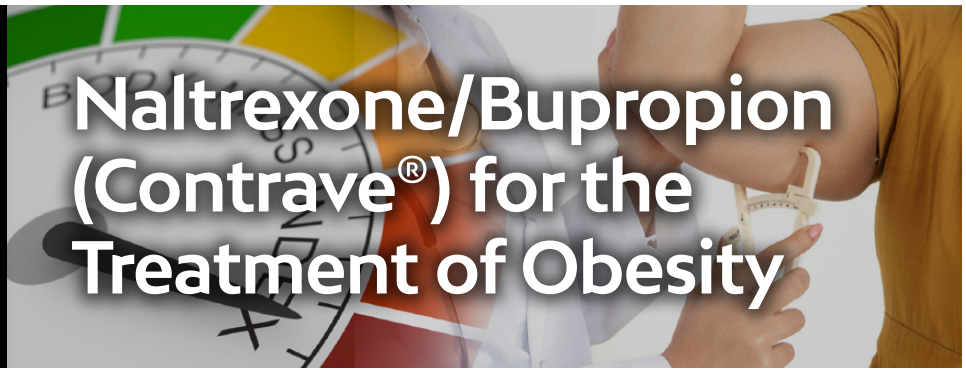
A RESEARCH REVIEW™
PRODUCT REVIEW

Naltrexone/Bupropion (Contrave®) for the Treatment of Obesity



Making Education Easy 2021

About the Expert

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Dr Ole Schmiedel is a consultant in endocrinology, diabetes, and general internal medicine at Auckland District Health Board (ADHB) and is also the Service Clinical Director of the Auckland Diabetes Centre. He qualified in medicine from Humboldt University in Berlin and completed his postgraduate training in diabetes and endocrinology at Cardiff University in Wales. He was awarded his MD for work in diabetes and microvascular complications. Ole's main clinical and research interests are in the management of diabetes, obesity and obesity-related complications, as well as lipid disorders and neuroendocrine tumours. He is involved in education, training and service development projects with a strong focus on supporting primary care teams. In addition, he specialises in all areas of endocrinology and consults in private practice at Greenlane Medical Specialists.

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Joseph Proietto is Professor Emeritus at the University of Melbourne in the Department of Medicine Austin Health and an Endocrinologist specialising in Diabetes and Obesity. He established the first obesity clinic in Victoria at the Royal Melbourne Hospital and until retirement was Head of the Weight control clinic at Austin Health. He has published over 200 articles and several book chapters on obesity and diabetes and is currently on the executive of World Obesity and is Chair of the Clinical Care Committee.

This article provides an overview of important pharmacological, dosage and administration, and clinical efficacy and tolerability properties and features of naltrexone/bupropion (Contrave® 8/90) in the treatment of adults who have overweight or obesity. This review is sponsored by an educational grant from Radiant New Zealand.

Introduction

Obesity is a chronic, relapsing, neurobehavioral disease, that has a genetic[1-3] or epigenetic[4,5] basis. Obesity increases the risk for several chronic medical conditions (including type 2 diabetes, hypertension, dyslipidaemia, and cardiovascular disease) and premature death.[6] The genetic basis of obesity explains why body weight is vigorously defended by powerful physiological mechanisms. To understand how the body defends weight, it is necessary to first understand how weight is regulated.

Body weight is controlled by the hypothalamus. In the arcuate nucleus of the hypothalamus, there are two types of neurons. One type expresses neuropeptide Y (NPY) and agouti-related protein (AgRP), both of which stimulate hunger. The other type of neuron expresses pro-opiomelanocortin (POMC) (from which alpha melanocyte stimulating hormone [αMSH] is cleaved) and cocaine and amphetamine-regulated transcript (CART). Both αMSH and CART inhibit hunger. At any particular time of the day, it is the activity of these neurons that determines whether we want to eat or not. The question is then what controls the activity of these arcuate nucleus neurons?

There are many inputs into the arcuate nucleus including from the nucleus of the tractus solitarius located in the brainstem, from pleasure pathways and from the cortex. In addition, ten circulating hormones also influence the activity of these particular neurons and therefore regulate food intake. These hormones come from the gut, the pancreas, and fat. The remarkable fact is that only one of these hormones (ghrelin) stimulates hunger, while nine (leptin, cholesytokinin, peptide YY, glucagon-like peptide-1, oxyntomodulin, uroguanylin, insulin, amylin and pancreatic polypeptide) inhibit it!

