Contrave®
(naltrexone HCl/bupropion HCl)
8 mg/90 mg • Extended-Release Tablets

A DUAL ACTION TREATMENT FOR WEIGHT MANAGEMENT

CONTRAVE®:

A DUAL ACTION TREATMENT FOR WEIGHT MANAGEMENT

Welcome

The purpose of this course is to provide information on Contrave®, a new medication for the management of obesity, and information on counselling patients managing weight loss.

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Disclaimer

This training does not endorse the medicine/product for sale but provides education opportunities to enable and consider the efficacy and safety of medicines/products sold, using an evidence-based approach and utilising available clinical information. Health professionals, have a duty of care to be aware of available clinical evidence that supports the therapeutic and marketing claims made about all medicines and products sold in their pharmacies

CONTRAVE®:

A DUAL ACTION TREATMENT FOR WEIGHT MANAGEMENT

Learning objectives

The learning objectives for this course are:

- Describe the mechanism of action of Contrave®
- Outline key product information for Contrave®
- Awareness on Contrave® clinical findings
- Outline of the key counselling points
- Contrave® dose escalation
- Patient Support Program outline

This course will take you approximately 30-90 minutes, depending on the level on detail you would like to go in to.
There are 5 questions at the end in order to complete the course

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CONTRAVE®:

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What will be covered in this training

- One: Summary
- Two: Overview
- Three: Clinical findings
- Four: Product information
- Five: Counselling points
- Six: Patient support
- Seven: Assessment

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One: **Summary of Contrave®**

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What you need to know about Contrave®[1]

- What is it?
- Dosage
- Adverse effects
- Precautions
- Contraindications
- Push On

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

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What is Contrave®

Contrave® is a dual action formulation containing 8mg naltrexone and 90mg bupropion.[1] The unique formulation targets the experiences of **hunger**, **satiety** and **craving** in the brain to **stimulate weight loss**.[1]

It is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults (over 18 years old) with:[1]

BMI ≥ 30 kg/m^2 **OR** BMI ≥ 27 kg/m2 with at least one weight-related comorbidity.

Recommended retail price of Contrave is $240 per month

Acts on areas of the brain associated with hunger and reward.[1]

Average **11.6%** weight loss from baseline, after 56 weeks.[2]

Sustained weight loss, through 56 weeks from baseline.[1]

Reduction in HbA1c cholesterol markers & waist circumference (for patients with T2D).[1]

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Reference: **1.** Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf 2. Fujioka K et al. Int J Obes 2016;40:1369–1375.)

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Dose and administration[1]

Dose escalation occurs in the first four weeks until the full dose has been reached (4 tablets).

Contrave® is taken;

- Orally,
- Twice daily,
- Swallowed whole,
- With a glass of water, and food.

If a dose is missed, patients should not take an additional dose, but take the next dose at the usual time. Treatment then continues for up to a total of 56 weeks.

Continued treatment should be evaluated after 16 weeks and discontinued if ≥ 5% of baseline weight has not been lost by 16 weeks.

Titration timeline:

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 4/8

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

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Adverse effects[1]

The most common adverse effects associated with Contrave® are;

- Nausea,
- Vomiting,
- Dry mouth and
- Constipation.

This usually occurs in the first four weeks then subside as the dose is increased.

Patients should be counselled regarding this and reminded to speak to their doctor if these symptoms are severe.

The long-term safety of Contrave® has not been established.

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Precautions[1]

The safety and tolerability of Contrave® should be assessed at regular intervals. Treatment should be discontinued if there are any concerns about the safety or tolerability of ongoing treatment, including concerns about raised blood pressure. The safety and efficacy of Contrave® for use (> 1 year) has not been established.

Note: The approved indication does not restrict the duration of use of Contrave® (although treatment should be discontinued if patients have not lost ≥5% of their initial body weight after 16 weeks).

- Psychiatric symptoms
- Seizures
- Opioid analgesic
- Allergic reactions
- Elevation of BP & HR
- Cardiovascular disease
- Hepatotoxicity

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Contraindications[1]

Contrave® is contraindicated in several situations.

- Hypersensitivity (to naltrexone, bupropion or any excipients)
- Uncontrolled hypertension
- Seizure disorder (or a history of seizures)
- Known CNS tumour
- Undergoing acute benzodiazepine or alcohol withdrawal
- History of bipolar disorder
- Use of other treatment with bupropion or naltrexone
- Current dependence on chronic opioids or opioid agonists (methadone)
- Patients in acute opiate withdrawal
- Patients taking monoamine oxidase inhibitors
  (at least 14 days should lapse between discontinuation of MAOI and initiation of treatment with Contrave®)
- Pregnancy
- Severe hepatic impairment
- End-stage renal failure

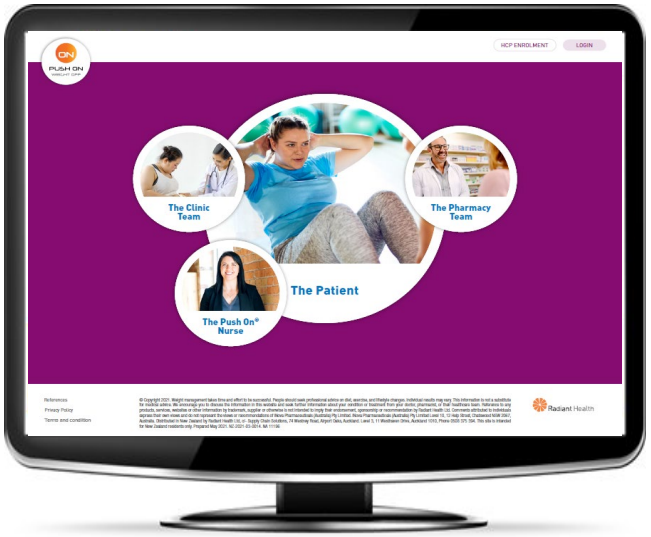
Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Push On®

Push On® is a patient support program.

It is an online platform, supporting patients along their weight loss journey by providing;

- Nurse to patient phone support
- Tools and resources on weight management
- Dashboard with their weigh loss and goals
- Collaborative team support from their clinic, pharmacy and Push On nurse



It is a complementary service for patients prescribed Contrave ® or Duromine ®.

Patients will need to be enrolled by their prescribing doctor

Healthcare professionals will be able to track their patient's journey through the program, including whether they are meeting their goals.

Pharmacies will need to enrol to be a participating pharmacy

To enrol go to: www.pushon.co.nz/enrol

Progress: 8/8

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Two: Overview of Obesity & Contrave®

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Why treat obesity?

Obesity is recognised as a 'serious, chronic, relapsing disease process of energy regulation'.[1] It is associated with several comorbidities and increased risk factors for other chronic diseases.

The primary treatment is weight loss; however, lifestyle measures alone provide only modest weight reductions in most patients. [1]

Measures beyond lifestyle changes are required in the management of several chronic diseases such as Type 2 Diabetes and Hypertension.[1] As with these chronic diseases, we have a responsibility to provide proactive management to patients with obesity.

Modest weight loss of 5-10% of baseline body weight is associated with a marked decrease in cardiovascular risk factors.[2]

Progress: 2/10

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: 1. Lee, PC and Dixon J. Pharmacotherapy for obesity. AFP Vol 46 (7). July 2017 [Cited Nov 2018]. Royal College of General Practitioners.2. Brown, Joshua D et al. Effects on cardiovascular risk factors of weight losses limited to 5-10. Translational behavioral medicine vol. 6,3 (2015): 339-46.

