A RESEARCH REVIEW™
SPECIAL REPORT

Food Cravings in Patients with Obesity: The Role of Pharmacotherapy

Making Education Easy 2021

About the Expert

Carl Peters
BHB, MBChB (Auckland); FRACP

Dr Carl Peters is a specialist endocrinologist and diabetologist. After New Zealand endocrinology training, Dr Peters moved to the UK to work as a clinician and clinical researcher at the Institute for Cellular Medicine, Newcastle University. Carl currently works as a Consultant at Waitemata DHB, Auckland, Honorary Senior Lecturer for the University of Auckland, Educational Supervisor for the RACP, reports bone densitometry for Auckland Bone Density, and in private practice at the Mercy Specialist Centre.

This review describes the issue of food cravings in patients with obesity, and the role that obesity pharmacotherapies can play in the management of this issue. Studies which have evaluated the effects of Medsafe-approved obesity pharmacotherapies on food cravings are discussed. This review has been created with an educational grant from Radiant Health.

Obesity and food cravings

The frequent and intense desire to consume a particular type of food can be defined as food craving.[1] Core components of food craving include intense and intrusive thoughts and multi-sensory imagery of a food, strong urges to seek out and consume a food, perception of poor self-control with food, and anticipation of positive and/or negative reinforcement if one eats the food.[2] Food cravings are positively correlated with body mass index (BMI), and are believed to account for up to 11% of the variance between individuals in eating behaviour and weight gain.[1,3]

Food cravings are governed by the mesolimbic dopaminergic reward system in the brain.[4] Dopamine and opioid systems interact to determine eating behaviour.[4] Opioids convey the reward sensation of desirable foods, while dopamine regulates the reward value of food and the motivation to obtain that food.[4,5]

A key component in the management of obesity and successful weight loss maintenance is the reduction and management of food cravings.[6] The effects of several obesity pharmacotherapies on food cravings have been investigated.[1]

Available obesity pharmacotherapies

Clinical practice guidelines recommend the use of pharmacotherapy as an adjunct to a reduced calorie diet and increased physical exercise in adults with a BMI ≥ 30 mg/kg^2, or a BMI of ≥ 27 kg/m^2 in the presence of a weight-related comorbidity, such as diabetes, dyslipidaemia or hypertension.[7-9] Four pharmacotherapies are approved in New Zealand for the treatment of obesity/overweight with comorbidities – naltrexone/bupropion, phentermine, liraglutide and orlistat (see **Table 1**).[10-13]

	Dosage and administration	Weight loss vs placebo (% or kg)	Typical adverse events	Approximate cost per month*
Naltrexone/ bupropion	32 mg/360 mg twice daily orally	4.8-5.2% at 56 weeks	Nausea, vomiting, constipation, dry mouth, headache, dizziness, insomnia	$240 for 112 tablets
Phentermine	15 or 30 mg once daily orally	3.6-4.5 kg at 6 months	Tachycardia, palpitations, hypertension, precordial pain	15 mg: $79 for 30 capsules 30 mg: $90 for 30 capsules
Liraglutide	0.6-3.0 mg once daily by subcutaneous injection	5.4% at 1 year	Nausea, vomiting, diarrhoea, constipation	$500 for 5 pens
Orlistat	120 mg three-times daily orally	2.9-3.5% at 1 year	Steatorrhea, oily spotting, flatulence with discharge, faecal incontinence	$156.80 for 84 capsules

Table 1. Summary of obesity pharmacotherapies approved in New Zealand.[7-13]

*RRP prices from www.pharmacydirect.co.nz/ (accessed August 2021) and personal communication from Novo-Nordisk and Radiant Health. Cost may vary over time and depending on site of purchase.

When considering pharmacotherapy for a particular patient, behavioural issues associated with obesity should be considered.[7,14,15] For example, does the patient describe cravings and addictive behaviour surrounding food?[14] Food cravings can be assessed by a number of questionnaires, including the Control of Eating Questionnaire (COEQ), the Food Craving Inventory (FCI), and several versions of the Food Craving Questionnaire (FCQ).[2] Furthermore, contraindications and possible drug interactions (as specified on the product data sheets) must be considered.[7,14] Other considerations are comorbidities, potential side effects/tolerability, mode of administration, and cost.[7]

Mechanism of action of obesity pharmacotherapies

Naltrexone/bupropion is believed to contribute to weight loss via two distinct mechanisms.[5,6] Firstly, bupropion-mediated stimulation of pro-opiomelanocortin neurons in the hypothalamus and naltrexone-mediated suppression of autoinhibitory pathways of the same pro-opiomelanocortin neurons leads to appetite suppression.[5,6] Secondly, regulation of mesolimbic dopaminergic pathways leads to a reduction in food cravings and improves control of eating behaviour.[5,6]

