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## Review

## Current Perspectives on Long-term Obesity Pharmacotherapy

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## ABSTRACT

Approximately 1 in 4 adult Canadians are obese and, thus, are at an elevated risk for developing type 2 diabetes, cardiovascular disease and other conditions. Current treatment guidelines recommend that obese individuals lose 5% to 10% of their starting weights to minimize the risk factors for cardiovascular disease and reduce the risk for developing type 2 diabetes or hypertension. All obesity-management strategies involve lifestyle management, but few patients will lose a significant amount of weight and manage to keep it off over the long term using just this strategy. Bariatric surgery is associated with significant long-term weight loss but is restricted to subjects with very high body mass indices, who often wait many years to undergo the procedure. Recent breakthroughs in understanding the mechanisms underlying the development and maintenance of elevated body fat have led to the arrival of new obesity pharmacotherapies. These novel antiobesity therapies, which work by reducing energy intake or through increasing satiety, decreasing hunger, or reducing absorption of calories, may be used indefinitely once patients have demonstrated significant responses (usually defined as  $\geq 5\%$  weight loss) over the first 12 weeks of treatment. To date, 2 long-term obesity pharmacotherapies have been approved and are available in Canada: liraglutide and orlistat. Here, I summarize the mechanisms and clinical features of medications for long-term obesity management that are available in Canada, as well as those available in other jurisdictions or are currently in development. Crown Copyright © 2016 Published by Elsevier Inc. on behalf of Canadian Diabetes Association. All rights reserved.

## R É S U M É

Approximativement 1 adulte canadien sur 4 est obèse, et par conséquent, exposé à un risque élevé de développer un diabète de type 2, une maladie cardiovasculaire et d'autres maladies. Les lignes directrices actuelles de traitement recommandent que les individus obèses perdent 5% à 10% de leur poids initial pour minimiser les facteurs de risque de maladies cardiovasculaires et réduire le risque de développement du diabète de type 2 ou de l'hypertension. Toutes les stratégies de prise en charge de l'obésité impliquent la prise en charge du mode de vie, mais peu de patients n'auront une perte de poids significative et ne réussiront à le conserver à long terme qu'à l'aide de cette stratégie. La chirurgie bariatrique est associée à une perte significative de poids à long terme, mais ne se limite qu'aux sujets ayant un indice de masse corporelle élevé, qui attendent souvent plusieurs années avant de subir l'intervention. Les récentes percées dans la compréhension des mécanismes qui sous-tendent le développement et le maintien de réserves lipidiques élevées ont mené à l'avènement de nouvelles pharmacothérapies contre l'obésité. Ces nouveaux traitements anti-obésité, qui agissent de manière à réduire l'apport énergétique ou à augmenter la satiété, à diminuer la faim ou à réduire l'absorption de calories peut être utilisé indéfiniment dès que les patients ont démontré une réponse significative (généralement définie comme étant une perte de poids  $\geq 5\%$ ) au cours des 12 premières semaines de traitement. À ce jour, 2 pharmacothérapies à long terme contre l'obésité ont été approuvées et sont offertes au Canada: le liraglutide et l'orlistat. Ici, je résume les mécanismes et les caractéristiques cliniques des médicaments qui prennent en charge à long terme l'obésité et qui sont offerts au Canada, ainsi que ceux qui sont offerts dans d'autres juridictions ou sont actuellement en développement.

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## Introduction

Approximately 1 of every 10 adults in the world is now considered obese (1). In Canada, the prevalence of adult obesity increased from 14% to 26% between 1978 to 1979 and 2009 to 2011 (2). Although overall obesity rates in Canada may have been stabilizing over recent years (3), there has been a disproportionate increase in the number of individuals with more severe obesity (classes II and III) (4). Obesity is an established risk factor for the development of cardiovascular disease, type 2 diabetes, hypertension and numerous other conditions (5,6). More than just a consequence of poor lifestyle choices, obesity is now viewed as a disease that is complex, multifactorial, chronic and resistant to many forms of treatment (7,8).

The body mass index (BMI) provides the most convenient population-level indicator of overweight and obesity, but it is of limited utility on an individual-patient basis (9). Because waist circumference measures central obesity and predicts health risk independently of BMI (10), the combined measurements of BMI and waist circumference are often recommended, especially for patients with BMIs between 25 and 35 kg/m<sup>2</sup> (11,12). Recently, the Edmonton Obesity Staging System has been proposed as a more accurate measurement of obesity-related health risks because it also incorporates the presence of comorbidities (Table 1) (13). Emerging data suggest that the Edmonton Obesity Staging System predicts mortality much more accurately than BMI and can predict mortality risk within each BMI category (14,15). This system allows clinicians to identify individuals with obesity who may receive the greatest benefits from weight management.