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Contributors to rebound weight gain

Weight loss is rarely sustained long-term and is often associated with rebound weight gain some time after the intervention is ceased.[1]

Rebound weight gain is influenced by several factors caused by the biological drive to regain lost weight including;[2-4]

- Increased hunger
- Increased food cravings
- Lower levels of satiety (feeling full)
- Decreased energy expenditure associated with daily life

Progress: 3/10

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: 1. Montesi, L et al. Long-term weight loss maintenance: a multidisciplinary approach. [InDiabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2016:9 37–46. Cited Nov 2018. 2. Melby C, Paris H, Foright R, Peth J. Attenuating the Biologic Drive for Weight Regain Following Weight Loss: Must What Goes Down Always Go Back Up? 2017;9(5):468. 3. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. International journal of obesity (2005). 2015;39(8):1188-96. Epub 2015/04/22. 4. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011; 365: 1597–1604.

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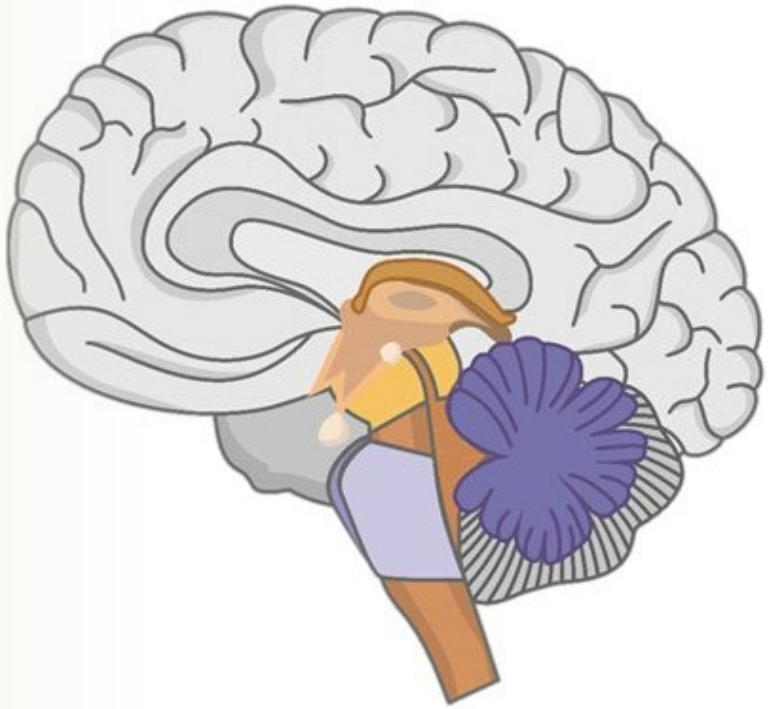
Obesity and the brain

It has been proposed that brain systems that balance energy are biased towards weight conservation.[1,2] This may play a role in the difficulty of maintaining weight loss long-term.

Obesity is associated with changes to neural signaling associated with hunger and feeling full.[1] These changes may play a role in the increased hunger and decreased satiety observed after weight loss.

Weight loss is associated with increases in brain activity relating to reward and value associated with food.[1]



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Progress: 4/10

Reference: **1.** Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and bodyweight. Nature 2006;443:289–95. **2**. Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL. Is the Energy Homeostasis System Inherently Biased Toward Weight Gain? Diabetes. 2003;52(2):232-8. doi: 10.2337/diabetes.52.2.232.

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The role of medication in the management of obesity

Pharmacotherapy for weight management is used as an adjunct to lifestyle intervention, as with other chronic diseases.[1] A common target for pharmacotherapy is a loss of 5-10% of body weight.

Pharmacotherapy acts physiologically to target[1]

- Appetite reduction
- Prolonged satiety
- Satiety following small meals

Recently, the psychological aspects of weight management, especially the role of cravings, has been emphasised.

Management of the reward aspect of food is an emerging goal of pharmacotherapy.[2]

Progress: 5/10

Reference: **1.** Lee, PC and Dixon J. Pharmacotherapy for obesity. AFP Vol 46 (7). July 2017 [Cited Nov 2018]. Royal College of General Practitioners **2**. Billes SK, Sinnay P and Cowley MA. Naltrexone/buproprion for obesity: An investigational combination pharmacotherapy for weight loss. Pharmacological research 84 (1-11). 2014 [Cited Nov 2018].

Introducing Contrave®

Contrave® is a novel dual action weight loss medication that was registered by the Medsafe in October 2020.[1]

It is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults (over 18 years old) with:[1]

BMI ≥ 30 kg/m^2 **OR** BMI ≥ 27 kg/m2 with at least one weight-related comorbidity.

For example:
- Type 2 Diabetes
- Controlled hypertension
- Dyslipidaemia

Contrave® is an oral dosage formulation.

Progress: 6/10

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Contrave® for weight management

Contrave® is a dual action formulation containing 8mg naltrexone and 90mg bupropion.[1] The unique formulation targets the experiences of hunger, satiety and craving in the brain to stimulate weight loss.[1]

Acts on areas of the brain associated with hunger and reward.[1]

Average **11.6%** weight loss from baseline, after 56 weeks.[2]

Sustained weight loss, through 56 weeks from baseline.[1]

Reduction in HbA1c cholesterol markers & waist circumference (for patients with T2D).[1]

Progress: 7/10

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: **1.** Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf 2. Fujioka K et al. Int J Obes 2016;40:1369–1375.)

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Mode of action

The neurochemical effects of naltrexone and bupropion are well understood. The exact neurochemical effects of Contrave® leading to weight loss are not well understood. Both medications appear to exert effects on the hypothalamus relating to the production of hormones that suppress appetite, both as individual agents and in combination.[1]

Bupropion stimulates POMC activity, a key component in hypothalamic regulation of appetite, whilst naltrexone inhibits POMC inhibition.

Naltrexone and bupropion have both also been shown to act in the mesolimbic reward system, as evidenced by their indications in the management of addiction disorders.[2]

Pre-clinical studies suggested these effects are independent but synergistic.[1]

Progress: 8/10

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: **1.** Billes SK, Sinnay P and Cowley MA. Naltrexone/buproprion for obesity: An investigational combination pharmacotherapy for weight loss. Pharmacological research 84 (1-11). 2014 [Cited Nov 2018]. **2**. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. International journal of obesity (2005). 2015;39(8):1188-96. Epub 2015/04/22.

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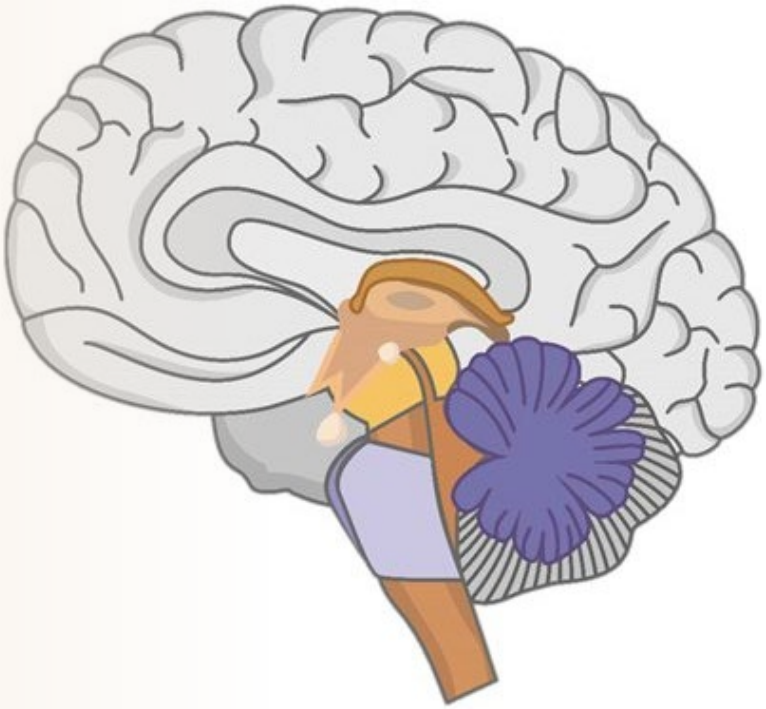
Mode of action

Contrave® acts via actions at the hypothalamus and the mesolimbic reward system to:[1]

- Reduce cravings
- Reduce hunger
- Increase energy expenditure
- Promote satiety[2]



Progress: 9/10

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: **1.** Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf **2**. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England). 2010;376(9741):595-605.

