Phase 3 Trials

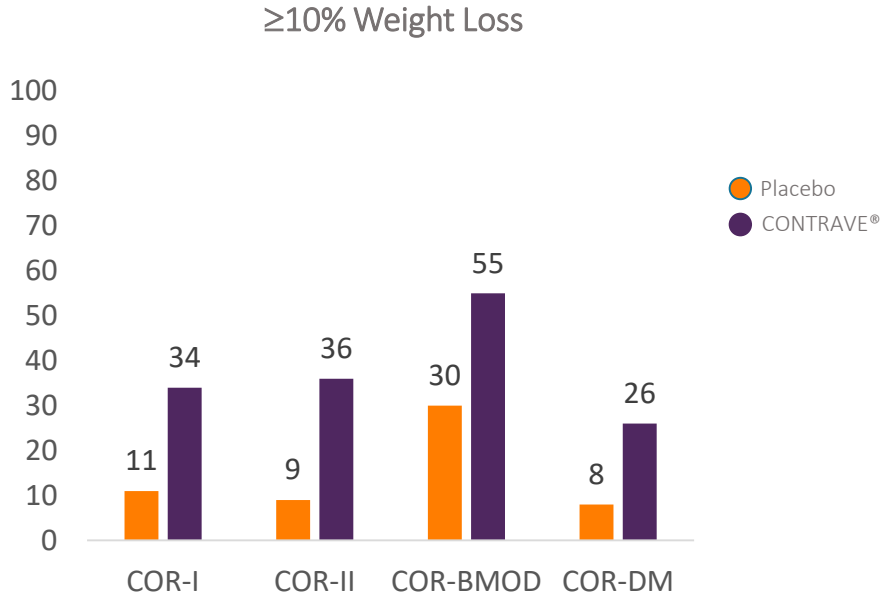


[a]BMI 30–45 kg/m^2; [b]BMI 27–45 kg/m^2 with comorbidities.
BMOD = behavior modification; ITT = intent-to-treat; DM = type 2 diabetes mellitus.

1. CONTRAVE [product monograph], February 12, 2018, Valeant Canada LP; Laval, QC.; 2. Greenway FL, et al. *Lancet*. 2010;376:595-605;3. Wadden TA, et al. *Obesity*. 2011;19:110-120;. 4. Hollander P, et al. *Diabetes Care*. 2013;36:4022-4029. 5. Apovian CM, et al. *Obesity*..13;21:935-943

The Percentage Of Subjects With ≥5% Or ≥10% Body Weight Loss Was Greater With CONTRAVE® Compared With Placebo In All Four Phase 3 Trials



