REVIEW

Medications that cause weight gain and alternatives in Canada: a narrative review

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Background: The cause of the obesity epidemic is multifactorial, but may, in part, be related to medication-induced weight gain. While clinicians may strive to do their best to select pharmacotherapy(ies) that has the least negative impact on weight, the literature regarding the weight effects of medication is often limited and devoid of alternative therapies.

Results: Antipsychotics, antidepressants, antihyperglycemics, antihypertensives and corticosteroids all contain medications that were associated with significant weight gain. However, there are several medication alternatives within the majority of these classes associated with weight neutral or even weight loss effects. Further, while not all of the classes of medication examined in this review have weight-favorable alternatives, there exist many other tools to mitigate weight gain associated with medication use, such as changes in dosing, medication delivery or the use of adjunctive therapies.

Conclusion: Medication-induced weight gain can be frustrating for both the patient and the clinician. As the use of pharmaceuticals continues to increase, it is pertinent for clinicians to consider the weight effects of medications prior to prescribing or in the course of treatment. In the case where it is not feasible to make changes to medication, adjunctive therapies should be considered.

Keywords: weight gain, weight loss, weight neutral, adverse effects of medications, obesity, adjunctive therapy

Introduction

Worldwide, rates of obesity continue to rise, resulting in concurrent increases in metabolic disorders, such as type 2 diabetes and hypertension, which often require pharmacotherapy. This poses a major public health concern. Interestingly, close to 50% of North Americans will have taken a medication for a therapeutic purpose in the last 30 days.[1,2] While pharmacotherapy is meant to be used for improving medical conditions, medications can be associated with a wide variety of adverse effects, including weight gain.[1,3] This has tremendous consequences as excess weight is associated with worse health outcomes which can result in medication nonadherence in patients. Given these potentially poor outcomes combined with the global obesity crisis, it is important that clinicians consider the weight effects of medications.

There are several clinical guidelines that categorize medications as those that promote weight loss, weight gain or have weight neutral effects. However, inconsistencies exist when defining the weight effects of medication. Further, existing weight estimates are sparse, which makes it challenging for clinicians to recommend medications while

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considering the weight effects. This can result in weight-related side effects of prescription medications being overlooked. Lastly, recently, some reviews have been published which examine the weight effect of medication.[4,5] However, similar to clinical guidelines, they are either devoid of or only provide estimates for some of the medications discussed. Thus, this paper will provide a comprehensive overview of the medications associated with weight change and suggest pharmaceutical substitutions to promote a more favorable body weight response. Medication classes were selected based on their use in prevalent medical conditions that are complications or comorbidities of obesity.

Classes of medications
Antipsychotics and mood stabilizers
Psychopathologies are tightly linked with weight changes.[6–9] Patients with mental health disorders are two to three times more likely to develop obesity than the general population.[10] A review examining psychiatric medication effect on weight suggests that over the course of treatment, ~70% of patients will experience some weight gain.[6] A list of commonly used antipsychotics and their weight effects can be found in Table 1.

Medications for schizophrenia are known to result in significant weight gain. Clozapine- and olanzapine-treated patients can gain on average 4.5–16.2[11,13] and 3.6–10.2 kg,[5,13–16] respectively. Nonetheless, there is considerable variability in the proportion of individuals that will experience

weight gain. Studies report that, on average, 29%–89%[11,12] of patients receiving clozapine will gain some weight and 8%–37% of patients taking olanzapine will gain ≥7% of their body weight.[15,17]

Aside from clozapine and olanzapine, commonly prescribed medications for schizophrenia such as chlorpromazine (0.6–15.9 kg[18,20]), quetiapine (−1.5 to +4.1 kg[20,22]), haloperidol (−0.1 to +4.0 kg[20,23,24]), sertindole (0.5–2.9 kg[13,20,25]), iloperidone (0.6–2.5 kg[20,24,26]) and risperidone (0.4–2.1 kg[13,20,24]) are also reported to elicit significant weight gain. Conversely, the use of paliperidone (−1.3 to +1.9 kg[20,26,27]), lurasidone (0.1–0.9 kg[20,26,28]), ziprasidone (−1.1 to 0.1 kg[13,16,20]) and aripiprazole (−1.4 to +0.2 kg[15,20,29]) is associated with the least amount of weight gain among medications for schizophrenia, and thus, may be a more weight-favorable alternative.

