

# Weight loss medications in Canada – a new frontier or a repeat of past mistakes?

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**Abstract:** Current methods for the treatment of excess weight can involve healthy behavior changes, pharmacotherapy, and surgical interventions. Many individuals are able to lose some degree of weight through behavioral changes; however, they are often unable to maintain their weight loss long-term. This is in part due to physiological processes that cannot be addressed through behavioral changes alone. Bariatric surgery, which is the most successful treatment for excess weight to date, does result in physiological changes that can help with weight loss and weight maintenance. However, many patients either do not qualify or elect to not have this procedure. Fortunately, research has recently identified changes in neurochemicals (i.e., orexigens and anorexigens) that occur during weight loss and contribute to weight regain. The neurochemicals and hormones may be able to be targeted by medications to achieve greater and more sustained weight loss. Two medications are approved in adjunction to lifestyle management for weight loss in Canada: orlistat and liraglutide. Both medications are able to target physiological processes to help patients lose weight and maintain a greater amount of weight loss than with just behavioral modifications alone. Two other weight management medications, which also target specific physiological processes to aid in weight loss and its maintenance, a bupropion/naltrexone combination and lorcaserin, are currently pending approval in Canada. Nonetheless, there remain significant barriers for health care professionals to prescribe medications for weight loss, such as a lack of training and knowledge in the area of obesity. Until this has been addressed, and we begin treating obesity as we do other diseases, we are unlikely to combat the increasing trend of obesity in Canada and worldwide.

**Keywords:** weight loss, pharmacological intervention, liraglutide, weight loss medication

## Introduction

In Canada, an estimated 4.3 million adults fit the criteria for obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>), with rates predicted to rise in all provinces until 2019.<sup>1</sup> These numbers reflect the elusiveness of effective obesity prevention and therapy. As excess weight is associated with an increased mortality<sup>2</sup> and risk of developing comorbidities,<sup>3,4</sup> effective intervention is needed. Available treatments for excess weight can be broken down into three categories: behavioral modifications, medications, and surgical interventions. As behavioral modifications have variable success rates,<sup>5,6</sup> and many patients eligible for bariatric surgery elect to not have surgery,<sup>7,8</sup> medications may be a way to bridge the gap and provide effective treatment for weight management.

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## Treatment options for excess weight

Behavioral modification, which can be comprised of physical activity, caloric restriction, or both, is the cornerstone of weight management. Results of several meta-analyses suggest that physical activity interventions, without calorie restriction are associated with significantly lower reductions in weight than dietary alone, or combined interventions.<sup>6,9,10</sup> Due to the differences in these behavioral modifications, there is considerable variability in the amount of weight loss achieved (range: 2%–13% of initial body weight loss).<sup>5,6</sup> While this suggests that some patients are able to achieve reductions in weight using these methods, those who participate in behavioral modifications appear to be poor at maintaining the weight loss long-term.<sup>6,11,12</sup> Weight regain, often referred to as weight cycling or yo-yo dieting, is a cyclical pattern which can increase the risk of developing cardiovascular disease or type 2 diabetes.<sup>13</sup>

Bariatric surgery, which has proven to be the most successful treatment for obesity, has until recently been reserved only for those in the highest BMI. While some medical centers are beginning to offer bariatric surgery to treat comorbidities in patients who are overweight or mildly obese,<sup>14</sup> current clinical guidelines in Canada still recommend bariatric surgery only for individuals with a BMI  $\geq 40$  kg/m<sup>2</sup>, or a BMI  $\geq 35$  kg/m<sup>2</sup> with an obesity related comorbidity, such as type 2 diabetes or hypertension.<sup>15</sup> Bariatric surgery is a relatively safe procedure with a low chance of mortality (range: 0.11%–0.34%) or complications (range: 1.44%–5.91%) following surgery.<sup>16</sup> Further, individuals who have bariatric surgery can have complete reversal of their comorbidity(ies).<sup>16</sup> Nonetheless, due to incorrect perceptions of risk, more than half of eligible patients state that they are not interested in bariatric surgery.<sup>7,8</sup> This begs the question of whether there is a solution for others, specifically patients living with obesity who do not want or do not qualify for surgery.

Pharmacotherapy is currently approved as an adjunct to lifestyle interventions for weight management in patients with a BMI  $\geq 30$  kg/m<sup>2</sup> or a BMI  $\geq 27$  kg/m<sup>2</sup> with at least one obesity related comorbidity.<sup>15</sup> Prior to 2010, attempts to introduce effective, evidenced-based pharmacotherapy for weight management were riddled with significant adverse effects, often cardiac in nature, resulting in sweeping withdrawals from the market.<sup>17,18</sup> However, recent findings within obesity research suggest that medications may play an important role in combating physiological processes that prevent patients from losing weight or cause patients to gain back the weight that they have already lost.

