New Options in Pharmacotherapy for Obesity

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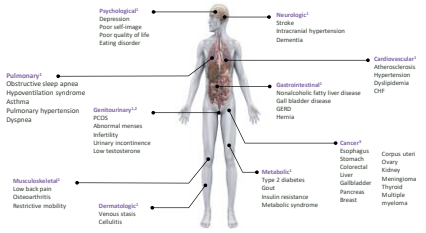
Disclosures

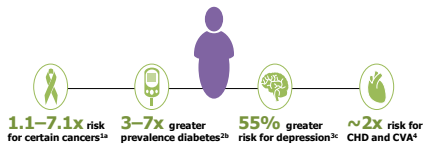
- Consulting: Orexigen, Takeda, iNova, Vivus, Novo Nordisk, Biologix, Amgen, Eisai, KVK, Rhythm, Novartis
- Boards of Directors: The Obesity Society, Obesity Action Coalition, Obesity Treatment Foundation, True Health Initiative, NASH Alliance, Global Liver Institute
- Textbook royalties: Johns Hopkins University Press, Lippincott Williams & Wilkins, Wolters-Kluwer

Obesity: A Major Contributor to Disease



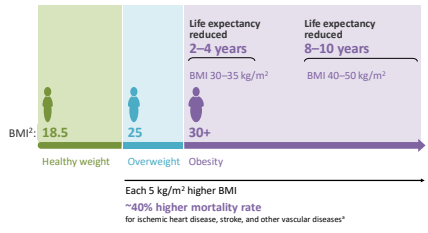
CHF=congestive heart failure; GERD=gastroesophageal reflux disease; PCOS=polycystic ovarian syndrome.
1. Catenacci VA et al. *Clin Chest Med.* 2009;30:415-444. **2.** Wang C et al. *Diabetes Care.* 2013;34:1669-1675. **3.** Lauby-Secretan B et al. *N Engl J Med.* 2016;375:794-798.

Obesity: A Major Contributor to Disease



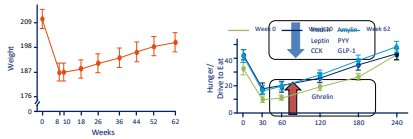
[a]Based on a review of >1000 epidemiologic studies to assess the effects of weight control on cancer risk, performed by a working group of the International Agency for Research on Cancer (IARC).
[b]Based on data from the 2001 Behavioral Risk Factor Surveillance Survey (BRFSS), including US residents aged 18 years and older.
[c]Based on a meta-analysis summarizing available prospective cohort studies (as of March 2008).
1. Lauby-Secretan B et al. *N Engl J Med.* 2016;375:794-798. **2.** Mokdad AH et al. *JAMA.* 2003;289:76-79. **3.** Luppino FS et al. *Arch Gen Psychiatry.* 2010;67:220-229. **4.** Mathew B et al. *J Am Board Fam Med.* 2008;21:562-568.

Obesity: A Major Contributor to Disease



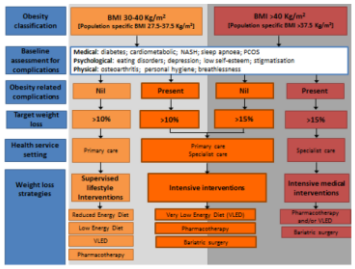
[a]Based on a meta-analysis of 57 international prospective studies predominantly based in Europe, the United States, Israel, and Australia, including BMI information for 894,576 adults.
1. Whitlock G et al. *Lancet.* 2009;373:1083-1096. **2.** Garvey WT et al. *Endocr Pract.* 2016;22(Suppl 3):1-203.

Physiology Fights Against Sustained Weight Loss



Sumithran P et al. N Engl J Med. 2011;365:1597–1604.

Australian Diabetes Society Obesity Treatment Algorithm



Developed in conjunction with ANZOS and representatives from RACGP

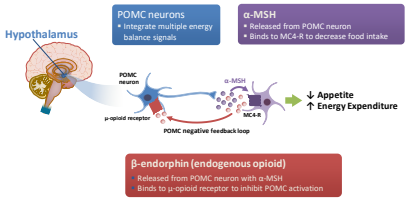
https://diabetessociety.com.au/documents/ObesityManagementAlgorithm18.10.2016FINAL.pdf

Obesity Pharmacotherapy Agents Approved in Australia

- Phentermine[1]
  - Sympathomimetic amine
  - Appetite suppression
- Liraglutide 3mg [2]
  - GLP-1 analogue
  - Central action to reduce hunger and prolong satiety
- Orlistat[3]
  - Inhibits intestinal lipase to reduce fat absorption[3]
- Naltrexone / Bupropion SR[4]
  - Anti-addiction therapies
  - Central action to reduce hunger and cravings