Lithium is commonly prescribed for the treatment of bipolar disorder and has been associated with lesser, yet relevant weight gain (1.1–9.9 kg[30,33]). Additionally, valproic acid, a second-line treatment option for bipolar disorder, is also associated with significant gain in weight (0.7–6.9 kg[34,36]), albeit slightly lesser than reported with lithium. Conversely, lamotrigine (−4.2 to +0.6 kg[32,34,36]) and carbamazepine (−3.1 to +0.4 kg[33,34,37]), mood stabilizers used in the treatment of epilepsy and bipolar disorder, are associated with weight neutral to weight loss properties and may be used in lieu of lithium or valproic acid as a more favorable weight alternative medication.

Antidepressants
Antidepressants consistently have a lower weight gain potential when compared to antipsychotics. However, antidepressants may carry a greater weight gain burden globally as they are prescribed more frequently than antipsychotics.[38] There are five classes of antidepressants – tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors and atypicals. Information on the weight effects of the five classes of antidepressants can be found in Table 2.

TCAs have been prescribed since the 1950s and are reported to elicit the greatest weight gain among antidepressants. Amitriptyline (0.4–7.3 kg[5,39,42]) and nortriptyline (0.3–4.1 kg[39,40,42]) appear to be associated with the greatest amount of weight gain for these types of antidepressants. Other TCAs, such as desipramine (−0.9 to +2.0 kg[40,41,43]), imipramine (+0.6–1.8 kg[39,44,45]) and doxepin (0.0–2.7 kg[46,49]) are associated with more weight neutral effects. Lastly,

Table 1 Treatment-emergent weight changes associated with antipsychotics and mood stabilizers

Drug name	Weight effect
Aripiprazole[15,20,29]	−[a]
Carbamazepine[33,34,37,b]	− −[a]
Chlorpromazine[18–20]	+ +
Clozapine[11–13]	+ +[a]
Haloperidol[20,23,24]	+ +[a]
Iloperidone[20,24,26]	+[a]
Lamotrigine[32,34,36,b]	− −[a]
Lithium[30–33]	+ +
Lurasidone[20,26,28]	Neutral
Olanzapine[5,13–16]	+ +[a]
Paliperidone[20,26,27]	+ & −[a]
Quetiapine[20–22]	+ + & −
Risperidone[13,20,24]	+[a]
Sertindole[13,20,25]	+[a]
Valproic acid[34–36,b]	+ +[a]
Ziprasidone[13,16,20]	−[a]

Notes: +=>1 kg. Neutral=±1 kg. −=<−1 kg. Additional + or − refers to >3 kg weight change. [a]Articles cited included ≥1 weight neutral estimate(s). [b]Anticonvulsant and mood stabilizer.

Table 2 Treatment-emergent weight changes associated with antidepressants

Drug name	Weight effect
Atypical	
Bupropion (norepinephrine–dopamine reuptake inhibitor)[5,42,47,51,66]	−[a]
Mirtazapine (noradrenergic and specific serotonergic)[5,42,71,72]	+[a]
Monoamine oxidase inhibitors	
Isocarboxazid[57,58]	−[a]
Phenelzine[45,49,54,55]	+ +[a]
Tranylcypromine[45,49,56]	+ +[a]
Selective serotonin reuptake inhibitor	
Citalopram[42,59–61]	+ +[a]
Escitalopram[42,60,64]	+[a]
Fluoxetine[5,41–43,48,50,61]	−[a]
Fluvoxamine[61–63]	+ & − −[a]
Paroxetine[42,61,65]	+[a]
Sertraline[42,61,66,67]	−[a]
Serotonin–norepinephrine reuptake inhibitor	
Desvenlafaxine[68–70]	+ & −[a]
Duloxetine[42,64,65]	+[a]
Venlafaxine[42,52,71,72]	+ & −[a]
Tricyclic antidepressant	
Amitriptyline[5,39–42]	+ +[a]
Desipramine[40,41,43]	+[a]
Doxepin[46–49]	+[a]
Imipramine[39,44,45]	+[a]
Nortriptyline[39,40,42]	+ +[a]
Trazodone[50–52]	−[a]