Phentermine is a sympathomimetic amine that is chemically related to amphetamine.[11] It acts on the noradrenergic and dopaminergic nervous systems to suppress appetite.[11] Liraglutide is a glucagon-like peptide 1 (GLP-1) agonist that binds to GLP-1 receptors in the brain to improve satiation and reduce hunger.[12] It also has a transient effect on gastric emptying.[12] Orlistat is a potent and selective inhibitor of pancreatic lipase that reduces intestinal breakdown and absorption of dietary fat.[13] It does not specifically target appetite or satiety mechanisms.[7]

A simple graphic of the sites of action of naltrexone/bupropion, phentermine, liraglutide, and orlistat is shown in **Figure 1.**[16]

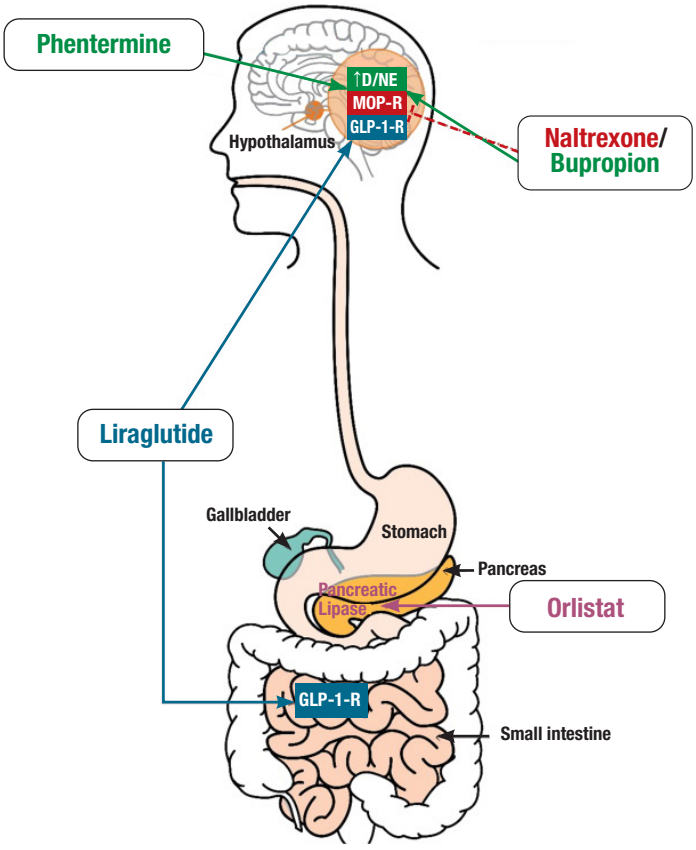

Figure 1. Sites of action for obesity pharmacotherapies approved in New Zealand (adapted from Kaszubska K, et al. [2016]).

Effects of obesity pharmacotherapies on food cravings

The obesity pharmacotherapy with the strongest evidence for a beneficial effect on food cravings is naltrexone/bupropion.[4] Canadian Adult Obesity Clinical Practice guidelines recommend naltrexone/bupropion as the first choice of therapy for patients with food cravings.[7] US clinical practice recommendations published by Saunders et al. state that patients who describe cravings for food and/or addictive behaviours related to food are good candidates for treatment with naltrexone/bupropion.[14] Some preliminary research suggests that liraglutide and phentermine may also be effective in targeting food cravings.[4]

Naltrexone/bupropion

The impact of naltrexone/bupropion on food cravings was assessed in four phase III trials involving a total of 4536 patients with obesity/overweight.[5,17-20] In an integrated analysis of the trials, naltrexone/bupropion was associated with significant improvement in item 19 of the COEQ (Generally, how difficult has it been to control your eating?) compared with placebo at all timepoints measured, from week 8 through to week 56.[5] Naltrexone/bupropion was also associated with improvements in other measures on the COEQ, including increased ability to resist food cravings and reduced incidence and strength of food cravings.[5] However, there were no significant differences between treatment groups in changes on the FCI total or subscale scores.[5]

Integrated analysis also showed that weight loss outcomes over 56 weeks were associated with early improvement of food cravings.[6] In particular, early improvements in the COEQ Craving Control and Craving for Sweet subscales throughout the trial period were predictive of greater reductions in BMI at the end of the trial.[6] When patients were categorised as responders or non-responders based on their change in Craving Control score at week 8, non-responders lost 3-4% less weight than responders.[6]

A phase IIIb trial of 242 patients with obesity/overweight showed that naltrexone/bupropion combined with a comprehensive lifestyle intervention (CLI; treatment consistent with prescribing instructions) programme improved patient-reported control of eating behaviour compared with usual care at 26 weeks.[21] Patients in the naltrexone/bupropion + CLI group also reported greater improvement in weight-related quality of life and sexual function than those in the usual care group.[21] This open-label trial approximated a real-world setting, including two treatment options a patient would be likely to receive when seeking treatment for obesity.

