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

Renuca Modi MD CCFP
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• Faculty: Renuca Modi, MD, CCFP
  Diplomate of the American Board of Obesity Medicine
  Medical Lead, Edmonton Adult Bariatric Clinic
  Assistant Clinical Professor, Department of Family Medicine, U of 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...

- Epigenetics
- Mutations
- Single nucleotide polymorphisms
- Altered levels of hormones and gastrointestinal peptides
- Altered homeostatic and reward system pathways
- Weight-positive medications
- Health conditions

**Diet**
- Inactivity
- Emotional factors
- Lack of sleep
- Smoking cessation

**Genetic**
- High heritability of body weight, especially at BMI extremes
- Genes in hypothalamus leptin-melanocortin pathway
  - LEP, LEPR, POMC, ADCY3, PCSK1, MC4R, and BDNF
- Single genetic mutations leading to obesity are rare, but variations in many genes may predispose to obesity

**Environmental**
- Socio-cultural factors
  - Traditions, belief systems, peer pressure
- Socio-economic factors
  - Education level
  - Affordability of healthy food
- Food environment
  - Availability of inexpensive, highly palatable food

**Behavioral**
- Diet
- Inactivity
- Emotional factors
- Lack of sleep
- Smoking cessation

**Physiological**
- Homeostasis (Neuroendocrine pathways)
  - Hypothalamus
  - Stomach, Gut, Adipose Tissue
- Hunger and reward (CNS Pathways)
  - Mesolimbic Region

**Other factors:**
- Microbiome
- Some medications

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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.

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 foods⁴

CNS = central nervous system; POMC = proopiomelanocortin. Figure adapted from Billes et al., © 2014, with permission from Elsevier.

CONTRAVER®:
Naltrexone/Bupropion
CONTRAVERE® Is a Combination of Two Compounds: Naltrexone and Bupropion

Naltrexone HCl\textsuperscript{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\textsuperscript{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
Regulation Of Hunger: Role Of Hypothalamic POMC Neurons

Hypothalamus

POMC neurons
- Integrate multiple energy balance signals

α-MSH
- Released from POMC neuron
- Binds to MC4-R to decrease food intake

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

β-endorphin (endogenous opioid)
- Released from POMC neuron with α-MSH
- Binds to μ-opioid receptor to inhibit POMC neuron activation (negative feedback loop)

Figure adapted from Billes et al., © 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 suppression.

- **Hypothalamus**
  - α-MSH
  - β-endorphin

**Naltrexone**
Indirectly increases POMC activity by blocking a natural negative feedback loop.

**Bupropion**
Directly increases POMC activity.

- Increased POMC activity
- Reduced hunger
- Reduced weight

**MSH** = melanocyte-stimulating hormone; **POMC** = pro-opiomelanocortin.

Figure adapted from Billes et al., 2014, with permission from Elsevier.

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

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)

<table>
<thead>
<tr>
<th>Co-Primary Endpoints</th>
<th>Percent change from weight from baseline</th>
<th>Percent of subjects achieving ≥5% weight reduction</th>
</tr>
</thead>
</table>

| Study Design | 56 weeks, placebo controlled, including 4-week dose escalation |

| Population | BMI 30-45 kg/m² | BMI 27-45 kg/m² (with comorbidities) | T2DM, BMI 27-45 kg/m² |

<table>
<thead>
<tr>
<th>Diet and Exercise</th>
<th>Diet and exercise counseling</th>
<th>Intensive BMOD</th>
<th>Diet &amp; exercise counseling</th>
</tr>
</thead>
</table>

| Dose and Randomization | NB16 & NB32 1:1:1 | NB32 2:1 | NB32 3:1 | NB32 2:1 |

**COR-I²** n = 1742  
**COR-II³** N=1496  
**COR-BMOD³** n = 793  
**COR-DM⁴** n = 505

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

CONTRAVERSE® Use in Phase III Clinical Trials

52 weeks at full dose: NB 32/360 mg

**4 week titration to full dose:**

<table>
<thead>
<tr>
<th>Week 1</th>
<th>1 tablet OD, morning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>1 tablet BID</td>
</tr>
<tr>
<td>Week 3</td>
<td>2 tablets morning + 1 table evening</td>
</tr>
<tr>
<td>Week 4</td>
<td>2 tablets BID</td>
</tr>
</tbody>
</table>

CONTRAVERSE® is available as prolonged release tablets that contain 8 mg naltrexone HCl and 90 mg bupropion HCl each.
### Phase 3 Clinical Development Program: Baseline Characteristics

<table>
<thead>
<tr>
<th><strong>Age</strong></th>
<th><strong>Gender</strong></th>
<th><strong>Body Mass Index (BMI)</strong></th>
<th><strong>Comorbidities</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mean = 46 years</td>
<td>• Men: 17%</td>
<td>• Baseline mean = 36 kg/m²</td>
<td>• Hypertension: 25%</td>
</tr>
<tr>
<td><strong>Waist Circumference</strong></td>
<td>• Women: 83%</td>
<td></td>
<td>• Dyslipidemia: 54%</td>
</tr>
<tr>
<td>• Baseline mean = 110 cm</td>
<td></td>
<td></td>
<td>• Prediabetes: 33% (defined FPG ≥5.7 mmol/L)</td>
</tr>
<tr>
<td><strong>Ethnicities</strong></td>
<td></td>
<td></td>
<td>• Type 2 diabetes: 11%</td>
</tr>
<tr>
<td>• White: 77%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Black: 18%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other: 5%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Primary endpoint: 28 weeks

**LS Mean Percent Change From Baseline**

**COR-I (n = 1742)**


*BMI 30–45 kg/m²; **BMI 27–45 kg/m² with comorbidities. BMOD = behavior modification; ITT = intent-to-treat; DM = type 2 diabetes mellitus.*
The Percentage Of Subjects With ≥5% Or ≥10% Body Weight Loss Was Greater With CONTRAVE® Compared With Placebo In All Four Phase 3 Trials

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

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

Eating Behaviours Among Patients Receiving NB Compared to Placebo

Phase 3 Integrated Data

- ** p<0.01 vs. Placebo
- *** p<0.001 vs. Placebo

Modified IIT-LOCF population

- NB (n=2043)
- Placebo (n=1319)

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)
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

**All weight management medications:**
- Pregnancy
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

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

- 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.
CONTRAVERSE® Dosing and Administration

CONTRAVERSE dosing should be escalated over a 4-week period

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4 and onward</td>
<td></td>
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</tr>
</tbody>
</table>

Administration

- Tablets should be taken by mouth in the morning and evening and should not be cut, chewed or crushed
- In clinical trials, CONTRAVERSE was administered with meals. However, CONTRAVERSE 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.
# 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
Questions
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?
Visit www.obesitycarementorship.ca
Access code: obesitycare1!

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