Notes: +=>1 kg. Neutral=±1 kg. −=<−1 kg. Additional + or − refers to ≥3 kg weight change. [a]Articles cited included ≥1 weight neutral estimate(s).

trazodone (−1.2 to +0.9 kg[50,52]) may have the most favorable weight profiles of all TCAs as a few studies have observed small amounts of weight loss with its use.

Studies consistently report that of the MAOIs, phenelzine elicits the greatest amount of weight gain.[53] While several studies compare the use of phenelzine with other classes of antidepressants, there are only a few studies which adequately report on weight. Some studies[45,54] report weight outcomes as no significant change with no weight estimate provided, while other studies examine weight gain as a side effect of phenelzine, but only report mean changes in the subpopulation experiencing these side effects, or based on a threshold. For example, one study observed a mean weight gain of 9.1 kg in 6 of 14 patients taking phenelzine[55] and another reported a 6.8 kg weight gain in 11 of 141 patients.[49] Conversely, tranylcypromine appears to have a more favorable weight change profile and is associated with lesser to no weight changes (0.0–4.1 kg[45,49,56]) in users. Additionally, isocarboxazid is reported to cause minor weight gain and even weight loss

(−2.6 to +0.8 kg[57,58]), and may be used as a more favorable weight alternative when the use of MAOIs is indicated.

Citalopram (−0.1 to +7.1 kg[42,59,61]) is associated with the greatest amount of weight gain and fluvoxamine (−3.5 to +1.7 kg[61,63]) with the greatest amount of weight loss for SSRIs. However, in contrast to TCAs and MAOIs, other commonly prescribed SSRIs appear to be relatively weight neutral. Escitalopram (−0.1 to +1.83 kg[42,60,64]), paroxetine (+0.1 to 1.7 kg[42,61,65]), sertraline (−1.6 to +1.0 kg[42,61,66,67]) and fluoxetine (−1.3 to +0.5 kg[5,41,43,48,50,61]) are all associated with weight changes of around ±2.0 kg. Thus, weight neutral SSRIs such as fluoxetine or sertraline or those that have a trend toward weight loss, such as fluvoxamine, may be used as an alternative to citalopram. Comparatively, serotonin–norepinephrine reuptake inhibitors are often weight neutral and include agents such as duloxetine (−0.5 to +1.1 kg[42,64,65]), desvenlafaxine (−1.3 to +1.3 kg[68,70]) and venlafaxine (−1.4 to +1.2 kg[42,52,71,72]).

Atypical antidepressants are newer medications with distinct mechanisms from other classes of antidepressants. Mirtazapine is a used atypical antidepressant which is associated with a mean weight gain of 0.4–2.4 kg,[5,42,71,72] while bupropion is associated with mean losses of 0.4 to 2.4 kg[5,42,47,51,66] and is commonly used as a substitute for some SSRIs.[18,19] Further, owing to the weight loss attributed to bupropion, it has been combined with naltrexone and approved as a weight management medication (Contrave®; Valeant, Bridgewater Township, New Jersey, USA). Additional information on Contrave can be found in the "Considerations for pharmaceutical treatment" section.

Antihyperglycemics

There is a high prevalence of comorbid obesity and diabetes, with over 80% of patients who have type 2 diabetes also having obesity. Metformin is a first-line treatment option for type 2 diabetes[73] and is associated with favorable weight outcomes. Weight loss is reported as a known side effect of this medication,[74] with average decreases of 1.0–2.9 kg[5,75,78] (Table 3).