Findings of an MRI study in 40 women with obesity/overweight suggested that naltrexone/bupropion-induced weight loss may be a result of change in cortical reactivity to food cues, particularly brain regions implicated in interoception, memory and self-control.[22]

Phentermine

In a randomised controlled trial of 77 patients with obesity, those who received phentermine combined with a meal replacement programme had significantly greater decreases in cravings for fats and sweets at 12 weeks, as assessed on FCI subscales, compared with those who received placebo.[23] However, there were no significant differences between groups in total FCI score, or in General FCQ-Trait or FCQ-State scores.[23]

Liraglutide

Liraglutide treatment for 17 days decreased activation of the parietal cortex in response to highly desirable food images in a randomised controlled trial of 21 patients with type 2 diabetes.[24] Decreased activation in the insula and putamen, areas involved in the reward system, was noted in a secondary analysis.[24]

In an exploratory analysis of a randomised controlled trial of 150 patients with obesity, patients who received liraglutide in combination with intensive behavioural therapy had greater reductions in global eating disorder psychopathology at 24 weeks, as assessed by the Eating Disorder Examination Questionnaire, compared with patients who received placebo.[25] However, changes were no longer significant at 52 weeks.[25] There were no differences between groups in food cravings, as assessed by the FCI, at either time point.[25]

EXPERT'S CONCLUDING COMMENTS

I often see patients who are frustrated by the journey they have had managing their obesity. They usually present with several clinical questions. What is the cause of my obesity? Why can I not lose weight despite all the effort? And what else can I do now?

The first question is usually directed at clinicians to explore an underlying reversible cause for obesity. Secondary causes of obesity in adulthood are rare. In modern practice hypothyroidism is usually detected early, and other causes have very low prevalence (e.g. Cushing's syndrome, craniopharyngioma, growth hormone deficiency, syndromic or monogenic causes). In most patients hypogonadism is usually a consequence of obesity, rather than a cause. People are usually disappointed to find that their obesity is often multifactorial, contributed to by a combination of risk alleles, individual behaviour, and environmental factors.

The second question usually encompasses patients' frustration of their journey. It is often asked alongside the first, with many patients feeling their lack of success must be due to a secondary cause that requires specific treatment. Most will have tried various strategies, with varying success, and over varied timeframes. Weight regain after a previous successful period of intervention is incredibly frustrating for patients. This question is usually the one I find has the greatest opportunity to open a conversation before moving on to the last. Here, you can explore patients' understanding of behaviour, and in particular appetite and food cravings. Despite most of us acknowledging the relevance of craving to substance-use disorders, the relevance of addiction features, including craving, to obesity is usually less well appreciated. Acknowledging patients' cravings and appetite normalises their experience and allows them to prepare for a discussion on potential strategies to manage these. The COEQ is an option to assess food cravings, and comprises 21 items designed to assess the intensity and type of food cravings an individual experiences. Patients respond according to their experience over the previous seven days.

The third question opens the opportunity to discuss pharmacologic therapy. Whilst patients can achieve meaningful weight loss in the absence of pharmacologic therapy, for many who come to seek the support of a health practitioner, they will expect you to have the ability to discuss available pharmacologic options. Except for orlistat, all of the medications work centrally to suppress appetite. Reducing food cravings through pharmacologic treatment represents an important aspect of appetite suppression to achieve meaningful weight reduction, and is supported by clinical guidelines. Recently, Dalton et al. found control of food cravings was the most significant predictor of BMI slope in persons undergoing pharmacotherapy for weight loss.[6] Where appropriate (in the absence of any contraindications), I discuss all four pharmacologic options for weight management, avoiding having a preconceived idea as to what one individual might be willing to pay for weight management therapies. An informed decision can only be made having considered all of the available options.

Discussion of options for weight management should be considered for all patients who are overweight or obese, and those who have an adiposity-associated complication. Pharmacotherapy for weight loss can be used for individuals with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with adiposity-related complications, in conjunction with nutrition therapy, physical activity and psychological interventions. Furthermore, pharmacotherapy may be considered to maintain weight loss that has been achieved by health behaviour changes, and to prevent weight regain. It should be part of the toolkit for most health practitioners, as most of us encounter these situations daily.

TAKE-HOME MESSAGES

- A key component in obesity management and successful weight loss maintenance is the reduction and management of food cravings
- The obesity pharmacotherapy with the strongest evidence for a beneficial effect on food cravings is naltrexone/bupropion.