Why is obesity relapsing?

Soon after the discovery of leptin in 1994, it was found that levels of this hunger-inhibiting hormone decrease dramatically after diet-induced weight loss.[7] In contrast, levels of the hunger-stimulating hormone ghrelin were found to increase after weight loss.[8] It was then shown that post prandial levels of cholecystokinin are also lower after weight loss.[9] These changes lead to increased hunger. In 2011, it was demonstrated that other hunger-regulating hormones also change in a direction designed to increase hunger and that these changes are long lasting.[10] These feedback loops explain why it is difficult to maintain weight loss in the long term, and why lifestyle advice only leads to modest weight loss. It is for this reason that hunger-suppressing medication is necessary both for weight loss and even more important, for long term weight maintenance.

Pharmacotherapy for obesity

When used as an adjunct to lifestyle intervention, weight-loss medications increase the likelihood of achieving clinically meaningful (≥5%) weight loss and reduce the likelihood of weight regain including post-bariatric surgery.[11] Pharmacotherapy enhances the magnitude of weight loss more than that which can be achieved with lifestyle changes alone and is beneficial in the prevention of weight regain.[12]

When initiating pharmacotherapy, the choice of which weight-loss medication should firstly be informed by patient co-morbidities and avoidance of contraindications and drug-drug interactions.[13] The next most important consideration is choosing a medication with a mechanism of action that targets the patient's eating behaviours. For example, for patients that describe having difficulty controlling cravings, emotional eating, or food addictions, bupropion/naltrexone is an appropriate choice.[14]

Rationale for combination pharmacotherapy

As with all medications, there are good and poor responders and patients that develop no side effects and those that develop severe side effects. This is why it is important to have a range of medications available so that the appropriate medication can be chosen for each individual patient. In addition, since nature uses nine hormones to suppress hunger after a meal, combining more than one medication may be required in some patients.

Naltrexone/bupropion

Naltrexone is a non-selective opioid receptor antagonist used to treat opioid and alcohol dependence. Bupropion is a dopamine and norepinephrine re-uptake inhibitor that is approved to treat depression in certain countries and nicotine addiction. Naltrexone/bupropion (Contrave® 8/90) is an extended-release oral formulation of naltrexone hydrochloride and bupropion hydrochloride.

Mechanism of action

Naltrexone and bupropion modulate two regions of the brain that control eating behaviour:

In the melanocortin system of the hypothalamus, naltrexone and bupropion act synergistically to reduce hunger.

There is evidence that both naltrexone and bupropion individually suppress hunger. However, the combination of the two agents together appears to have a synergistic effect (**Figure 1**).[15] The reason for this was shown in *in vitro* studies using mouse hypothalamus. Bupropion activates POMC neurons, increasing the production of proopiomelanocortin (POMC), which can be cleaved into αMSH and β-endorphin. As mentioned above, αMSH powerfully inhibits food intake. In contrast, it was hypothesized that β-endorphin, acting through the μ-opioid receptor, inhibits the activity of POMC neurons.[16,17] Thus, inhibiting the action of β-endorphin with naltrexone has the effect of increasing POMC activity (**Figure 2**).[15] This is the mechanism for the enhanced activation of POMC neurons seen when bupropion is combined with naltrexone.[18]

In the mesolimbic dopamine reward pathway of the midbrain, naltrexone and bupropion regulate feelings of pleasure when eating to help control cravings.[19]

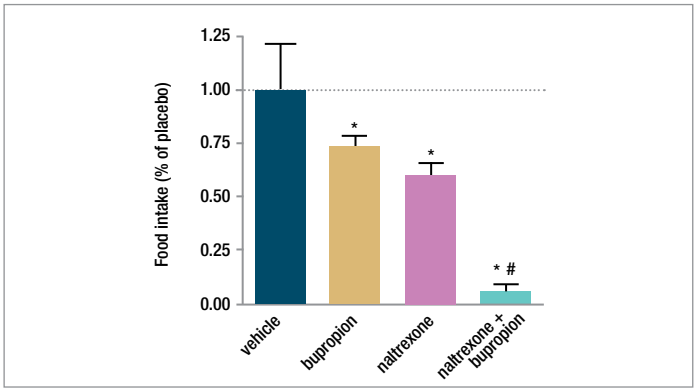

Figure 1. Effect of bupropion, naltrexone and their combined effect following administration to food-deprived mice.[15]

Data are mean (SD). *p<0.01 compared with vehicle; #p=0.0025 for an interaction between bupropion and naltrexone.