Alternative treatment options for patients with type 2 diabetes include thiazolidinediones. These medications carry a lower risk of hypoglycemia than other antihyperglycemic medications as they lower the blood sugar by making the body more sensitive to insulin rather than by increasing the production. However, thiazolidinediones are associated with the most weight gain of antihyperglycemics, second only to insulin. Pioglitazone and rosiglitazone are associated with gains in weight of 2–3.9[5,79,81] and 1.2–5.3 kg,[78,82,83] respectively.

Table 3 Treatment-emergent weight changes associated with antihyperglycemics

Drug name	Weight effect
α-glucosidase inhibitors	
Acarbose[5,77,87,105]	–[a]
Glucagon-like peptide 1 receptor	
Exenatide[5,100,108,109]	– –
Liraglutide[5,91,102]	– –
Inhibitors of dipeptidyl peptidate-4	
Alogliptin[97–100]	Neutral
Linagliptin[90,100,106,107]	–[a]
Saxagliptin[100,103–105]	–[a]
Sitagliptin[100–103]	–[a]
Insulin[85,86,88,118]	+ +[a]
Insulin secretagogues	
Meglitinides	
Nateglinide[5,95,96]	Neutral
Repaglinide[79,89,109,a]	+[a]
Sulfonylurea drugs	
Chlorpropamide[84–86]	+ +
Gliclazide[75,80,94]	+ +[a]
Glimepiride[5,90–93]	+ & –[a]
Glyburide[78,88,89]	+ +[a]
Tolbutamide[5,76,87]	++
Insulin sensitizers	
Biguanides	
Metformin[5,75–78]	–
Thiazolidinedione	
Pioglitazone[5,79–81]	+ +
Rosiglitazone[78,82,83]	+ +
SGLT2 inhibitors (or gliflozin)	
Canagliflozin[93,110,111]	– –
Dapagliflozin[112–114]	– –[a]
Empagliflozin[115–117]	–

Notes: +=>1 kg. Neutral=±1 kg. –=<–1 kg. Additional + or – refers to ≥3 kg weight change. [a]Articles cited included ≥1 weight neutral estimate(s).

Insulin secretagogues are another alternative treatment option for diabetes. Sulfonylurea drugs such as chlorpropamide and tolbutamide are associated with weight gains of 2.6–5.3[84,86] and 1.6–2.8 kg,[5,76,87] respectively. This side effect associated with taking these medications may be why other more weight neutral sulfonylureas, such as glyburide (–0.9 to +1.6 kg[78,88,89]), glimepiride (–1.4 to +1.2 kg[90,93]) and gliclazide (–1.0 to +0.8 kg[75,94]), are more frequently prescribed. It is important to note that patients who are given sulfonylureas as a first-line treatment regimen may experience greater weight gain. More pronounced gains of 3.6[89] and 4.2 kg[80] have been reported in patients prescribed glyburide and gliclazide as the first-line diabetes treatment, respectively. Other insulin secretagogues, such as meglitinides, are associated a lower risk of hypoglycemia and may be a more weight-favorable

alternative than sulfonylurea drugs. Indeed, repaglinide and nateglinide are associated with weight neutral to lesser weight gain properties, with changes of –0.2 to +1.8[79,89,95] and 0.3–0.9 kg,[5,95,96] respectively.

Inhibitors of dipeptidyl peptidate-4 (DPP-4) are essentially weight neutral and include alogliptin, sitagliptin, saxagliptin and linagliptin. Alogliptin is the most weight neutral DDP-4 inhibitor and associated with a weight change of –0.9 to +0.7 kg.[97–100] Conversely, sitagliptin, saxagliptin and linagliptin are associated with modest weight losses ranging from 0.1 to –2.6,[100–103] 2.1 to 0.5[100,103–105] and 2.1 to 0.6 kg,[90,100,106,107] respectively. Acarbose, an α-glucosidase inhibitor, is limited in its use due to gastrointestinal side effects, but is associated with modest weight loss of 0.4–2.8 kg.[5,77,87,105]