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Contrave® for weight management

Treatment with Contrave® aims to result in a reduction in baseline body weight of 5% within the first 16 weeks of treatment.[1]

Patients who do not achieve 5% weight loss in this time frame should discontinue treatment as they are unlikely to benefit from ongoing treatment.[1]

Progress: 10/10

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: **1.** Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf **2**. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England). 2010;376(9741):595-605.

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Three: Clinical Findings

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Clinical data for the combination of naltrexone and bupropion

Naltrexone (ReVia®) and bupropion (Zyban®) are both medications that have a long history of use, with listings in 1998 (Revia®)[1] and 2000 (Zyban®)[2,3] respectively. However, their use in combination, and for the indication of weight management is relatively new.

Preclinical studies demonstrated that naltrexone and bupropion have independent actions in two areas of the brain that influence energy balance. The acute effects of this have been maintained in both animal and human studies.[4]

Clinical trials found:

- The combination of naltrexone and bupropion led to more weight loss compared to placebo[5]*
- This combination with intensive behaviour modification (BMOD) led to more weight loss compared to placebo with BMOD*[6]
- The combination led to more weight loss compared to placebo in patients with diabetes*[7]

The percentages of subjects with ≥5% or ≥ 10% weight loss from baseline was greater than placebo in all studies.[5-7]

**Participants were prescribed mild hypocaloric diet and exercise.*

Note: *Another study referred to as the COR-II study replicated the results of the COR-I study. As the study design and results are comparable, this study will not be examined in this module*

Progress: 2/7

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The Contrave Obesity Research (COR)-I trial[1]

The COR I study assessed the effect of a combination of sustained release naltrexone and bupropion on bodyweight in overweight and obese participants vs placebo. Naltrexone and bupropion exhibited significantly greater weight loss, improvement in cardiometabolic risk factors and weight related quality of life. Participants lost an average of 6% body weight, compared to 1.3% for placebo at 56 weeks from baseline (primary analysis population).

- Study design
- Weight loss results
- Health benefit results

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 3/7

Reference: **1.** Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England). 2010;376(9741):595-605.

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The Contrave Obesity Research (COR)-I trial[1]

Study design

Weight loss results

Health benefit results

COR-I was a phase 3, randomised, double-blinded, placebo-controlled study conducted from October 2007- May 2009 in 34 centres in the USA.

Patients were men and women aged 18-65 years with BMI 30-45 kg/m^2 and uncomplicated obesity or BMI 27-45 kg/m^2 and controlled hypertension and/or dyslipidaemia. Women of childbearing age were required to
use effective contraception for the duration of the trial. All participants underwent a three-week dose escalation.

Participants were randomised 1:1:1 into three groups, receiving two doses twice a day*:

- 8mg naltrexone/90mg bupropion
- 4mg naltrexone/90mg bupropion (not available in Australia)
- Placebo

Clinical trial has been supplied to view exclusion criteria.

* Participants were prescribed mild hypocaloric diet and exercise.

Progress: 3/7

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: **1.** Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England). 2010;376(9741):595-605.

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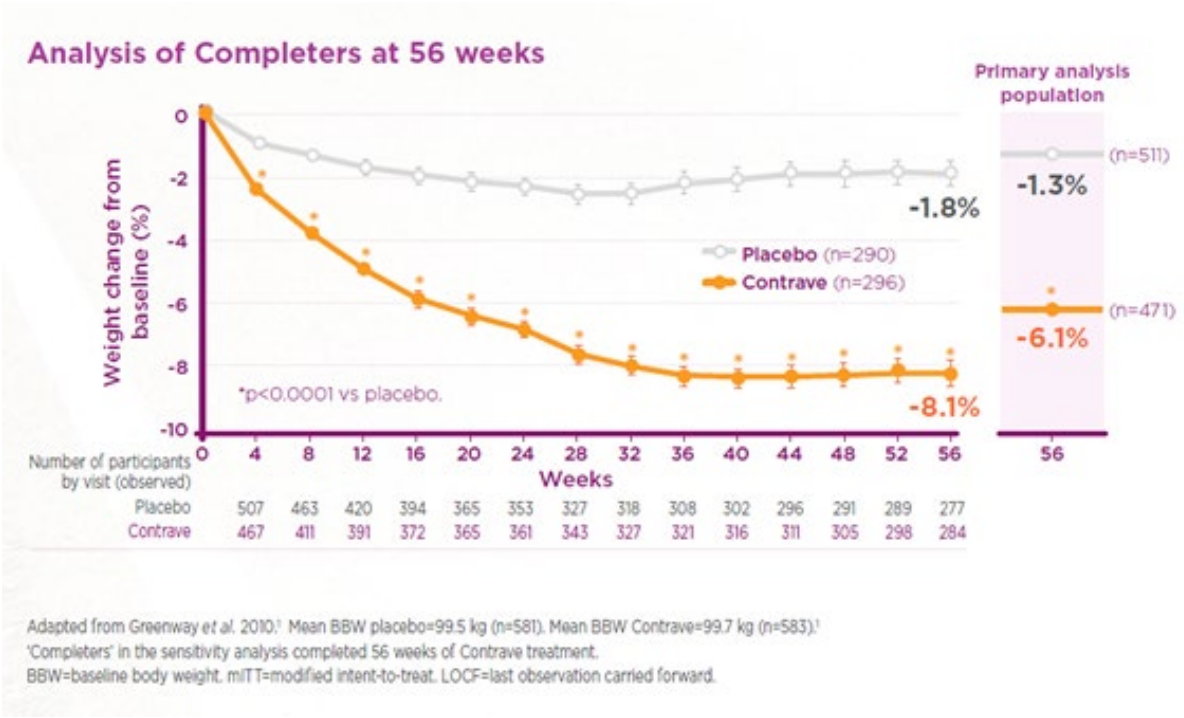
The Contrave Obesity Research (COR)-I trial[1]

- Study design
- Weight loss results
- Health benefit results



Adapted from Greenway *et al.* 2010.[1] Mean BBW placebo=99.5 kg (n=581). Mean BBW Contrave=99.7 kg (n=583).[1]
'Completers' in the sensitivity analysis completed 56 weeks of Contrave treatment.
BBW=baseline body weight. mITT=modified intent-to-treat. LOCF=last observation carried forward.

Progress: 3/7

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: **1.** Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England). 2010;376(9741):595-605.

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The Contrave Obesity Research (COR)-I trial[1]

Study design

Weight loss results

Health benefit results

The study also measured secondary end points related to health benefits and quality of life.

Participants in the naltrexone plus bupropion group showed significant improvements in: waist circumference; insulin resistance; and concentrations of HDL cholesterol and triglycerides.

Participants in the active group also showed greater improvements in weight-related quality of life.

They also showed:

- Less cravings
- Increased ability to control eating
- Increased feelings of fullness

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Progress: 3/7

Reference: **1.** Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England). 2010;376(9741):595-605.

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The COR-BMOD trial[1]

This 56-week, randomised, placebo-controlled trial examined the efficacy and safety of a combination of naltrexone and bupropion as an adjunct to intensive behaviour modification compared to placebo with behaviour modification. The naltrexone and bupropion group exhibited an average weight lost of 9.3% compared to 5.1% with placebo at week 56 from baseline (p <0.001).

Click below for details of the trial.

- Study design
- Weight loss results
- Health benefit results


Weight Loss With Naltrexone SR/Bupropion SR Combination Therapy as an Adjunct to Behavior Modification: The COR-BMOD Trial

Progress: 4/7

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Reference: 1. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring, Md). 2011;19(1):110-20. Epub 2010/06/19

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The Contrave Obesity Research (COR)-I trial[1]

Study design

Weight loss results

Health benefit results

The study design was similar to COR-I. Patients were men and women aged 18-65 years with BMI 30-45 kg/m^2 and uncomplicated obesity or BMI 27-45 kg/m^2 and controlled hypertension and/or dyslipidaemia. Women of childbearing age were required to use effective contraception for the duration of the trial.