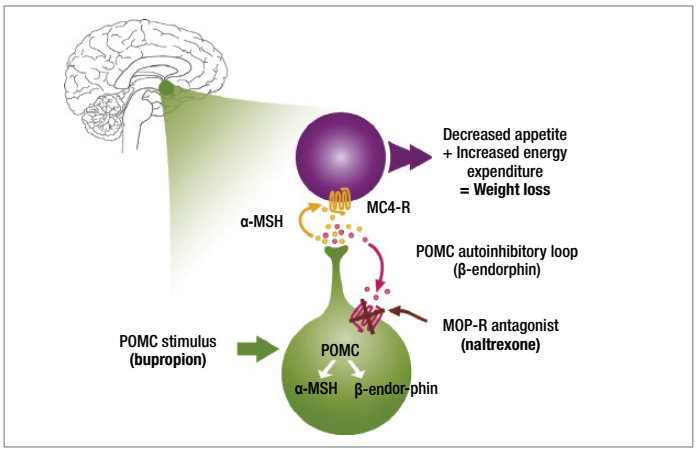

Figure 2. Synergistic mechanism of action of naltrexone/bupropion in the melanocortin system of the hypothalamus, which regulates appetite and energy expenditure.[15]

Abbreviations: αMSH = alpha-melanocyte stimulating hormone; MC4-R = melanocortin-4 receptor; MOP-R = mu-opioid receptor; POMC = pro-opiomelanocortin

Dosage and administration

Naltrexone/bupropion is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the treatment of weight in adult patients (aged ≥18 years) with an initial 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 comorbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension).[19]

Naltrexone/bupropion 8 mg/90 mg modified-release tablets should be swallowed whole with water and preferably be taken with food.[19] The dose should be escalated over a 4-week period according to the following schedule:

	Morning dose	Evening dose
Week 1	1 tablet	None
Week 2	1 tablet	1 tablet
Week 3	2 tablets	1 tablet
Week 4 and beyond	2 tablets	2 tablets

Table 1. Dosing schedule for naltrexone/bupropion.[19]

The maximum recommended daily dose of naltrexone/bupropion is two tablets taken twice daily (i.e., naltrexone 32 mg and bupropion 360 mg), which is reached at the start of week 4.[19]

The need for continued treatment with naltrexone/bupropion should be evaluated 16 weeks after treatment commencement.[19] Naltrexone/bupropion should be discontinued in patients who have not lost ≥5% of their initial body weight after 16 weeks.

Dosage adjustment is recommended in patients with moderate or severe renal impairment due to the risk of having higher drug concentrations, which could result in an increase in adverse drug reactions: the maximum recommended daily dose is one tablet twice daily.[19]

Due to an increased risk of renal impairment in elderly patients, cautious dose selection and renal function monitoring in elderly patients may be helpful.[19]

Important contraindications

Naltrexone/bupropion is contraindicated in the following settings:[19]

- Patients with seizure disorder or a history of seizures (due to the role of bupropion in lowering seizure threshold).
- Patients with a history of bipolar disorder (risk of manic switch when antidepressants are used alone in this group).
- Patients with uncontrolled hypertension (>145/95mm Hg in clinical trials). May be controlled with anti-hypertensive drugs.
- Patients currently receiving monoamine oxidase inhibitors (MAOIs) due to an increased risk of hypertensive reactions with concurrent use of bupropion (14-day washout period required).
- Patients undergoing acute alcohol or benzodiazepine withdrawal.
- Patients currently dependent on long-term opioids or opioid agonists (e.g., methadone) or patients undergoing acute opiate withdrawal.
- Patients with end-stage renal failure or those with severe hepatic impairment.