Recently, there have been two new classes of diabetes medications that have made it to the market: glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose co-transporter 2 (SGLT-2) inhibitors with promising weight reduction properties. GLP-1s have been on the market slightly longer than SGLT-2 inhibitors. Unlike other antihyperglycemics, GLP-1R agonists are administered as an injection like insulin. Exenatide, a GLP-1 analog, is associated with weight loss ranging from 1.2 to 4.0 kg,[5,100,108,109] while liraglutide 1.8 mg is associated with slightly more modest weight loss of 1.7–3.4 kg.[5,91,102] Additional information on the use of liraglutide 3.0 mg as a weight management pharmaceutical (Saxenda®, Novo Nordisk A/S, Bagsværd, Denmark) can be found in the "Considerations for pharmaceutical treatment" section. In regards to SGLT-2 inhibitors, there are currently three approved medications in Canada that fall into this class of antihyperglycemic medication: canagliflozin, dapagliflozin and empaliflozin. Similar to GLP-1s, all of the approved medications in this class are associated with weight loss in clinical trials, with the greatest weight loss observed in patients taking canagliflozin (1.9–4.0 kg[93,110,111]), followed by dapagliflozin (1.0–4.5 kg[112,114]) and empaliflozin (1.5–2.9 kg[115,117]).

Weight gain is a well-known side effect of insulin and can range from 0.4 to 4.8 kg.[85,86,88,118] However, currently, insulin is the only treatment option for type 1 diabetics and is used for type 2 diabetics when they cannot tolerate or are not responsive to other hypoglycemics, which prevents the use of alternative treatments. There is considerable variability in the amount of weight gain associated with the use of insulin. Aside from genetics, other factors which can contribute to insulin-related weight gain, such as drug administration, dose and speed of release (rapid vs slow), can be manipulated to decrease the weight gain potential of this medication. For example, a study examining the weight and glycemic effects

of once a day insulin injection vs the use of an intermediate-acting insulin observed significantly greater weight gains in those using the intermediate compared to the once-daily insulin injection (+1.9 vs +0.4 kg) over a 6-month period.[118]

Antihypertensives

Hypertension is a prevalent condition among individuals with excess weight. In fact, gaining weight is associated with increases in both systolic and diastolic blood pressure.[119] Dietary changes and weight management are typical first-line treatments for hypertension,[120] and as such, medications which are associated with weight gain should be avoided. Fortunately, the majority of medications within this class appears to be weight neutral or associated with weight loss (Table 4).

Diuretics, more specifically hydrochlorothiazide, are associated with modest weight losses of 0.4–2.7 kg.[121–124]

Table 4 Treatment-emergent weight changes associated with antihypertensives

Drug name	Weight effect
Alpha-blockers	
Clonidine[155,156]	+[a]
Prazosin[157,158]	Neutral
ACE inhibitors	
Enalapril[131–133]	– –[a]
Lisinopril[124,137,138]	–[a]
Perindopril[134–136]	+ & – –[a]
Ramipril[139–141]	–[a]
ARBs	
Irbesartan[161,165,166]	Neutral
Losartan[131,163,164]	– –[a]
Olmesartan[161,162,165]	Neutral
Telmisartan[159–162]	–[a]
Valsartan[167–169]	+[a]
Beta-blockers	
Acebutolol[153,154]	Neutral
Atenolol[143–145]	+ +[a]
Metoprolol[148,149]	+[a]
Propranolol[146,147]	+[a]
Timolol[150–152]	–[a]
CCBs	
Amlodipine[170–172]	Neutral
Diltiazem[173–175]	+[a]
Direct renin inhibitors	
Aliskiren[176–178]	Neutral
Diuretics	
Chlorthalidone[122,125,126,a]	–[a]
Furosemide[122,123,130a]	– –
Hydrochlorothiazide[121–124,a]	–[a]
Indapamide[127–129,a]	–[a]

Notes: +=>1 kg. Neutral=±1 kg. –=<–1 kg. Additional + or – refers to ≥3 kg weight change. [a]Articles cited included ≥1 weight neutral estimate(s).
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

This is a consistent characteristic of this class of medication, with other commonly prescribed diuretics including chlorthalidone (−1.8 to 0.2 kg[122,125,126]), indapamide (−2.7 to 0.5 kg[127,129]) and furosemide (−4.1 to +0.3 kg[122,123,130]) being similarly associated with weight neutral to weight loss effects.

