NALTREXONE/BUPROPION COMBINATION AIDS WEIGHT MANAGEMENT BY SUPPRESSING HUNGER AND REDUCING CRAVING

Dr. Kevin Lee, Consultant Endocrinologist and Specialist Physician, and Professor Dr. Norlaila Mustafa, Consultant Endocrinologist, discussed the role of naltrexone HCl 8 mg/bupropion HCl 90 mg prolonged-release tablets in weight management among patients with obesity during a recent symposium in Kuala Lumpur.

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CONTRAVE® SUPPORTS HOLISTIC APPROACH TO WEIGHT MANAGEMENT

Eating behaviour is driven by both cravings or hedonic eating and hunger thus controlling both is part of a holistic and ideal approach to weight management. Now available in Malaysia, Contrave® (naltrexone HCl 8 mg/bupropion HCl 90 mg) prolonged-release tablet is the only oral anti-obesity medication that can control cravings and hunger.[1-6] Contrave®'s unique, dual mode of action is a result of its components bupropion HCl and naltrexone HCl acting in two regions of the brain namely, the hypothalamus and the mesolimbic system.[1]

In the hypothalamus or arcuate nucleus, the integration of peripheral and central signals determines if body weight is homeostatically correct; weight homeostasis is determined by food intake or metabolism. The neuropeptide Y/agouti-related peptide (NPY/AgRP) and proopiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) neurons in the arcuate nucleus are involved in weight homeostasis. The hunger hormone, ghrelin will stimulate the NPY neurons to promote hunger while other hormones including insulin promote satiety.[7-9]

Acting via the hypothalamus, the bupropion component of Contrave® has been found to increase the POMC activity resulting in satiety. At the same time, the naltrexone component inhibits the breakdown of neuropeptides thus promoting the activity of the POMC neurons. Both bupropion and naltrexone jointly regulate neurotransmitters in the mesolimbic system—a reward pathway system involving dopamine—with the end result of reduced sweet and savoury cravings. Contrave® essentially gives dual input into the hypothalamus and the mesolimbic system.[1-3]

CASE STUDIES[10]

Case 1: A 45-year-old working mother of two boys aged 10 and 14 years old, weighed 120 kg with BMI 45 kg/m^2, had hypertension and on candesartan 16 mg OD, and had impaired fasting glucose. She was referred by her local GP because of progressive weight gain, which she experienced since her teenage years. Her weight increased markedly after having her children. She admitted to regular bouts of comfort food eating, also known as emotional eating or stress-related eating. She was intolerant to liraglutide due to bloating and severe reflux. She was advised on mindfulness eating and was open to eating a high protein, high fibre, and low carbohydrate diet, with 16:8 intermittent fasting. She was guided on managing comfort food eating with one tablet of Contrave® in the morning with her meal (**Figure 1**). She was also started on low-dose metformin and titrated to 1000 mg daily. She was asked to perform incidental activity rather than exercise.

At 2 months, the patient's weight was reduced to 111.5 kg. She was constipated and advised to take adequate fibre in every meal and to drink enough water. She did not need laxatives. Contrave® dose was reduced to 1 tablet BD. At 3 months, her weight reduced to 102.9 kg. She did not have constipation anymore, so Contrave® dose was increased to 2 tablets BD. At 4 months, her weight reduced to 96.5 kg. At the last review 1 year later, her weight was 94.2 kg, with a total weight loss of 21.5%. Due to postural symptoms, candesartan dosage was reduced to 8 mg daily. She was discharged back to her GP for follow up.