Important cautions and considerations

Cautions and considerations of note in the use of naltrexone/bupropion include the following:[19]

- Monitor blood pressure and heart rate prior to initiation of therapy and at regular intervals. Discontinue if unacceptable increases occur.
- Patients with recent (within 6 months) myocardial infarction, unstable heart disease, or class 3 or 4 heart failure - use with caution as minimal safety data for this population.
- Naltrexone/bupropion will reduce the effects of any opioid-containing pain medications.
- Bupropion has an effect on the cytochrome P450 enzyme system, in particular CYP2D6 and CYP2B6. There is potential for drug interactions with some centrally-acting agents, beta-blockers, and platelet inhibitors. The reader is advised to consult the Medsafe data sheet or product sponsor for detailed information.

Efficacy

The efficacy of naltrexone/bupropion as an adjunct to reduced caloric intake and increased physical activity in overweight or obese adults (BMI range 27–45 kg/m^2) has been evaluated in four randomised, double-blind, placebo-controlled, phase III trials with study durations of 56 weeks: COR-I,[20] COR-II,[21] COR-BMOD,[22] and COR-diabetes.[23]

Co-primary endpoints in all trials were the percentage change in bodyweight from baseline and the proportion of patients with ≥5% reduction in baseline bodyweight after 28[21] or 56[20-23] weeks of treatment. Modest weight loss of 5–10% is associated with clinically-relevant improvements in many cardiometabolic risk factors, including fasting glucose and HbA1c for type 2 diabetes, as well as improvements in measures of quality of life (QOL).[24]

As well as the four phase III clinical studies, a randomised open-label effectiveness trial has assessed naltrexone/bupropion in a real-world context,[25,26] including longer-term use of naltrexone/bupropion (78 weeks).[25]

Weight loss

Naltrexone/bupropion produced significantly greater percentage bodyweight reductions from baseline than placebo after 28 or 56 weeks, and a significantly greater proportion of patients achieved ≥5% bodyweight reductions with naltrexone/bupropion than with placebo (**Table 2**).[20-23,27]

The significantly ($p<0.001$ vs placebo) greater percentage bodyweight reductions from baseline with naltrexone/bupropion were observed as early as week 4.[20-23,27] After 56 weeks' treatment, significantly ($p<0.001$ vs placebo) more naltrexone/bupropion recipients achieved reductions in bodyweight from baseline of ≥10%.

Trial	Treatment	No. of patients†	No. of 56-week completer patients	% (LSM) change in body weight from BL in responder-completer patients#	% (LSM) change in body weight from BL†	% of patients achieving ≥5% reduction in BL bodyweight†
				Week 16	Week 56	Week 56
COR-I[20,27]	NB	471	296	-11.6%^	-6.1**	48**
	PL	511	290		-1.3	16
COR-II[21,27]	NB	825	434	-11.6%^	-6.4*	50.5*
	PL	456	267		-1.2	17.1
COR-BMOD[22,27]	NB + BMOD	482	301	-13.6%	-9.3*	66.4*
	PL + BMOD	193	106		-5.1	42.5
COR-Diabetes[23,27]	NB	265	175	-9.0%	-5.0*	44.5*
	PL	159	100		-1.8	18.9

Abbreviations: BL = baseline; BMOD = behaviour modification; LSM = least squares mean; ITT = modified intent-to-treat population; NB = naltrexone/bupropion 32/360; PL = placebo. # Responder-completers are patients with ≥5% reduction in baseline body weight at week 16 who completed the trial; ^ COR-1 and COR-II data combined; * $p<0.001$ vs PL; ** $p<0.0001$ vs PL. †Data for the COR-I trial is based on the primary analysis population. Data for the COR-II, COR-BMOD, and COR-Diabetes trials are based on the mITT analyses.

Table 2. Efficacy (co-primary endpoints) of oral naltrexone/bupropion as adjunctive therapy to reduced-calorie diet and increased physical activity in obese or overweight adults based on phase III trials data.[20-23,27]

Weight loss beyond the clinically-meaningful threshold of ≥5% loss was clearly illustrated in the COR-I trial in which significantly more patients who received naltrexone/bupropion achieved a reduction in bodyweight of ≥5%, ≥10%, and ≥15% at week 56 than did patients who received placebo (**Figure 3**).[19,20]