Of the commonly prescribed angiotensin-converting enzyme inhibitors, enalapril (−3.0 to +0.4 kg[131,133]) and perindopril (−3.2 to +1.1 kg[134,136]) are associated with the greatest amount of weight loss. Lisinopril (−1.5 to 0.0 kg[124,137,138]) and ramipril (−1.5 to +1.0 kg[139,141]) may also be associated with weight loss, but appear to be more weight neutral.

Beta-blockers are typically associated with weight gain for the first few months of treatment, followed by a plateau. However, the amount of weight gain associated with beta-blockers is moderate and may not be clinically significant.[142] Of the commonly prescribed beta-blockers, atenolol (–0.5 to +3.4 kg[143,145]), propranolol (–0.5 to +2.3 kg[146,147]) and metoprolol (1.2–2.0 kg[148,149]) are associated with the highest weight gain. Conversely, timolol (–1.8 to +0.4 kg[150,152]) and acebutolol (–0.6 to 0.0 kg[153,154]) appear to be weight neutral and may even have some weight loss properties. For alpha-blockers, weight gain is not a commonly reported side effect. In general, changes in weight for alpha-blockers appear to be minor or nonexistent, with the average changes in weight following clonidine (0.4–1.4 kg[155,156]) and prazosin (0.0–0.5 kg[157,158]) being <1.5 kg.

Angiotensin II receptor blockers and calcium channel blockers are the second-line treatment options for hypertension that are commonly compared in efficacy trials. Of the most commonly used angiotensin II receptor blockers, telmisartan (–2.1 to +0.2 kg[159,162]) and losartan (−4.2 to –0.1 kg[131,163,164]) are associated with the greatest amount of weight loss. Olmesartan (–0.5 to +0.3 kg[161,162,165]) and irbesartan (–1.0 to +0.2 kg[161,165,166]) are associated with weight neutral effects and valsartan (0.6–2.4 kg[167,169]) is primarily weight neutral, but can be associated with modest weight gains. Conversely, the two most commonly used calcium channel blockers, amlodipine (–0.7 to +0.8 kg[170,172]) and diltiazem (–0.1 to +1.2 kg[173,175]), are relatively weight neutral with <1.5 kg weight changes on average.

In 2008, a new class of hypertension medications was approved for use in Canada, called direct renin inhibitors. Currently, aliskiren is the only medication within this class approved for use and appears to have weight neutral effects (0.0–1.0 kg[176,178]).

Corticosteroids

Corticosteroids including cortisone and other glucocorticosteroids can be used for the treatment of conditions such

as asthma, dermatological or inflammatory disorders and rheumatic or autoimmune diseases.[179] The short-term use of corticosteroids has not been shown to be associated with significant changes in body weight[180] (Table 5). Conversely, literature on the long-term usage (≥3 months) of corticosteroids suggests the opposite,[181] with prednisone (1.7–5.8 kg[182,184]), prednisolone (1.5–4.4 kg[185,186]) and cortisone (1.5–8.4 kg[187,189]) being associated with significant weight gains. Additionally, there is considerable variability in the amount of weight gain that patients will experience while taking this class of medication, with one study reporting weight gains of ≥10 kg in more than one-fifth of patients taking prednisone at 1 year.[182] Very few alternatives exist for the use of corticosteroids. However, changes in treatment regimen can be useful in reducing weight increases.[190] Alternate day dosing schedule for prednisone may be beneficial as it has been shown to attenuate weight gains and even promote weight loss.[190]

Considerations for pharmaceutical treatment

Improving clinical indicators and patient's health is paramount when selecting pharmaceutical treatment options and there are several factors that need to be taken into consideration. Given that weight gain is a commonly reported side effect for many medications, clinicians should strive to prescribe medication(s) with more favorable weight-related outcomes whenever clinically possible. With the overwhelming evidence of the health risk of excess weight and the association of gaining weight and nonadherence to medication, it is important to discuss and evaluate this potential side effect with the patient when prescribing a medication.