Participants were randomised in a 1:3 ratio, receiving two doses twice a day (following a four-week dose escalation) of:

- Placebo
- Naltrexone 32mg per day / bupropion 360 mg per day

The behaviour modification program was completed by participants in both groups. It consisted of 90 min sessions (including weigh-ins) weekly for the first 16 weeks, fortnightly for the following 12 weeks and monthly thereafter. Sessions were delivered by dieticians, behavioural psychologists or exercise specialists. They covered a variety of topics related to behaviour modification and weight management.

Progress: 4/7

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

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The Contrave Obesity Research (COR)-I trial[1]

- Study design
- Weight loss results
- Health benefit results

Progress: 4/7

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The Contrave Obesity Research (COR)-I trial[1]

Study design

Weight loss results

Health benefit results

The study also measured secondary end points related to health benefits and weight-related quality of life.

Participants in the naltrexone plus bupropion group showed significant improvements in; waist circumference, insulin resistance and cholesterol balance.

In addition, patients in this group reported greater improvements than those in the placebo group in:

- Weight-related quality of life
- Physical function
- Self-esteem

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 4/7

Reference: 1. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring, Md). 2011;19(1):110-20. Epub 2010/06/19

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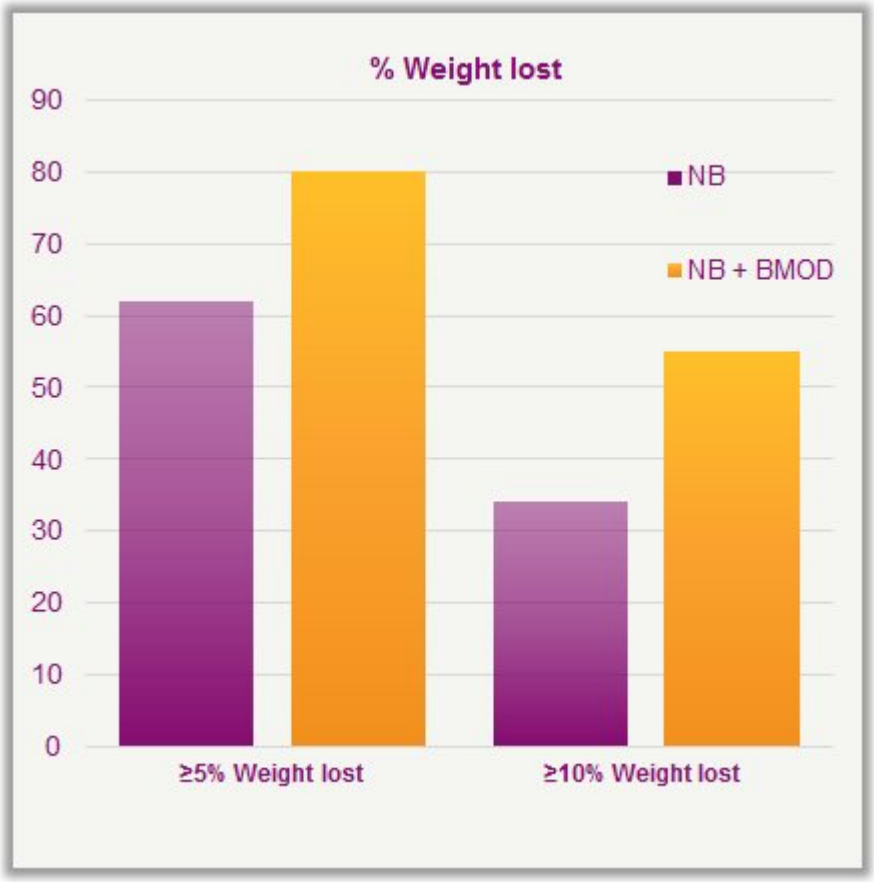
COR-I vs COR-BMOD

Whilst all participants in the COR-I trial were prescribed a mild hypocaloric diet and increased exercise, the COR-BMOD trial added intensive behaviour modification.

The inclusion of intensive behaviour modification appears to yield increased weight loss compared to the use of naltrexone and bupropion with a mild hypocaloric diet and exercise.[1]

However, as these interventions were not directly compared this is hard to generalise.



Progress: 5/7

Reference: 1. Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes care. 2013;36(12):4022-9.

The COR-DM trial[1]

The COR-I and COR-BMOD trials excluded patients with type 2 diabetes, a common comorbidity of obesity. The COR-DM trial built from these studies, to assess the combination of naltrexone and bupropion in patients with type 2 diabetes mellitus.

Details of the trial.

- Study design
- Weight loss results
- Health benefit results

Effects of Naltrexone Sustained-Release/Bupropion Sustained-Release Combination Therapy on Body Weight and Glycemic Parameters in Overweight and Obese Patients With Type 2 Diabetes

Progress: 6/7

Reference: 1. Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes care. 2013;36(12):4022-9.

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

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The COR-DM trial[1]

Study design

Weight loss results

Health benefit results

This 56-week, randomised, double blinded, placebo-controlled study was conducted from 2007-2009.

Participants were smoking or non-smoking, men or women aged 18-70 years with:

- Type 2 diabetes
- BMI ≥27 and ≤45
- HbA_{1c} 7-10%
- Fasting blood glucose <270mg/DL
- On stable doses of oral anti-diabetic medications

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 6/7

Reference: 1. Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes care. 2013;36(12):4022-9.

Radiant Health

The COR-DM trial[1]

Study design

Weight loss results

Health benefit results

The two primary end points were:

- Proportion of participants with a decrease in baseline bodyweight of 5% or more at 56 weeks compared to placebo
- Percentage of participants achieving ≥5% reduction in bodyweight from baseline, when compared with placebo

Participants treated with naltrexone and bupropion lost significantly more weight than those on placebo (5% loss vs 1.8% loss, $p < 0.001$).

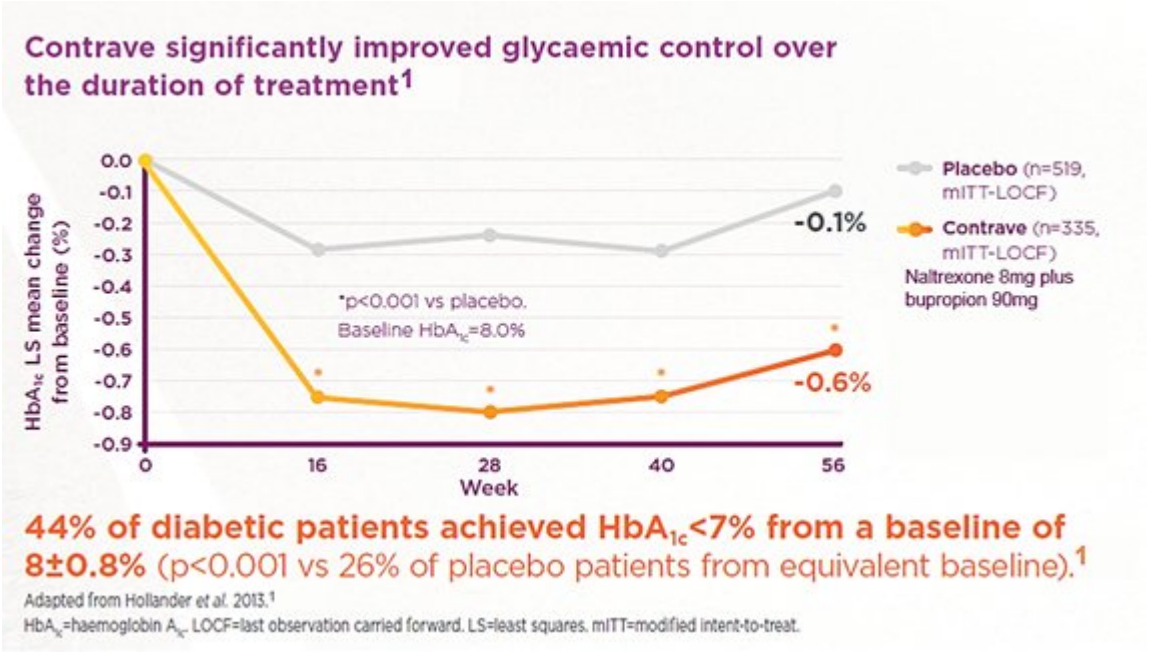
More patients on the combination achieved ≥5% (primary end-point) and ≥10% (secondary end-point) reduction than placebo.