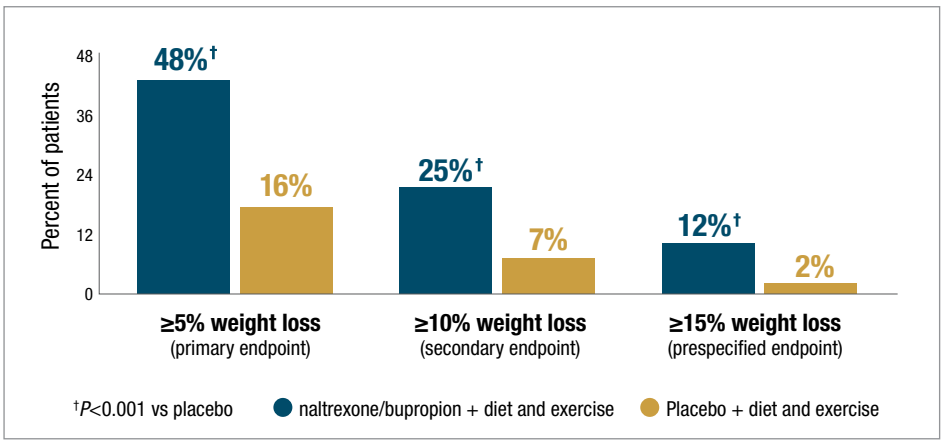

Figure 3. Proportion of patients who lost ≥5%, ≥10%, and ≥15% of baseline weight at week 56 in the COR-I phase III trial based on primary population analysis.[19,20]

Additionally, the results of the COR-BMOD study indicate that additional benefit is gained from combining naltrexone/bupropion with a comprehensive programme of behaviour modification (BMOD) versus BMOD alone (**Table 2**).[22]

In the randomised open-label effectiveness study, which was designed to reflect primary care practice, naltrexone/bupropion in combination with comprehensive lifestyle intervention (phone and internet-based support) significantly increased weight loss in overweight or obese adults compared with usual care alone (general weight loss advice received from a physician): 8.52% difference at 26 weeks ($p<0.0001$).[25] The initial weight loss achieved at 26 weeks was was sustained for 78 weeks (weight loss was >10% at 78 weeks (weight loss was >10% at 78 weeks), a longer duration than was assessed in the four randomised double-blind trials.

Cardiometabolic risk factors

Across the four randomised double-blind phase III studies, naltrexone/bupropion was variably associated with significantly ($p\leq0.01$ vs placebo) greater improvements in triglyceride, HDL-cholesterol, C-reactive protein, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) values after 56 weeks' treatment.[20-22]

The large cardiovascular outcome (non-inferiority) trial 'Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors' enrolling 8,910 participants was halted early due to release of interim information; however, in the 50% interim analysis, the pre-specified major cardiovascular event occurred in 102 patients (2.3%) in the placebo group and 90 patients (2.0%) in the naltrexone/bupropion group (HR 0.88; adjusted 99.7% CI, 0.57-1.34).[28] This led to the approval of the medication in the USA (FDA) in 2014 and in Europe (CHMP) in 2015.

In terms of waist circumference as a cardiometabolic risk factor, all four phase III studies demonstrated significantly ($p\leq0.006$ vs placebo) greater reductions in waist circumference measurement in patients treated with naloxone/bupropion (**Figure 4**).[20-23] The International Atherosclerosis Society (IAS) and International Chair on Cardiometabolic Risk (ICCR) Working Group on Visceral Obesity recommend that waist circumference should be adopted as a routine measurement in clinical practice alongside BMI to classify obesity.[29] Similarly, the NZ weight management guidelines recommend BMI and waist circumference for assessing and monitoring obesity.[30]

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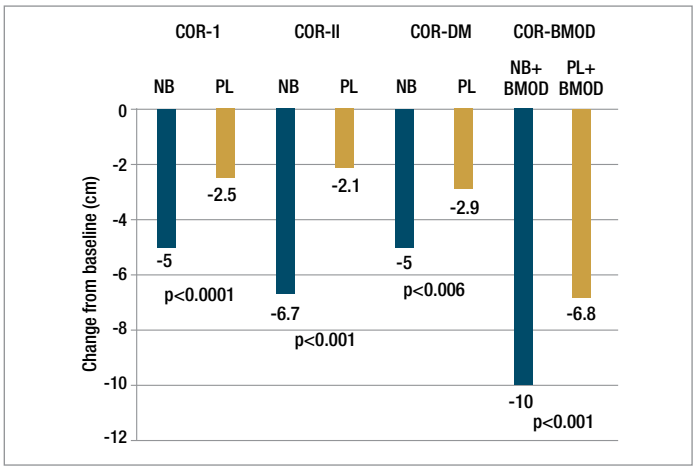

Figure 4. Reductions in waist circumference at 56 weeks in patients treated with naltrexone/bupropion (NB) versus placebo (PL) in four phase III trials.[20-23] Data for the COR-I trial is based on the primary analysis population. Data for the COR-II, COR-BMOD, and COR-DM trials are based on the mITT analyses.