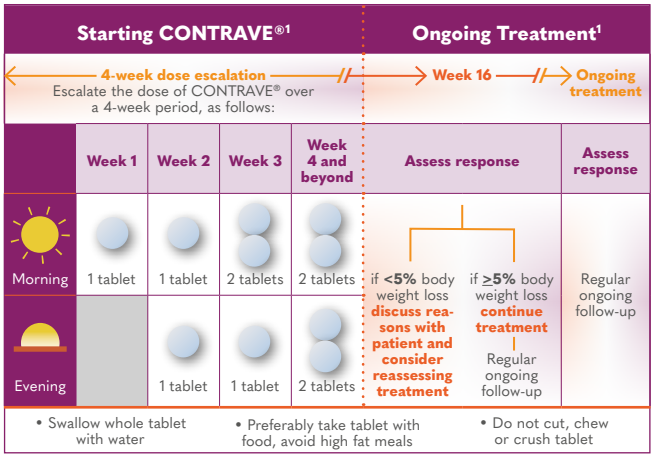

Figure 1: Dosing regimen for Contrave®[1]

Case 2: A 36-year-old working mother of two children, weighed 78 kg with BMI 29 kg/m^2. She had progressive weight gain after childbirth. She had bilateral knee pain due to weight gain and required regular analgesia. She had obstructive sleep apnoea (OSA) and used continuous positive airway pressure (CPAP) device intermittently. She had reflux, which was treated with intermittent omeprazole use. She had mood disorder and was prescribed sertraline. She joined commercial weight loss programmes after her first baby, and her weight reduced but not to her pre-pregnancy weight. She also tried very low energy diets but was not successful. She was given liraglutide and lost some weight in 3 months. When switched to semaglutide, she was able to maintain her weight. Due to shortage of semaglutide, she was switched back to liraglutide, which was not effective enough. Hence, she was given liraglutide and Contrave®.[10*]

* **DISCLAIMER:** The safety and effectiveness of CONTRAVE® in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

PRACTICE TIPS[10]

- When starting patients on Contrave®, they should be encouraged to follow a healthy lifestyle they are most likely to comply with especially healthy, balanced meals.
- Patients should be asked if they have postural symptoms (such as dizziness) after they lose 10% of weight.[11] A reduction in their systolic blood pressure (BP) of ≥20 mmHg or diastolic BP of 10 mmHg from lying to standing position indicates postural hypotension.[12]
- The dosage of antihypertensive medication should be reviewed and reduced if patients have postural symptoms.
- The overall trend of weight reduction is more important than periodic fluctuations.
- The key factors in weight management are nutrition, physical activity, stress management, and sleep.

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CONTRAVE®'S ROLE IN WEIGHT MANAGEMENT IN MALAYSIA

In Malaysia, the National Health and Morbidity Survey showed obesity prevalence increased from 15.1% in 2011 to 17.7% in 2015, and 19.7% in 2019.[13-15] To further improve obesity management in Malaysia, the newly launched 2nd edition of Clinical Practice Guidelines (CPG) on the Management of Obesity included new BMI classifications: 23–27.4 kg/m^2 for overweight and ≥27.5 kg/m^2 for obesity.[16] Measurement of BMI and waist circumference are recommended as they are simple methods of assessing patients' weight loss target in GP clinics and Klinik Kesihatan. Waist circumferences of >80 cm for women and >90 cm for men indicate abdominal obesity, which is an important risk factor for cardiovascular disease and diabetes.[16]

The new CPG recommends pharmacotherapy as an adjunct to lifestyle modification and behavioural therapy, with a weight loss target of 5–10%. Lifestyle modification includes physical activity and meal replacement-based plans incorporated in a structured calorie-restricted diet advised by a dietitian. A new chapter is introduced in the CPG, where behavioural therapy and the psychological aspect of weight management is discussed. It entails the inclusion of psychiatrists and psychologists with the aim of helping patients to sustain lifestyle changes. Pharmacotherapy available in Malaysia include Contrave®, phentermine, orlistat, topiramate in combination with phentermine, high dose liraglutide, and high dose semaglutide.[16]

Contrave®, a combination of naltrexone and bupropion, is now available in Malaysia and indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 along with hypertension, diabetes, or dyslipidaemia.[1] Contrave® suppresses appetite and controls cravings via the hypothalamus and the mesolimbic system. Patients on Contrave® were able to maintain significant weight loss up to 56 weeks.[17]

KEY TAKEAWAYS:

1. Now available in Malaysia, Contrave® (naltrexone HCl 8 mg/bupropion HCl 90 mg) prolonged-release tablet is the only oral anti-obesity medication that can control cravings and hunger.[1-6]
2. Contrave®'s unique, dual mode of action is a result of its components bupropion HCl and naltrexone HCl acting in two regions of the brain namely the hypothalamus and the mesolimbic system.[1]
3. In Malaysia, the National Health and Morbidity Survey showed obesity prevalence increased from 15.1% in 2011 to 17.7% in 2015, and 19.7% in 2019.[13-15]
4. To further improve obesity management in Malaysia, the newly launched 2nd edition of Clinical Practice Guidelines (CPG) on the Management of Obesity included new BMI classifications: 23–27.4 kg/m^2 for overweight and ≥27.5 kg/m^2 for obesity.[16]
5. The new CPG recommends pharmacotherapy as an adjunct to lifestyle modification and behavioural therapy, with a weight loss target of 5–10%.[16]

AgRP, agouti-related peptide; **BD,** twice daily; **BMI,** body mass index; **BP,** blood pressure; **CART,** cocaine- and amphetamine-regulated transcript; **CPAP,** continuous positive airway pressure; **CPG,** clinical practice guidelines; **GP,** general practitioner; **NPY,** neuropeptide Y; **OD,** once daily; **OSA,** obstructive sleep apnoea; **POMC,** proopiomelanocortin.

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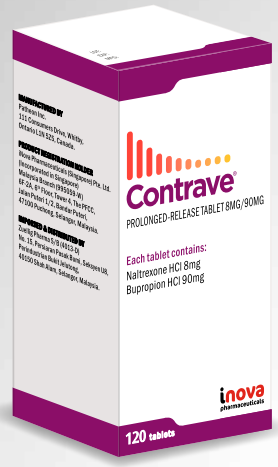
(naltrexone HCl/bupropion HCl)
8 mg/90 mg • Prolonged-Release Tablets



THE ONLY ORAL ANTI-OBESITY MEDICATION THAT CAN CONTROL **CRAVINGS & HUNGER**[1–6]

Contrave® controls cravings & hunger[1-3]

TARGETS more than one **driver of eating**[7]

Significant weight loss from **WEEK 4***[8–11]

Double-digit weight loss at 56 weeks†[12]

*The phase III Contrave® Obesity Research (COR) program consisted of four multicentre, randomised, double-blind, placebo-controlled clinical trials designed to assess the efficacy and safety of naltrexone HCl 32 mg/bupropion HCl 360 mg over 56 weeks in subjects aged 18-65 years with a BMI 30–45 kg/m^2 or a BMI 27–45 kg/m^2 plus controlled hypertension and/or dyslipidaemia. Co-primary endpoints for COR-I, COR-Behaviour Modification Therapy (COR-BMOD) and COR-Diabetes (DM) were percentage change in body weight and proportion of subjects with a decrease in body weight of ≥5% from baseline at Week 56. COR-II co-primary endpoints were percent weight change and proportion achieving ≥5% weight loss at Week 28, though the study continued to Week 56.[8-11]

†At 1 year, average weight loss (using last observation carried forward [LOCF] methodology) among Week 16 responders who received Contrave® was 11.3%, with 55% losing ≥10% body weight. Additionally, Week 16 responders who received Contrave® had a high retention rate, with 87% completing 1 year of treatment.[1,12]

Prescribe Contrave® in conjunction with reduced-calorie diet and increased physical activity.

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REFERENCES: 1. Contrave® Product Information. **2.** Billes SK, *et al.* Pharmacol Res 2014;84:1–11. **3.** Australian and New Zealand Obesity Society. Australian Obesity Management Algorithm. Available at: www.anzos.com/publications (accessed October 2020). **4.** Duromine Product Information. **5.** Saxenda Product Information. **6.** Orlistat ARTG Public Summary. **7.** Acosta A, *et al.* Obesity 2021;29:662–671. **8.** Greenway FL,*et al.* Lancet 2010;376:595–605. **9.** Apovian CM, *et al.* Obesity 2013;21:935–943. **10.** Wadden TA, *et al.* Obesity 2011;19:110–120. **11.** Hollander P, *et al.* Diabetes Care 2013;36:4022–4029. **12.** Fujioka K, *et al.* Int J Obes 2016;40:1369–1375.

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