Progress: 6/7

Reference: 1. Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes care. 2013;36(12):4022-9.

The COR-DM trial[1]

- Study design
- Weight loss results
- Health benefit results



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Progress: 6/7

Reference: 1. Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes care. 2013;36(12):4022-9.

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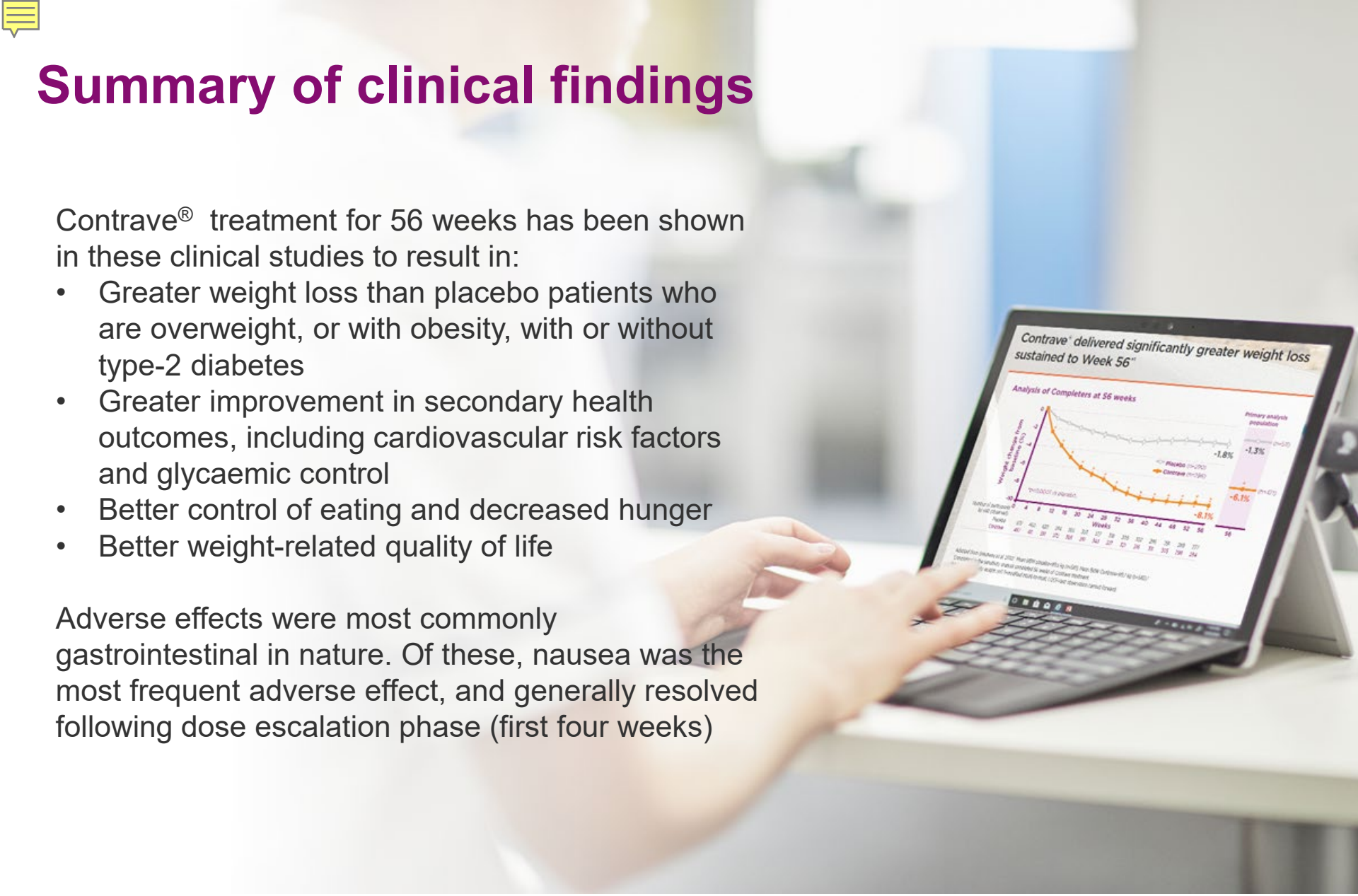
Summary of clinical findings

Contrave® treatment for 56 weeks has been shown in these clinical studies to result in:

- Greater weight loss than placebo patients who are overweight, or with obesity, with or without type-2 diabetes
- Greater improvement in secondary health outcomes, including cardiovascular risk factors and glycaemic control
- Better control of eating and decreased hunger
- Better weight-related quality of life

Adverse effects were most commonly gastrointestinal in nature. Of these, nausea was the most frequent adverse effect, and generally resolved following dose escalation phase (first four weeks)



Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 7/7

Reference: **1.** Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and bodyweight. Nature 2006;443:289–95. **2**. Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL. Is the Energy Homeostasis System Inherently Biased Toward Weight Gain? Diabetes. 2003;52(2):232-8. doi: 10.2337/diabetes.52.2.232.

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CONTRAVE®:

A DUAL ACTION TREATMENT FOR WEIGHT MANAGEMENT

What will be covered in this training

- One: Summary
- Two: Overview
- Three: Clinical findings
- Four: Product information
- Five: Counselling points
- Six: Patient support
- Seven: Assessment

Contrave® (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

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Four: **Product information**

Contrave® (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

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What you need to know about Contrave®[1]

- What is it?
- Benefits
- Dosage
- Adverse effects
- Monitoring
- Other information

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

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What you need to know about Contrave®[1]

- **What is it?**
- Benefits
- Dosage
- Adverse effects
- Monitoring
- Other information

Contrave® is a combination medication that targets **two areas of the brain** that are associated with **hunger and cravings**.

This medication helps patients to **take control** of their hunger and cravings and **break the weight loss/regain cycle.**

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 3/13

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

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What you need to know about Contrave®[1]

- What is it?
- Benefits
- Dosage
- Adverse effects
- Monitoring
- Other information

When used in co**mbination with a reduced calorie diet and increased physical activity**, Contrave® is expected to result in weight loss of 5-10% of current weight.

Weight loss of 5-10%

People also **report feeling more in control** of their eating, with a reduction in both hunger and cravings.

Weight loss also results in imp**rovement in other markers**, including waist measurement, and glucose control.

Control over cravings

Patients should be made aware of the fact that if 5% weight loss has not been achieved after 16 weeks treatment should be ceased.

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 4/13

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

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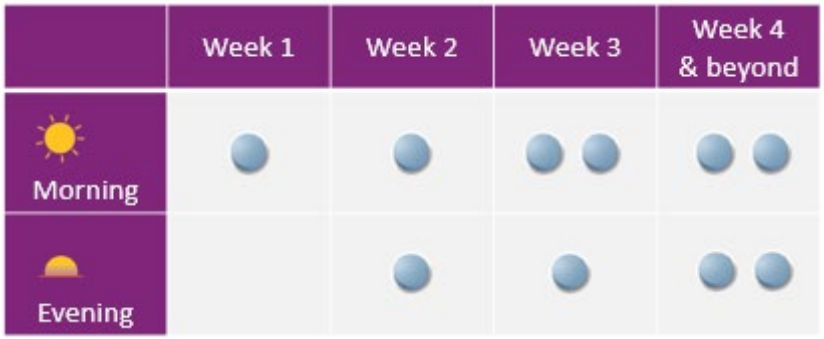
What you need to know about Contrave®[1]

- What is it?
- Benefits
- Dosage
- Adverse effects
- Monitoring
- Other information

The dose of Contrave® is **increased slowly** to decrease the risk of adverse events. Patients should be counselled on their **four-week dose escalation**, and how they will manage the increase.