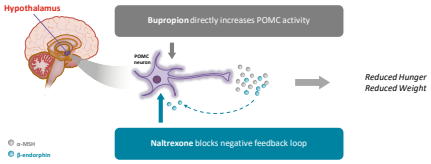
1. Duromine Product Information. 2. Saxenda Product Information. 3. Xenical Product Information. 4. Contrave Product Information

POMC Neuron Role in Appetite



α-MSH=α-melanocyte-stimulating hormone; MC4-R=melanocortin-4 receptor; POMC=proopiomelanocortin.
Billes SK et al. *Pharmacol Res*. 2014;84:1-11.

Naltrexone and Bupropion Act Synergistically



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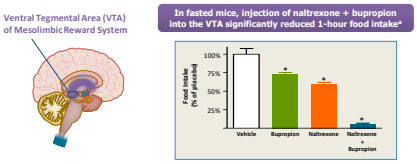


*P<0.01 compared to vehicle.
*One-hour food intake following intra-ventral tegmental area injection of naltrexone 1 μg, bupropion 1 μg, or naltrexone 1 μg/bupropion 1 μg in 16-hour fasted mice (n=8/group).
Billes SK et al. *Pharmacol Res*. 2014;84:1-11.

Naltrexone/Bupropion Phase 3 Trials

	NB-301 (COR-I)[1] N=1742	NB-303 (COR-II)[2] N=1496	Intensive Counseling NB-302 (COR-BMOD)[3] N=793	Type 2 diabetes NB-304 (COR-DM)[4] N=505
Study Design	56 weeks, placebo-controlled, including 3-week dose escalation (COR-II: primary endpoint 28 weeks)			
Population	BMI 30–45 kg/m² BMI 27–45 kg/m² (with comorbidities)			T2DM, BMI 27–45 kg/m²
Diet and Exercise	Diet and exercise counseling		Intensive BMOD[a]	Diet and exercise counseling
Dose and Randomisation	NB16 and NB32 1:1:1	NB32 2:1	NB32 3:1	NB32 2:1

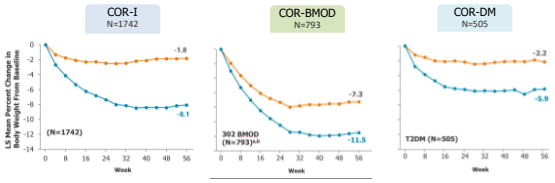
[a]BMOD consisted of group sessions led by dietitians, psychologists, or exercise specialists to educate subjects on weight control techniques. Subjects were also asked to follow individualized hypocaloric diets and were encouraged to increase moderately vigorous physical activity from 180 min/week to 360 min/week. BMI=body mass index; BMOD=behavior modification; NB16=naltrexone 16 mg SR/bupropion 360 mg SR; NB32=naltrexone 32 mg SR/bupropion 360 mg SR; T2DM=type 2 diabetes mellitus. **1.** Greenway FL et al. *Lancet*. 2010;376:595-605. **2.** Apovian CM et al. *Obesity*. 2013;21:935-943. **3.** Wadden TA et al. *Obesity*. 2011;19:110-120. **4.** Hollander P et al. *Diabetes Care*. 2013;36:4022-4029.

Phase 3 Clinical Trial Development

Randomized patients	COR-I N=1742	COR-II N=1496	COR-BMOD N=793	COR-DM N=505
Age (years), mean	44	44	46	54
Female, %	85	85	90	56
Race, %				
Caucasian	75	84	70	79
African American	19	14	24	16
Other	6	3	6	5
Ethnicity, %				
Hispanic or Latino	13	8	10	12
Weight (kg), mean	100	100	101	105
BMI (kg/m^2), mean	36	36	37	36
Hypertension, %	21	21	16	62
Dyslipidemia, %	49	55	44	84

1. Greenway FL et al. *Lancet*. 2010;376:595-605. **2.** Apovian CM et al. *Obesity*. 2013;21:935-943. **3.** Wadden TA et al. *Obesity*. 2011;19:110-120. **4.** Hollander P et al. *Diabetes Care*. 2013;36:4022-4029.

Weight Loss In Patients Completing 1 Year



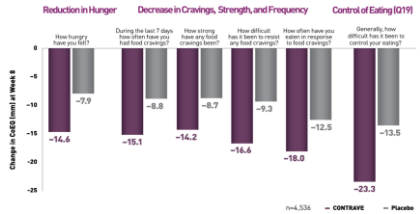
Greenway FL et al. *Lancet*. 2010;376:595-605. Wadden TA et al. *Obesity*. 2011;19:110-120. Hollander P et al. *Diabetes Care*. 2013;36:4022-4029.