BMOD = intensive behaviour modification; DM = diabetes.

There is a strong link between obesity and the development of insulin resistance, prediabetes, and type 2 diabetes.[31] In the COR-Diabetes phase III study, treatment with naltrexone/bupropion in overweight/obese patients with type 2 diabetes resulted in significant (p<0.001 vs placebo) reductions in both body weight and HbA1c levels over 56 weeks compared with placebo (**Figure 5**).[23] Significantly (p<0.01) more naltrexone/bupropion recipients achieved weight loss targets of ≥5% and ≥10% and HbA1c target levels of <7.0% and <6.5% at week 56. Changes in HbA1c levels were significantly (p<0.05) correlated with changes in bodyweight for both the naltrexone/bupropion (p<0.001) and placebo (p<0.05) treatment groups.

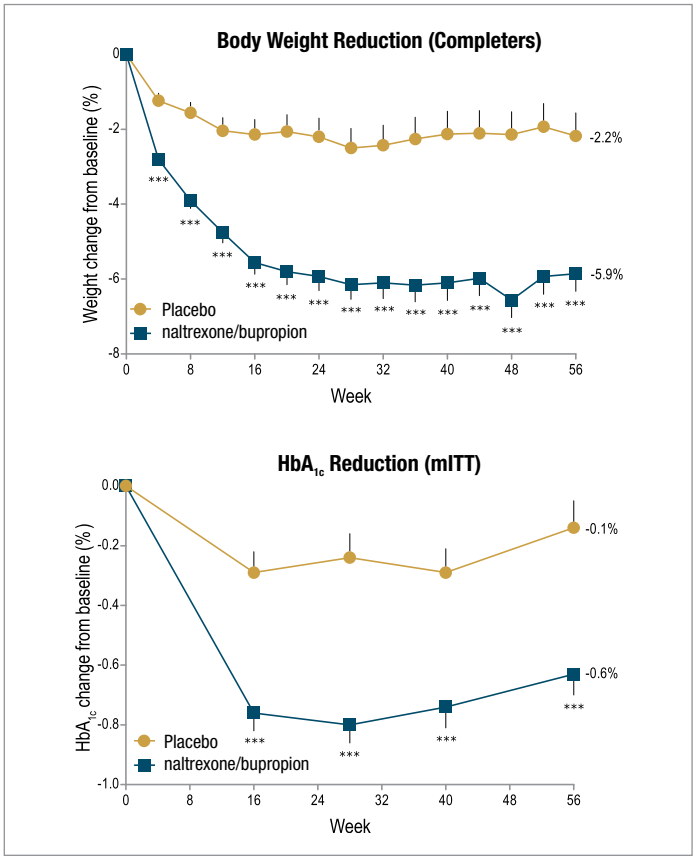

Figure 5. Change in body weight and HbA1c from baseline to week 56 in patients treated with naltrexone/bupropion or placebo in the COR-Diabetes phase III trial.[23]

***p<0.001 vs placebo. mITT = modified intention-to-treat population.

Patient-reported outcomes

In a pooled analysis of the four phase III trials (n=3362) that assessed changes at 56 weeks in QOL measured by the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire, improvements in the IWQOL-Lite total score were significantly (p<0.0001) greater in recipients of naltrexone/bupropion than in recipients of placebo.[32]

In addition, the randomised open-label effectiveness trial designed to approximate a primary care setting found that treatment with naltrexone/bupropion plus a comprehensive lifestyle intervention programme for 26 weeks resulted in significantly (p<0.001 vs usual care) greater improvements in weight-related QOL (IWQOL-Lite) and control overeating behaviour (Binge Eating Scale).[26] In patients with sexual dysfunction at baseline, significantly more patients who received naltrexone/bupropion plus lifestyle intervention no longer met the criteria for sexual dysfunction at week 26 (p<0.002 vs usual care).