Contrave® is best taken with food, to maximise absorption.

If a dose is missed, patients should not take an additional dose, but take the next dose at the usual time.



Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 5/13

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Radiant Health

Counselling patients on Contrave®[1]

- What is it?
- Benefits
- Dosage
- **Adverse effects**
- Monitoring
- Other information

The long-term safety of Contrave® has not been established.

The **most common adverse effects** associated with Contrave® are nausea, vomiting, dry mouth and constipation. This **usually occurs in the first four weeks** then subside as the dose is increased.

Patients should be counselled regarding this and reminded to speak to their doctor if these symptoms are severe.

The patient (and their care-givers) should also be counselled to be aware of any suicidal behaviour or thoughts and unusual changes in behaviour, particularly for those at high risk. Counsel to seek medical advice immediately if these symptoms present.

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Counselling patients on Contrave®[1]

- What is it?
- Benefits
- Dosage
- Adverse effects
- **Monitoring**
- Other information

Patients may develop elevated blood pressure or heart rate during Contrave® treatment. Blood pressure and pulse should be measured prior to therapy, and at regular intervals.

Treatment should be discontinued if there are ongoing concerns about safety and tolerability, including increased blood pressure.

As Contrave® is subject to ongoing monitoring, patients should be counselled to report any adverse effects to their doctor (or pharmacist).

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 7/13

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Radiant Health

Counselling patients on Contrave®[1]

- What is it?
- Benefits
- Dosage
- Adverse effects
- Monitoring
- Other information

Interactions

Contrave® interacts with other medicines. Patients should be counselled to alert medical professionals to their treatment.

Patients should be counselled that they will not experience the same effects with opioid medicines whilst taking Contrave®. Patients should avoid using opioid medications, and not increase doses to achieve the desired effect. This can be dangerous and potentially fatal. Patients should also be advised that they may be more sensitive to opioids once treatment is ceased.

Alcohol

The consumption of alcohol during Contrave® treatment should be minimised or avoided.

Driving

Contrave® may affect the ability to perform tasks that require judgement or motor and cognitive skills. Patients should exercise caution before driving or operating machinery until they are reasonably certain that Contrave® does not affect their performance.

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

Precautions[1]

The safety and tolerability of Contrave® should be assessed at regular intervals. Treatment should be discontinued if there are any concerns about the safety or tolerability of ongoing treatment, including concerns about raised blood pressure. The safety and efficacy of Contrave® for use (> 1 year) has not been established.

Note: The approved indication does not restrict the duration of use of Contrave® (although treatment should be discontinued if patients have not lost ≥5% of their initial body weight after 16 weeks).

- Psychiatric symptoms
- Seizures
- Opioid analgesic
- Allergic reactions
- Elevation of BP & HR
- Cardiovascular disease
- Hepatotoxicity

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

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Contraindications[1]

Contrave® is contraindicated in several situations.

- Hypersensitivity (to naltrexone, bupropion or any excipients)
- Uncontrolled hypertension
- Seizure disorder (or a history of seizures)
- Known CNS tumour
- Undergoing acute benzodiazepine or alcohol withdrawal
- History of bipolar disorder
- Use of other treatment with bupropion or naltrexone
- Current dependence on chronic opioids or opioid agonists (methadone)
- Patients in acute opiate withdrawal
- Patients taking monoamine oxidase inhibitors
  (at least 14 days should lapse between discontinuation of MAOI and initiation of treatment with Contrave®)
- Pregnancy
- Severe hepatic impairment
- End-stage renal failure

Progress: 11/13

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf

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Obesity management

Contrave® is indicated as an adjunct to lifestyle modification.[1]

Obesity, like most chronic diseases, benefits from a multi-disciplinary approach to management.[2] Patients may or may not have been referred to a dietician for support in developing a low-calorie meal and exercise plan.

In either case, healthcare professionals are well placed to support patients in reinforcing their diet and exercise plans or assisting patients to develop their own goals.

Progress: 12/13

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: **1.** Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf). **2.** Bischoff SC, Boirie Y, Cederholm T, Chourdakis M, Cuerda C, Delzenne NM, et al. Towards a multidisciplinary approach to understand and manage obesity and related diseases. Clinical nutrition (Edinburgh, Scotland). 2017;36(4):917-38. **3.** Department of Health & Human Services, State Government of Victoria, Australia. Weight loss: A healthy approach. Better Health Channel [Webpage]. 30 Oct 2012 [Cited April 2019]. Available at: https://www.betterhealth.vic.gov.au/health/healthyliving/weight-loss-a-healthy-approach.

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Increasing activity

Whilst patients may have been informed by health professionals that they need to 'exercise' this can be challenging, especially if the baseline is little to no physical activity.

Healthcare professionals can assist patients by providing support and encouragement, alongside tailored education to those that need it.

Tips to try:

- Encourage small increases in activity[3] – going for a ten-minute walk three times a week may be a good start
- Suggest incidental activity on top of exercise[3] – take the stairs, or get off public transport at an earlier stop
- Tailor advice to the patient[3] – a person will only do what they are comfortable with
- Encourage patients to be kind to themselves – change takes time!

Progress: 13/13

Contrave® (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Reference: **1.** Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf). **2.** Bischoff SC, Boirie Y, Cederholm T, Chourdakis M, Cuerda C, Delzenne NM, et al. Towards a multidisciplinary approach to understand and manage obesity and related diseases. Clinical nutrition (Edinburgh, Scotland). 2017;36(4):917-38. **3.** Department of Health & Human Services, State Government of Victoria, Australia. Weight loss: A healthy approach. Better Health Channel [Webpage]. 30 Oct 2012 [Cited April 2019]. Available at: https://www.betterhealth.vic.gov.au/health/healthyliving/weight-loss-a-healthy-approach.

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Diet modification

Patients may or may not be knowledgeable about healthy eating. Health professionals can provide basic education, but in-depth education may be required for some patients.

Others may know the basics of healthy eating but require support to problem solve and stay on track.

Some tips to try:

- Approach eating as a lifestyle rather than a 'diet'[3]
- Rather than depriving yourself of foods you love, try to swap for a healthier alternative
- Identify the situations that cause you to overindulge[3] – is it sitting on the couch in the evening, or is it eating out?

Reference: **1.** Contrave Data Sheet: https://www.medsafe.govt.nz/Profs/Datasheet/c/Contravetab.pdf). **2.** Bischoff SC, Boirie Y, Cederholm T, Chourdakis M, Cuerda C, Delzenne NM, et al. Towards a multidisciplinary approach to understand and manage obesity and related diseases. Clinical nutrition (Edinburgh, Scotland). 2017;36(4):917-38. **3.** Department of Health & Human Services, State Government of Victoria, Australia. Weight loss: A healthy approach. Better Health Channel [Webpage]. 30 Oct 2012 [Cited April 2019]. Available at: https://www.betterhealth.vic.gov.au/health/healthyliving/weight-loss-a-healthy-approach.

CONTRAVE®:

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Five: Counselling

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Progress: 1/3

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Dispensing Contrave®

A 'Physician Prescribing Checklist' has been created. This checklist can be used to screen for precautions and contraindications and its completion is a condition of dispensing.

If the prescribing doctor has not completed the checklist, the pharmacist may complete the checklist with the patient.