Categorical Weight Loss In Patients Completing 1 Year Of Treatment

*P<0.01 vs placebo; **P<0.001 vs placebo.
BMOD=behavior modification; DM=diabetes mellitus; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares.

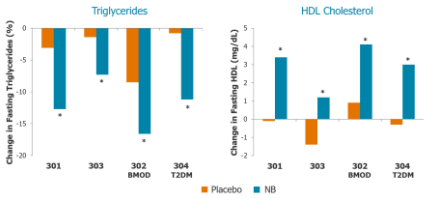
Greenway FL et al. *Lancet*. 2010;376:595-605. Wadden TA et al. *Obesity*. 2011;19:110-120. Hollander P et al. *Diabetes Care*. 2013;36:4022-4029.

Control of Eating Improves as Early as Week 8

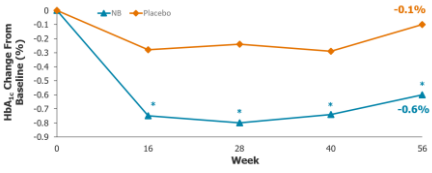


Dalton M, Finlayson G, Hill A, Blundell J. Preliminary validation and principal components analysis of the Control of Eating Questionnaire (CoEQ) for the experience of food craving. Eur J Clin Nutr. 2015;69:1313-1317.

Changes in Lipids Across Trials



Changes in HbA1c in Patients with T2D



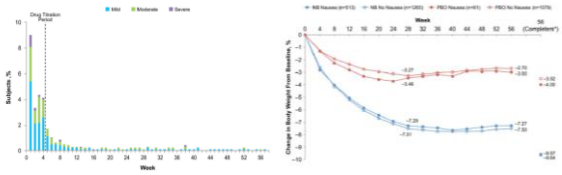
1. Hollander P et al. *Diabetes Care*. 2013;36:4022-4029

Adverse Effects Across Clinical Trials

Adverse Reaction	Naltrexone/Bupropion 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%

*Adverse events occurring in greater than 2% of patients are shown.
Contrave [prescribing information]. La Jolla, CA: Orexigen Therapeutics, Inc.; 2016.

Weight Loss is Independent of Nausea



Hong, K. et al 2014. Clinical obesity 6, 305-312

Naltrexone/Bupropion Indications

Naltrexone HCl

- Opioid receptor antagonist
- Indications: treatment of **alcohol dependence** and prevention of relapse to **opioid dependence**
- TGA approved since **1998**

Bupropion HCl

- Dopamine/norepinephrine reuptake inhibitor
- Indications: as an adjunct to **smoking cessation in Australia**
- TGA approved since **2000.**

CONTRAVE is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of:

- ≥ 30 kg/m^2 or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)

1. Contrave Approved Product Information

Naltrexone/Bupropion Dosing

Recommended daily dose of naltrexone/bupropion is 2 tablets twice daily for a total of 32 mg naltrexone HCl and 360 mg bupropion HCl, which is reached at the start of week 4

CONTRAVE® dosing should be escalated over a 4-week period

	Morning	Evening
Week 1	●	
Week 2	●	●
Week 3	● ●	●
Week 4 and onwards	● ●	● ●

1. Contrave Product Information

Naltrexone/Bupropion Treatment Should be Evaluated after 16 Weeks and Regularly Thereafter

<5% weight loss

CONTRAVE should be discontinued if a patient has *not* lost at least 5% of baseline weight at 16 wk

≥5% weight loss

CONTINUE CONTRAVE if patient loses at least 5% of baseline weight at 16 weeks

1. Contrave Product Information

Contraindications

- Uncontrolled hypertension
- Seizure disorder or a history of seizures
- Known central nervous system tumour
- Undergoing acute alcohol or benzodiazepine withdrawal
- Bipolar disorder
- Chronic opioids or opiate agonists, or acute opiate withdrawal
- Pregnancy
- Patients with severe hepatic impairment
- Patients with end-stage renal failure

Contrave Product Information

Summary

- Obesity is a major contributor to disease
- Complex neuro-hormonal mechanisms underpin hunger and make sustainable weight loss difficult
- Newer pharmacotherapy options hold promise to improve patients' weight and health outcomes
- Naltrexone / bupropion is the newest available option, when combined with diet and exercise leads to increased weight loss and improved comorbidities

Thank you.

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