## Current research on the mechanisms of weight loss and weight maintenance

During weight loss, the production of weight gaining neurochemicals (orexigens) increases.<sup>19</sup> Orexigens, such as ghrelin, induce hunger, lower metabolism and promote cravings for calorie-dense foods.<sup>19</sup> Simultaneously, weight losing neurochemicals (anorexigens), decrease during weight loss which promotes weight regain and the maintenance of patients' heaviest weight.<sup>20</sup> This highlights the importance of choosing a course of treatment which addresses physiological responses to weight loss or weight regain may be imminent. Bariatric surgery, despite its invasive nature, has been shown to successfully boost anorexigens and dampens the release of orexigens.<sup>21</sup> Consequently, it has been argued that a primary mechanism of weight loss due to surgery relates to neurochemical modulation rather than simply mechanical restriction or malabsorption.<sup>22,23</sup> While this modality is unlikely a scalable option due to cost and expertise requirements, pharmacotherapy may be a more accessible means of large-scale treatment.

Obesity is a complex and multifactorial disease that develops from the interaction of metabolic, genetic, social, behavioral and cultural factors. Consequently, a collection of diverse medications designed around the biology of weight changes must be developed and approved for improved treatment. Where science had previously failed to develop safe and reliable weight management medications, likely owing to the limited body of evidence surrounding weight mechanisms, research has progressed rapidly over the past 20 years.<sup>18,24</sup> This has revealed hormones, neurochemicals and microbiomes that are directly related to weight changes,<sup>18,24</sup> which pharmaceutical agents may be able to target to aid patients in not only losing weight but also maintaining their weight loss.

## Pharmacotherapy for obesity

Currently, options for the pharmacological treatment of obesity remain limited. While some medications (i.e., bupropion/naltrexone combination and lorcaserin) await approval for weight management in Canada, two medications have been approved as a treatment option – orlistat and liraglutide.

Orlistat, which was approved by Health Canada in 1999, is currently recommended for weight reduction and maintenance in conjunction to lifestyle management.<sup>25</sup> Patients are instructed to take 120 mg during or up to 1 hour after meals, 3 times per day.<sup>25</sup> Several meta-analyses which

evaluated the efficacy of orlistat observed that patients taking orlistat lost 2.7 to 2.9 kg more than controls.<sup>26–28</sup> Patients who continued to take orlistat also appeared to maintain a greater amount of weight loss. A study by Sjöström et al<sup>29</sup> observed that when patients consumed a weight maintenance diet, those taking orlistat regained less weight than those who discontinued orlistat and those who remained on the placebo.

While orlistat does not target neurochemical and hormonal alterations, it aids patients in reducing their weight by blocking lipase activity which prevents approximately 30% of dietary fat from being broken down into free fatty acids.<sup>30</sup> Thus, rather than dietary fat being absorbed in the intestines it is excreted in feces. The mechanisms of action for orlistat likely contribute to its side-effects which are primarily gastro-intestinal in nature and include oily stools and fecal incontinence.<sup>25</sup> These side-effects can result in the discontinuation of orlistat, with the results of a meta-analysis suggesting that patients prescribed orlistat are 1.59 times more likely to withdraw from the intervention than those taking the placebo.<sup>31</sup>

The newest addition to pharmacological weight loss medications in Canada, liraglutide 3 mg, was approved for use in August 2015.<sup>32</sup> As the prescription of liraglutide as a weight management therapy is relatively new, there are no meta-analyses that examine the efficacy of this medication at its clinical dose of 3 mg. Nonetheless, several large scale randomized control trials (RCTs) have demonstrated the efficacy of liraglutide 3 mg as an adjunct to lifestyle for weight management with patients losing 4.2 to 5.9 kg more than those taking the placebo.<sup>33–36</sup> Similar to orlistat, it appears that patients must continue taking liraglutide to maintain their weight loss. One study observed that patients who discontinued liraglutide for 12 weeks regained more weight (2.9%) than patients who continued taking (0.7%), or never took the medication (0.3%).<sup>35</sup> Further, Astrup et al<sup>33</sup> directly compared weight loss outcomes on liraglutide and orlistat, and observed that individuals taking liraglutide lost on average 3.0 kg more than those prescribed orlistat. This greater weight loss observed in patients taking liraglutide may in part be due to its mechanism of action. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor stimulator. GLP-1, which is naturally secreted by the body when glucose or fat is ingested, binds to receptors in the hypothalamus resulting in the suppression of appetite<sup>37</sup> and a reduction in gastric emptying.<sup>38</sup> Thus, unlike orlistat which just prevents the absorption of food once consumed, liraglutide works to prevent patients from even consuming these calories in the first place.