PLEASE ATTACH PHYSICIAN PRESCRIBING CHECKLIST TO ORIGINAL PRESCRIPTION

Contrave

CONTRAVE PHYSICIAN PRESCRIBING CHECKLIST

Treatment with Contrave should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

PATIENT DETAILS

DOES THE PATIENT HAVE:

DOES THE PATIENT HAVE:

Discontinue treatment if there are concerns with the safety or tolerability of ongoing treatment. The safety and efficacy of CONTRAVE for long term use (>1 year) has not been established.

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Progress: 2/3

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What does your patient need to know®

Dose escalation to full dose

Side effects and how to manage them

In conjunction with diet and exercise

The benefit and cost

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Six: Patient support

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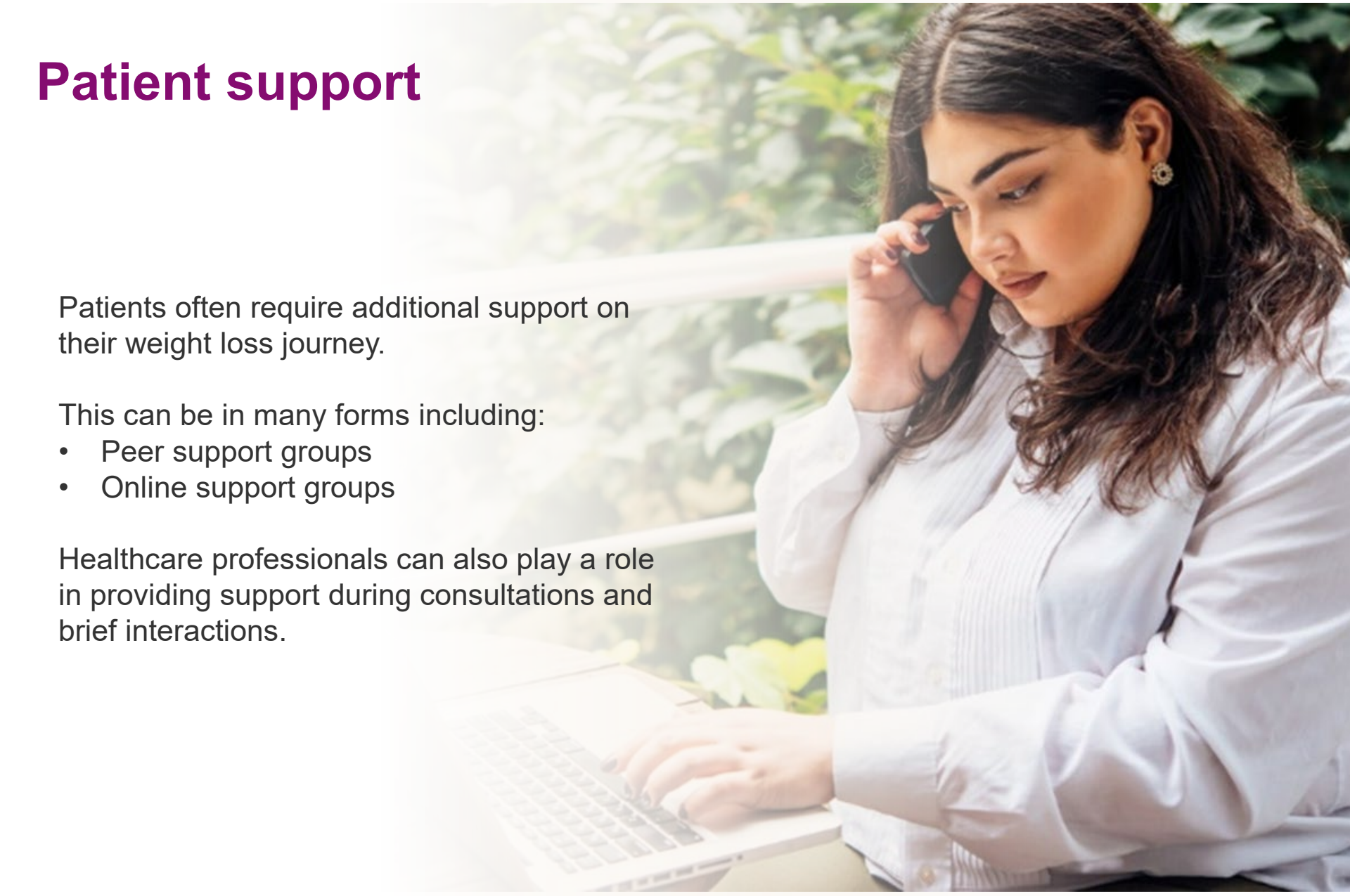
Patient support



Patients often require additional support on their weight loss journey.

This can be in many forms including:

- Peer support groups
- Online support groups

Healthcare professionals can also play a role in providing support during consultations and brief interactions.

Patient support

Losing weight can be overwhelming and frustrating, especially when you aren't seeing results.

Health professionals can help patients become empowered to manage their own weight loss journey rather than relying on medication alone to reach their goals.

Many health professionals find it difficult to discuss weight loss, or the behaviour change that may be required for weight loss.[1]

Adopting a Motivational Interviewing style of communication may assist to confidently discuss behaviour change with patients.[2] This style of communication is inherently collaborative, employing empathy and active listening to build trust and rapport.

Whilst this style of communication is often employed as part of a consultation, the spirit of collaborative, empathetic counselling can also be applied to brief conversations.

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

Progress: 3/11

Reference: **1.** Reims K, Ernst D. Using Motivational Interviewing to Promote Healthy Weight. Family practice management. 2016;23(5):32-8. **2.** Sharma A et al. Motivational interviewing: Empowering patients to change behaviors. Pharmacy Today. 2015 [Cited Nov 2018].

Radiant Health

Behavioural therapy

Behavioural therapy is a key part of weight management. It provides patients with skills that allow patients to connect their behaviours to outcomes.

There are several ways that this style of intervention can be delivered, including online.

Key components include:[1]

- Self-monitoring
- Education
- Social support
- Goal setting

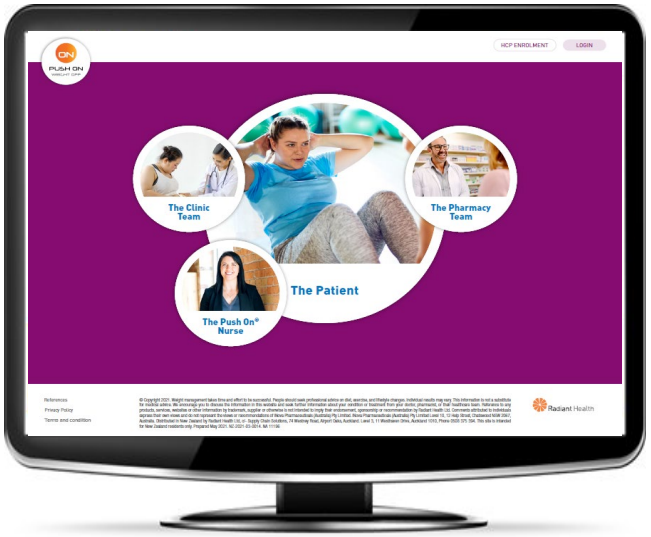
Reference: **1.** Kelley CP, Sbrocco G, Sbrocco T. Behavioral Modification for the Management of Obesity. Primary care. 2016;43(1):159-75

Push On®

Push On® is a patient support program.

It is an online platform, supporting patients along their weight loss journey by providing;

- Nurse to patient phone support
- Tools and resources on weight management
- Dashboard with their weigh loss and goals
- Collaborative team support from their clinic, pharmacy and Push On nurse



It is a complementary service for patients prescribed Contrave ® or Duromine ®.

Patients will need to be enrolled by their prescribing doctor

Healthcare professionals will be able to track their patient's journey through the program, including whether they are meeting their goals.