Tolerability

Naltrexone/bupropion was generally well tolerated in the four phase IIII clinical trials of ≤56 weeks' duration, with a tolerability profile that was consistent with those of its individual components.[20-23] The most common adverse events were mild-to-moderate gastrointestinal (e.g., nausea, vomiting, constipation, and dry mouth) and CNS symptoms (e.g., headache, dizziness, and insomnia).

Nausea

Nausea was the most commonly reported adverse event with naltrexone/bupropion, occurring more often with naltrexone/bupropion than placebo.[20-23] Nausea was generally of mild to moderate intensity, transient, and its onset generally occurred in the first 4 weeks of treatment (i.e., during the dosage escalation period). Nausea did not contribute to the bodyweight reductions associated with naltrexone/bupropion and behavioural modification, i.e., weight loss, was independent of nausea.[33]

Nausea of one to two weeks' duration can be expected to occur in about one-third of patients during the dosage escalation period.[33] The nausea most likely results from the local effects of naltrexone on opioid signalling in the GI tract.Prior to commencing naltrexone/bupropion therapy, physicians should discuss with patients the potential for nausea to occur, its transient nature, and suggest approaches to help them manage nausea and adhere to therapy.[33]

Psychiatric adverse events

Medications that have activity in the CNS have the potential to affect mood and hence should be assessed for psychiatric adverse effects (PAEs).[34]

In a post hoc analysis of five RCTs of naltrexone/bupropion (the four phase III trials[20-23] plus one phase II trial[35]), PAEs were mostly mild-to-moderate in intensity, transient, and generally emerged in the dose-escalation period.[34] Although anxiety and sleep disorder-related PAEs occurred more often with naltrexone/bupropion than with placebo, depression-related PAEs were less common with naltrexone/bupropion.

Antidepressants have been associated with an increased risk of suicidality in adolescents and young adults;[36] however, naltrexone/bupropion was not associated with suicidal ideation or behaviour in the clinical trial populations of overweight or obese adults in the post hoc analysis.[34]

Naltrexone/Bupropion (Contrave®) for the Treatment of Obesity

OLE SCHMIEDEL: HOW TO USE NALTREXONE/BUPROPION IN CLINICAL PRACTICE

Before choosing a weight loss medication it is important to conduct a comprehensive assessment and jointly plan a management programme. Only then can the patient experience the full benefit of the intervention and maintain the weight loss achieved.

Part of this assessment will include evaluating medications the patient is using that can lead to weight gain,[37] the comorbidities that may also prevent the use of certain weight-loss medications (e.g., phentermine in patients with cardiovascular disease or at risk of atrial fibrillation) and potential barriers to adherence (cost, mode of administration, e.g., oral vs subcutaneous). At this point it is helpful to assess eating behaviours such as satiety, satiation, meal sizes as well as emotional eating, cravings, and eating pathologies such as binge eating disorder, night-time eating, or food addiction. This can be done with a number of questionnaires such as 3FEQ (Three-Factor Eating Questionnaire), FCQ-T-r (Food Craving Questionnaire – Trait, Reduced), HADS (Hospital Anxiety and Depression scale) or Yale Food addiction Questionnaire, supported by a comprehensive clinical assessment.

Based on this assessment it is possible to aim for a targeted use of weight-loss medications. Emerging evidence supports an approach of individualising weight-loss medications based on co-morbidities, dual benefit (naltrexone/bupropion for smoking cessation and weight gain), and predominant eating behaviours. As part of my clinical assessment I generally enquire about what 'drives' a person to eat. These 'drivers for eating' can be (1) reduced satiation at meals, making it hard for a person to stop eating, (2) constant hunger, or (3) emotional eating and cravings. If cravings and emotional eating patterns emerge, my preferred medication choice would be Naltrexone/Bupropion (Contrave).

There is significant inter-individual variability to any pharmacological intervention and it is important to consider changing the medication if clinically meaningful success has not been achieved after three months treatment with maximal tolerated dose and no other causes for the lack of success established.

In NZ there are now four medications registered for weight management, i.e., orlistat, phentermine, liraglutide, and now the combination of naltrexone/bupropion. Each has a specific mechanism of action, side-effect profile, and potential benefits. It is important to consider the approach outlined above when deciding which medication to use.