REFERENCES

1. Myers CA, Martin CK, Apolzan JW. Food cravings and body weight: a conditioning response. Curr Opin Endocrinol Diabetes Obes. 2018 Oct;25(5):298-302.
2. Taylor M. A review of food craving measures. Eat Behav. 2019 Jan;32:101-110.
3. Boswell RG, Kober H. Food cue reactivity and craving predict eating and weight gain: a meta-analytic review. Obes Rev. 2016 Feb;17(2):159-77.
4. Rebello CJ, Greenway FL. Reward-Induced Eating: Therapeutic Approaches to Addressing Food Cravings. Adv Ther. 2016 Nov;33(11):1853-1866. doi: 10.1007/s12325-016-0414-6.
5. Billes SK, Sinnayah P, Cowley MA. Naltrexone/bupropion for obesity: an investigational combination pharmacotherapy for weight loss. Pharmacol Res. 2014 Jun;84:1-11.
6. Dalton M, Finlayson G, Walsh B, et al. Early improvement in food cravings are associated with long-term weight loss success in a large clinical sample. Int J Obes (Lond). 2017 Aug;41(8):1232-1236.
7. Pedersen SD, Manjoo P, Wharton S. Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy in Obesity Management. Available from: https://obesitycanada.ca/wp-content/uploads/2021/05/Pharmacotherapy-v6-with-links.pdf [Accessed July 2021].
8. Apovian CM, Aronne LJ, Bessesen DH, Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Feb;100(2):342-62.
9. Lee PC, Dixon J. Pharmacotherapy for obesity. Aust Fam Physician. 2017;46(7):472-477.
10. Contrave 8/90 New Zealand data sheet (October 2020). Auckland: iNova Pharmaceuticals (NZ) Ltd. 2020. Available from: https://www.medsafe.govt.nz/profs/datasheet/c/Contravetab.pdf [Accessed July 2021].
11. Duromine New Zealand data sheet (January 2018). Auckland: iNova Pharmaceuticals (NZ) Ltd. 2018. Available from: https://medsafe.govt.nz/profs/datasheet/d/durominecap.pdf [Accessed July 2021].
12. Saxenda New Zealand data sheet (November 2018). Auckland: Novo Nordisk Pharmaceuticals Ltd. 2018. Available from: https://www.medsafe.govt.nz/profs/Datasheet/s/saxendainj.pdf [Accessed July 2021].
13. Xenical (120 mg capsules) New Zealand data sheet (November 2017). Auckland: Pharmaco (NZ) Ltd. 2017. Available from: iNova Pharmaceuticals (NZ) Ltd. 2020. https://medsafe.govt.nz/Profs/Datasheet/x/Xenicalcap.pdf [Accessed July 2021].
14. Saunders KH, Shukla AP, Igel LI, Aronne LJ. Obesity: When to consider medication. J Fam Pract. 2017 Oct;66(10):608-616.
15. Roberts CA, Christiansen P, Halford JCG. Tailoring pharmacotherapy to specific eating behaviours in obesity: Can recommendations for personalised therapy be made from the current data? Acta Diabetol. 2017 Aug;54(8):715-725.
16. Kaszubska K, Budzynska B, Biala G. Contemporary pharmacological obesity treatments. Curr. Issues Pharm. Med. Sci., 2016 Jun;29(2):57-60.
17. Greenway FL, Fujioka K, Plodkowski RA; COR-I Study Group. 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. 2010 Aug 21;376(9741):595-605.
18. Apovian CM, Aronne L, Rubino D; COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring). 2013 May;21(5):935-43.
19. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring). 2011 Jan;19(1):110-20.
20. Hollander P, Gupta AK, Plodkowski R; COR-Diabetes Study Group. 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 Dec;36(12):4022-9.
21. Halseth A, Shan K, Gilder K, et al. Quality of life, binge eating and sexual function in participants treated for obesity with sustained release naltrexone/bupropion. Obes Sci Pract. 2018 Feb 23;4(2):141-152.
22. Wang GJ, Tomasi D, Volkow ND, et al. Effect of combined naltrexone and bupropion therapy on the brain's reactivity to food cues. Int J Obes (Lond). 2014 May;38(5):682-8.
23. Moldovan CP, Weldon AJ, Daher NS, et al. Effects of a meal replacement system alone or in combination with phentermine on weight loss and food cravings. Obesity (Silver Spring). 2016 Nov;24(11):2344-2350.
24. Farr OM, Sofopoulos M, Tsoukas MA, et al. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. Diabetologia. 2016 May;59(5):954-65.
25. Chao AM, Wadden TA, Walsh OA, et al. Effects of Liraglutide and Behavioral Weight Loss on Food Cravings, Eating Behaviors, and Eating Disorder Psychopathology. Obesity (Silver Spring). 2019 Dec;27(12):2005-2010.

Radiant Health

This publication has been created with an educational grant from Radiant Health Ltd. The content is entirely independent and based on published studies and the author's opinions. It may not reflect the views of Radiant Health. Please consult the full Data Sheets for any medications mentioned in this article at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician. All trademarks mentioned in this review are the property of their respective owners.