To enrol go to:
www.pushon.co.nz/enrol

Progress: 5/11

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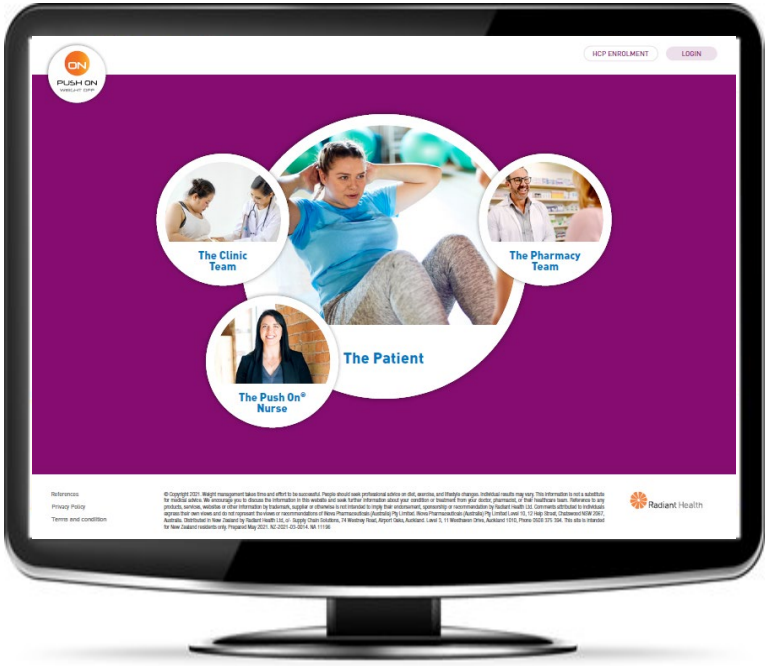
Push On®

- Patient enrolment
- Benefits
- Cost
- Available resources
- Pharmacy help



www.pushon.co.nz

Progress: 6/11

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Push On®

- **Patient enrolment**
- Benefits
- Cost
- Available resources
- Pharmacy help

The **prescribing doctor** will need to enrol their patient, this is done through the website.

Patients who are enrolled will have access to:

- A collaborate health care team
- Ongoing telephonic nurse support from the Push On Nurse
- A Weight tracker
- Menu plans
- Tips and tricks for weight loss
- Medicine reminders – refill script/visit their doctor

The enrolled doctor will be able to track their patient progress through the program, as well as their goal progress between visits.

Progress: 7/11

Push On®

- Patient enrolment
- Benefits
- Cost
- Available resources
- Pharmacy help

The Push On® program;

- Empowers and educates patients
- Provides additional support.
- Helps facilitate behaviour changes,
- Sets and tracks goal
- Additional support through ongoing Nurse check-ins that help your patient keep on track

Progress: 8/11

Contrave® (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

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Push On®

- Patient enrolment
- Benefits
- Cost
- Available resources
- Pharmacy help

A free, flexible programme

It is a complementary service for patients prescribed Contrave or Duromine.

Progress: 9/11

Contrave (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

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Push On®

- Patient enrolment
- Benefits
- Cost
- Available resources
- Pharmacy help

Patients can access:

- Information about their prescribed drug
- Resources and information about weight loss such as meal plans, blogs and exercise diaries
- Nurse support and a chat facility
- Dashboard with their weigh loss and goals

Progress: 10/11

Push On®

- Patient enrolment
- Benefits
- Cost
- Available resources
- Pharmacy help

Enrolled pharmacies will be able to help their patients as part of the collaborative team.

At each **pharmacy visit**, the pharmacy will need to:

- Provide the patient with any **additional medicine support** they may need whilst on treatment
- **Weigh the patient**
- **Measure the patients blood pressure**

This information as well as the date the results were taken will need to provided to the Push On registered nurse by:

- **Clicking the link** in the patient appointment email sent from the Push On nurse and completing the fields
- **Emailing the nurse directly** with the patient's name in the subject line. Email address: nurse@pushon.co.nz

Enrol your pharmacy at www.pushon.c.nz/enrol

Progress: 11/11

Contrave® (naltrexone HCl/bupropion HCl) 8 mg/90 mg • Extended-Release Tablets

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Congratulations, you have now completed the learning component of this course

You should now be able to:

- Describe the mechanism of action of Contrave®
- Outline key product information for Contrave®
- Identify the clinical findings of Contrave® in the management of excess weight and obesity
- Identify the safety consideration for patients prescribed Contrave® including common adverse events
- Outline the key counselling points that should be provided to patients prescribed Contrave®
- Recall the dose escalation schedule for Contrave®
- Outline the Patient Support Programs available to patients prescribed Contrave®

Resources

- Prescribing checklist
- Counselling Guide
- Push On® Drop Card
- Push On® food and exercise diary
- Mode of action video

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Radiant Health

Contrave® Data sheet

CONTRAVE® is a prescription medicine. Please review the full Data Sheet before prescribing, available on the Medsafe website www.medsafe.govt.nz. **CONTRAVE®** 8/90 (naltrexone hydrochloride and bupropion hydrochloride extended release tablets). **Indications:** 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 (obese) 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). Treatment with CONTRAVE should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight. **Contraindications**: Hypersensitivity to bupropion, naltrexone or any of the excipients, uncontrolled hypertension, seizure disorder or a history of seizures, patients with a known central nervous system tumour, patients undergoing acute alcohol or benzodiazepine withdrawal, patients with a history of bipolar disorder, use of concomitant treatment containing bupropion or naltrexone, current or previous diagnosis of bulimia or anorexia nervosa, patients currently dependent on chronic opioids or opiate agonists, or patients in acute opiate withdrawal, pregnancy, patients with severe hepatic impairment, patients with end-stage renal failure, and in concomitant administration with monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with CONTRAVE. Starting CONTRAVE in a patient treated with reversible MAOIs is also contraindicated. **Warnings and Precautions**: Safety and tolerability should be assessed at regular intervals. Safety and efficacy of CONTRAVE for longer than a year has not been established. Suicidal ideation has been reported in post marketing reports with CONTRAVE and patients should be supervised closely. There is a small increase in the risk of seizure. In patients requiring intermittent opiate treatment, CONTRAVE should be temporarily discontinued and lower doses of opioids may be needed. A patient should stop taking CONTRAVE and consult a doctor if experiencing any allergic symptoms during treatment. Use with caution in those with controlled hypertension, predisposing factors that increase the likelihood of seizing, reduced renal clearance, underlying liver disease, history of mania and patients aged greater than 65. Caution in performing activities requiring mental alertness e.g. driving and operating machinery. **Pregnancy and lactation:** Category B2. Safe use of orphenadrine has not been established with respect to adverse effects on foetal development. **Adverse Effects**: Decreased lymphocyte count, palpitations, tinnitus, vertigo, nausea, constipation, vomiting, dry mouth, toothache, upper abdominal pain, feeling jittery, dizziness, tremor, dysgeusia, disturbance in attention, lethargy, hot flush, hyperhidrosis, pruritus and alopecia. **Interactions**: Contraindicated in use with MAOIs, drugs containing bupropion, chronic opioid use or opiate agonist therapy. CONTRAVE may increase the availability of other medicines metabolised by CYP2D6 substrate. Medicines metabolised by the CYP2B6 isozyme may interact with CONTRAVE. Use with caution with drugs that lower the seizure threshold and dopaminergic drugs. Avoid or minimise the use of alcohol. **Dosage and Administration**: Swallow tablets whole with water, and preferably with food. Dose should be escalated over a 4-week period from initiation. The recommended starting dose is 1 tablet in the morning for 1 week, increasing to 1 tablet in the morning and 1 at night in the second week, 2 tablets in the morning and 1 tablet at night in the third week. The maintenance dose from week 4 onward is 2 tablets in the morning and 2 at night.

Contrave®
(naltrexone HCl/bupropion HCl)
8 mg/90 mg • Extended-Release Tablets

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