Naltrexone/bupropion induces satiety and reduces cravings and is the recommended first-choice weight-loss medication for craving, depression, and smoking in the recent Canadian guidelines on the pharmacotherapy for management of obesity.[38]

Use of naltrexone/bupropion is supported by substantial prescriber and patient experience, allowing the clinician to identify patients most suited to this treatment. This includes addictive and compulsive eating behaviours, and when cravings or night-time eating have been noted. Naltrexone/bupropion can reduce the desire to eat, allows a person to notice when satisfied, and can reduce the 'liking of unhealthy foods'. It is beneficial for people who gained weight when they stopped smoking or those that intend to stop.[39] To put it in the words of a patient: "I was satisfied with having healthy foods and did not feel deprived."

JOSEPH PROIETTO: THE AUSTRALIAN EXPERIENCE

The naltrexone/bupropion combination was launched in Australia in February 2019. Contrave is marketed as blue tablets each containing 8 mg of naltrexone and 90 mg of bupropion.

As mentioned above, because the combination can cause nausea that settles with continued use, it is advised to gradually increase to the full dose. It is important to stress that there is a wide range of responses to all medications, in both efficacy and side effects. I have found that this is also true for Contrave. The above schedule of gradual increase will suit a majority of patients, but not all. Therefore, be prepared to slow down the rate of increase in dose if the nausea has not settled after one week at that dose. I have found that if the drug is very effective at a lower dose, say one tablet morning and evening, there is no reason to increase the dose further.

The best way to assess if the drug has good efficacy, is to assess the percent weight loss at week 16. If it is at least 5%, then the patient is a good responder. A study has shown that a weight loss of 5% at week 16 was associated with a weight loss of 11.7% at week 56.[39]

The COR-BMOD study[22] showed once again that more weight loss can be achieved when a strict diet is combined with medication, in this case the combination of naltrexone and bupropion.

The best diet is a very low energy diet (VLED) involving the replacement of breakfast and lunch with a VLED product such as Optifast® or Optislim® to supply all of the vitamins and minerals that we normally ingest from food daily.[41] Ketosis is achieved by having a carbohydrate-free dinner consisting of 150 g of protein (any type of meat, fish or seafood, eggs, and tofu) and ~2 cups of non-starchy vegetables and salad (a list of non-starchy vegetables can be obtained via the internet). A small amount of fat daily (e.g., a tablespoon of oil on the salad) is important to empty the gall bladder and reduce the risk of developing gall stones. The daily meal can be lunch if the occasion calls for it, and allows socialisation.

Naltrexone/Bupropion (Contrave®) for the Treatment of Obesity

TAKE HOME MESSAGES

- Oral naltrexone/bupropion as an adjunct to a reduced-calorie diet and increased physical activity is an effective and well tolerated weight-loss medication in overweight or obese adults with at least one bodyweight-related comorbidity.
- More weight loss can be achieved by combining naltrexone/bupropion with a VLED-based ketogenic diet.
- Naltrexone/bupropion has a novel dual mode of action to facilitate weight loss:
  1. Acts synergistically in the hypothalamic hunger centre to reduce appetite and increase energy expenditure; and
  2. Synergistically modulates the mesolimbic reward system to control food cravings and modify eating behaviour.
- Naltrexone/bupropion has been shown in large, randomised, placebo-controlled trials to:
  - Achieve significantly greater % weight loss from 4 weeks versus placebo that is sustained for the longer term (56 weeks).
  - Achieve weight reductions of ≥5%, ≥10%, and ≥15% in significantly more patients versus placebo.
  - Produce significantly greater improvements versus placebo in cardiometabolic risk factors associated with 56 weeks treatment.
  - Achieve significant improvements in QOL measures associated with weight loss versus placebo.
  - Produce significantly greater weight loss and improvements in cardiovascular risk factors and glycaemic control versus placebo in patients with type 2 diabetes.
- Naltrexone/bupropion significantly reduced bodyweight and improved QOL versus usual care in a real-world study, with weight loss being sustained for 78 weeks.
- Naltrexone/bupropion is generally well-tolerated:
  - Mild-to-moderate nausea being the most common adverse event. Slow titration and close observation are key to successful use.
  - Important medication interactions, contraindications and cautions need to be considered (see above)
  - Patient counselling may be beneficial in the management of nausea and maintaining adherence to medication.
  - The right patient choice and the right approach are key to successful use of this medication.

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