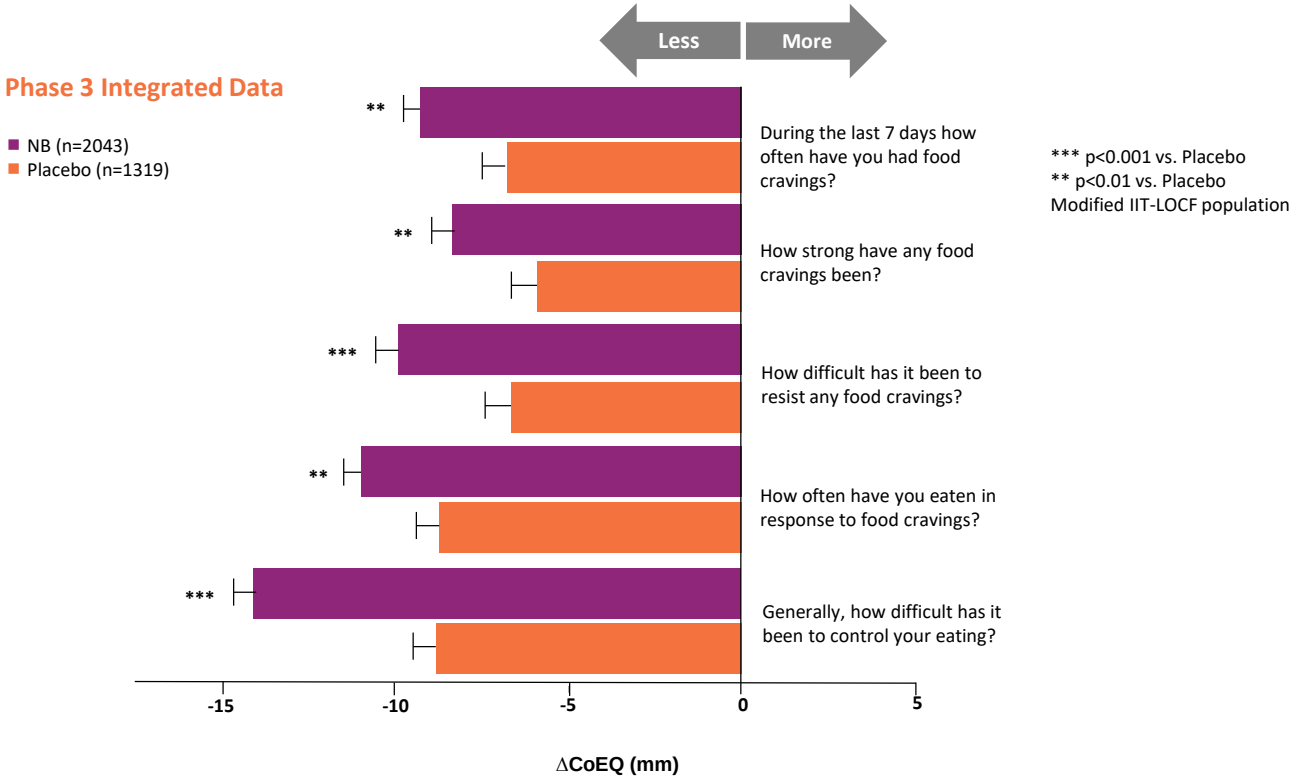


[a]Completer population; COR-II based on 28-week endpoint, all others based on 56-week endpoint.

BMOD=behavior modification; **DM**=type 2 diabetes mellitus.

1. CONTRAVE [summary of product characteristics]. Dublin, Ireland: Orexigen Therapeutics Ireland Limited; 2017.

Eating Behaviours Among Patients Receiving NB Compared to Placebo



1. Dalton M et al. Poster presented at The Obesity Society Meeting 2014. 2. Greenway, FL et al. Lancet. 2010; 376(9741):595-605. 3. Apovian CM, et al. Obesity (Silver Spring). 2013; 21(5): 935-943. 4. Wadden TA et al. Obesity (Silver Spring). 2011; 19(1): 110-120. 5. Hollander P, et al. Diabetes Care. 2013; 36(12):4022-4029.

CONTRAVE® Indication

CONTRAVE® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management
in adults with an initial body mass index (BMI) of:

- **30 kg/m²** or greater (obesity) or
- **27 kg/m²** or greater (overweight) in the presence of at least one weight-related **comorbidity** (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia)

CONTRAVE [product monograph], February 12, 2018, Valeant Canada LP; Laval, QC.

Contraindications

Naltrexone-related

- Chronic opioid use
- Abrupt discontinuation of alcohol or drug use

Bupropion-related

- Uncontrolled hypertension
- Bupropion containing drugs
- Seizures, Bulimia, Anorexia
- MAOI use
- Thioridazine use

- Severe hepatic impairment
- Severe renal impairment

- Severe hepatic impairment
- Severe renal impairment

All weight management medications:
Pregnancy

CONTRAVE [product monograph], February 12, 2018, Valeant Canada LP; Laval, QC

Safety Evaluated in 4754 Patients with Overweight/Obesity up to 56 Weeks

- The most frequent adverse reactions for naltrexone/bupropion
  - Nausea, constipation, vomiting, dizziness, and dry mouth

Incidence of the most frequent GI adverse events

Adverse Reaction	CONTRAVE* n = 2545 (%)	Placebo n = 1515 (%)
Nausea	32.5	6.7
Constipation	19.2	7.2
Headache	17.6	10.4
Vomiting	10.7	2.9
Dizziness	9.9	3.4
Insomnia	9.2	5.9
Dry mouth	8.1	2.3
Diarrhea	7.1	5.2

- The vast majority of subjects treated with CONTRAVE® who experienced nausea reported the event within 4 weeks of starting treatment. Events were generally self-limited; the majority
  of events resolved within 4 weeks and almost all resolved by Week 24.

*3239 subjects treated with naltrexone/bupropion and 1515 subjects treated with placebo.

CONTRAVE [product monograph], February 12, 2018, Valeant Canada LP; Laval, QC.

CONTRAVE® Dosing and Administration

CONTRAVE dosing should be escalated over a 4-week period

Administration

- Tablets should be taken by mouth in the morning and evening and should not be cut, chewed or crushed
- In clinical trials, CONTRAVE was administered with meals. However, CONTRAVE should not be taken with a high-fat meal because of a resulting significant increase in bupropion and naltrexone systemic exposure.

The need for treatment should be evaluated after 16 weeks and reevaluated annually

CONTRAVE [product monograph], February 12, 2018, Valeant Canada LP; Laval, QC

TOS Guidelines: Comprehensive Lifestyle Recommendations

Nutrition

- -500 to -750 kcal/day
- 1200-1500 kcal/day women; 1500-1800 kcal/day
- Evidence-based diet that restricts certain food types

Activity

- Minimum 150 min/week of moderate activity
- 200-300 min/week for weight maintenance

Behaviour therapy-structured program

Self-monitoring

- Food intake
- Activity
- Weight

TOS = The Obesity Society.
Jensen, MD et al. *Circulation* 2014: 129;5102-38.

Questions

OBESITY C.A.R.E. Mentorship Program

Are you ready to take the next steps to manage obesity in your practice?

Novo Nordisk's Obesity C.A.R.E. Mentorship Program offers healthcare providers the opportunity to shadow and work alongside an obesity specialist to gain valuable experience in the management of obesity.

Learn how to have **practical discussions with your patients** about obesity

Discover ways to effectively **employ** evidence-based **treatments** for the management of obesity

Optimize your practice for the management of obesity

How do I apply?

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Access code: obesitycare1!

Please note that spaces in the Obesity C.A.R.E Mentorship Program are limited.

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