Whereas patients with obesity generally aspire to lose nearly one-third of their starting weights, such extreme weight loss is generally unrealistic without bariatric surgery. Fortunately, lower degrees of weight loss can be effective in reducing the risk for morbidities (16). Indeed, a reduction of only 5% to 10% of baseline weight is associated with improvements in a number of cardiovascular disease risk factors, including levels of cholesterol, triglycerides and blood pressure (17,18). This magnitude of weight loss has also been found consistently to reduce the risk for developing type 2 diabetes or hypertension by more than 50% (19–21). Accordingly, current treatment guidelines recommend that individuals who are obese lose 5% to 10% of their starting weights to attain health benefits (11,22).

The backbone of all obesity management strategies involves lifestyle management, including behavioural therapies, diet and

physical activity (2,11). However, few patients using this strategy will lose a significant amount of weight and manage to keep it off over the long term (23–25). Bariatric surgery is generally reserved as an option for subjects with BMIs  $\geq 40$  or BMIs between 35 and 40 kg/m<sup>2</sup> plus comorbidities (11). Although surgery is associated with significant long-term weight loss (between 13% and 27%) (26), it is typically not available for patients with lower BMIs because of the risk for peri- and postoperative morbidity and mortality (27). Furthermore, even for those who qualify for bariatric surgery, the demand far outstrips the availability. Waiting times at various bariatric centres range from 3 to  $\geq 10$  years (28), and only ~0.1% of eligible Canadian patients ever receive publicly funded bariatric surgery (29). Thus, a large proportion of patients with obesity may fail to respond to lifestyle interventions and yet be ineligible for or have limited access to bariatric surgery.

A third treatment option, pharmacotherapy, is recommended as an adjunct to physical activity and diet intervention for patients with BMIs  $\geq 30$  kg/m<sup>2</sup> or BMIs  $\geq 27$  kg/m<sup>2</sup> plus comorbidities (11). However, because of the lack of pharmacologic options until only recently and the poor safety profiles of several older obesity drugs (since withdrawn from the market) (Table 2), pharmacotherapy is used in only approximately 20% of cases (30).

Recent breakthroughs in understanding the homeostatic and pathologic mechanisms underlying the development and maintenance of elevated body fat have identified potentially important targets for pharmacologic intervention (31). With these developments, new obesity pharmacotherapies are being developed, some of which have reached the Canadian, American or European markets. These novel antiobesity therapies have been developed for long-term use and may be used indefinitely once patients have demonstrated significant responses (usually defined as  $\geq 5\%$  weight loss) over the first 12 weeks of treatment.

Here, I summarize the mechanisms and clinical features of the medications for long-term obesity management that are available in Canada, as well as those available in other jurisdictions or currently in development.

## Methods

MEDLINE, Embase and Google Scholar were searched in January 2015 for relevant articles published between 1990 and 2015 and employing the following search terms and headings: obesity, weight loss, pharmacotherapy, medication and drug. Reference lists in

**Table 1**  
Proposed Edmonton Obesity Staging System (EOSS)<sup>a</sup>

Stage	Description	Management
0	No apparent obesity-related risk factors (e.g. blood pressure, serum lipids, fasting glucose, etc., within normal range), no physical symptoms, no psychopathology, no functional limitations and/or impairment of well-being	Identification of factors contributing to increased body weight; counselling to prevent further weight gain through lifestyle measures, including healthful eating and increased physical activity
1	Presence of obesity-related subclinical risk factors (e.g. borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.); mild physical symptoms (e.g. dyspnea on moderate exertion, occasional aches and pains, fatigue, etc.); mild psychopathology, mild functional limitations and/or mild impairment of well-being	Investigation for other (not weight-related) contributors to risk factors; more intense lifestyle interventions, including diet and exercise, to prevent further weight gain; monitoring of risk factors and health status
2	Presence of established obesity-related chronic disease (e.g. hypertension, type 2 diabetes, sleep apnea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder, etc.), moderate limitations in activities of daily living and/or well-being	Initiation of obesity treatments, including considerations of all behavioural, pharmacologic and surgical treatment options; close monitoring and management of comorbidities, as indicated
3	Established end-organ damage such as myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis, significant psychopathology, significant functional limitations and/or impairment of well-being	More intensive obesity treatment, including consideration of all behavioural, pharmacologic and surgical treatment options; aggressive management of comorbidities, as indicated
4	Severe (potentially end stage) disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations and/or severe impairment of well-being	Aggressive obesity management as deemed feasible; palliative measures, including pain management, occupational therapy and psychosocial support

<sup>a</sup> Adapted from Sharma and Kushner (13).

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