Reports of side-effects from RCTs suggest patients taking liraglutide tend to experience side-effects that are gastro-intestinal in nature, such as nausea and vomiting.<sup>33–35</sup> However, these side-effects tend to be transient in nature and can be mitigated by a slow dose titration.<sup>39</sup> When directly comparing rates of side-effects in patients taking liraglutide and orlistat, Astrup et al<sup>39</sup> observed that those taking liraglutide experienced more minor (94.6%) and severe (1.0%) adverse events than those taking orlistat (minor: 85.3%, severe: 0.0%). While a greater proportion of patients taking liraglutide withdrew from the trial due to side-effects (liraglutide: 5.4% versus orlistat: 3.2%) the overall withdrawal rate in the trial was greater in those taking orlistat (liraglutide: 12% versus orlistat: 17%).<sup>39</sup>

Liraglutide appears to be associated with greater improvements in metabolic health than orlistat in the only study to compare the two drugs head to head. Following a 20 week RCT where patients were randomized to receive liraglutide, orlistat, or placebo, patients taking liraglutide had greater improvements in fasting glucose, and hemoglobin A1c.<sup>39</sup> The liraglutide group also had a greater reduction in the prevalence of metabolic syndrome and prediabetes at follow-up than those randomized to orlistat.

## Emerging anti-obesity medications in Canada

Currently, there are two other weight management medications that are approved for use in the US and are pending approval with Health Canada: a bupropion/naltrexone combination and lorcaserin. Bupropion and naltrexone are currently approved in Canada as a monotherapy for depression/smoking cessation,<sup>40</sup> and the treatment of opioid/alcohol dependence,<sup>41</sup> respectively. The combination medication is thought to decrease weight by stimulating the release of anorexic hormones from the hypothalamus while simultaneously inhibiting the release of hormones which would counteract these effects.<sup>42</sup> Lorcaserin, which is a selective serotonin receptor agonist, is also thought to activate receptors in the hypothalamus, which results in increased satiety.<sup>43</sup>

Several RCTs have examined the efficacy of these medications for weight management and suggest that both of these agents are associated with significantly greater weight loss than taking a placebo.<sup>44–47</sup> The results of the phase 3 clinical trials indicate that the bupropion/naltrexone combination results in a 8.1% total weight loss<sup>45</sup> and 5.8% total weight loss for lorcaserin.<sup>46</sup> While adverse events were reported for both medications, these side-effects were generally considered minor and were not associated with patients discontinuing the intervention.<sup>45,46</sup>

## Barriers to the prescription of medications for weight management

As we cautiously yet optimistically embark on a new horizon of obesity treatment, additional reforms in the framework of obesity medicine and research are warranted. First, it has become clear that the majority of health care professionals (HCPs) lack the resources and/or knowledge to provide meaningful and adequate obesity treatment to their patients.<sup>48</sup> Lack of appropriate training, and significant adverse effects of previously failed or withdrawn anti-obesity drugs may result in HCPs being reluctant to prescribe medications for treatment. HCPs must be receptive to supplementary training on obesity science and stay current with the latest findings in obesity research. Organizations such as the American Board of Obesity Medicine and the Canadian Obesity Network are available resources to cater to these needs.

In recognition of the Canadian Medical Association's designation of obesity as a disease, individual HCPs should follow through on acknowledging obesity in the same manner as other chronic diseases by embracing effective treatments, such as surgery and pharmacotherapy. Further, research advancements on patients living with obesity should be conducted to target populations who will respond most favorably to a certain obesity medication. Essentially, we have to be open to a new and diverse generation of safe and effective anti-obesity medications that cater to different predictors of obesity to provide the highest quality of care available. Finally, long-term research and surveillance is necessary to assess the durability of these medications, and to detect potential adverse effects.

## Conclusion

Rates of obesity continue to increase within Canada and abroad, yet there remains insufficient prevention and treatment options. Behavioral modification, which is the cornerstone of weight management, has had limited success when used on its own. While bariatric surgery remains the most effective treatment for obesity, it is not scalable and is considered risky and too invasive by many patients and HCPs. Thus, the need for effective and low risk pharmacological treatments is paramount. Currently, Canada has approved orlistat and liraglutide 3 mg for weight management, with two more medications awaiting approval. It is time for HCPs, patients, and all stakeholders to learn from recent scientific and clinical findings in obesity research, and start using pharmacotherapy appropriately. By avoiding the evidence, it will ensure we continue to remain in the dark.

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## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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