In order for fluctuations in weight to be monitored, baseline weight measurements should be taken prior to initiating a pharmaceutical treatment. A weight gain of >2.0 kg within a month, in the absence of health and lifestyle changes suggests that intervention may be necessary.[8] Prior to making changes to medication, changes to dietary and physical activity may be able to counteract the weight gaining effects of medications. Indeed, research

has suggested that individuals taking psychiatric medications that are associated with weight gain can still lose a clinically significant amount of weight by participating in a lifestyle intervention without the need to alter their medication.[191,192] If lifestyle changes alone do not result in the desired amount of weight loss, changes to medication should be considered. Where possible, changes to the dose or delivery of the medication should be attempted prior to medication substitution. When it is not feasible, clinicians should consider substituting medications. Fortunately, many of the medications examined in this review have more weight-favorable outcomes.

Once the decision has been made to change medications, clinicians should be cognizant to switch only one medication at a time, so that the effects on weight and medical efficacy can be appropriately evaluated.[190] A protocol highlighting clear instructions should be created for the patient to minimize the potential of withdrawal symptoms. When switching to a more weight-favorable medication, non-weight-related side effects must also be taken into consideration. For example, while bupropion is often recommended as an alternative therapy to other antidepressants due to its weight loss side effects, it is also associated with a risk of seizures. Further, cost is an important consideration as it can contribute to nonadherence. This may be the case with liraglutide 1.8 mg, which is associated with a better side effect and weight profile than other antihyperglycemic medications, but costs considerably more.

During the course of treatment, switching pharmacotherapies may not be feasible due to a variety of reasons such as cost and efficacy. In such cases, adjunctive therapies may be used to better manage treatment-induced weight gain. Currently, there are three medications approved for weight management in Canada. Orlistat, a lipase inhibitor, has been available since the 1970s and is associated with placebo-subtracted weight losses of 4.3 kg.[193] Unfortunately, the common side effects of this medication include oily and loose stools, which can ultimately lead to nonadherence and discontinuation. In comparison, liraglutide 3.0 mg, at a clinical dose of 3.0 mg, is also approved for weight management and has been associated with placebo-subtracted weight losses of 4.5–6.0 kg.[4,27] While there are beneficial effects such as improved HbA1c levels, there are some more severe rare side effects such as gallstones and pancreatitis.[194] In 2018, Health Canada approved Contrave, which is a combination medication of bupropion, an norepinephrine-dopamine reuptake inhibitor, and naltrexone, an opiate antagonist. Results of a Phase 3 clinical trial suggest that the use of Contrave, as an adjunct

Table 5 Treatment-emergent weight changes associated with corticosteroids

Drug name	Weight effect
Cortisone[187–189]	++
Prednisolone[185,186]	++
Prednisone[182–184]	++

Notes: +=>1 kg. Additional + refers to ≥3 kg weight change.

to a lifestyle intervention, results in superior weight loss to placebo (5.0%–6.1% vs 1.3%), but as with other weight management medications, nausea appears to be a common side effect.[195]

Where it is not possible to add an adjunctive therapy due to drug interactions or cost, patients should be made aware of the weight change potential, and research suggests that implementing lifestyle changes (ie, quality of diet and increased physical activity) may be beneficial to combat the weight gaining effects. For example, a study which compared metformin therapy alone and in addition to a lifestyle modification program observed greater weight loss in the group participating in the lifestyle modification (5.6 vs 2.1 kg[196]).

There are several limitations that warrant mentioning. Due to the number of pharmaceuticals approved for treatment worldwide, it is not possible to examine the weight effect of every agent. As such, this review is not an exhaustive list, rather it evaluates commonly used pharmaceuticals that have been approved for use in Canada. The effect of pharmaceutical medications on weight depends of a multitude of factors; thus, the associations in this paper need to be interpreted with caution. As population demographics have shifted dramatically in the last 30 years, findings of studies examined may be dated and may not be generalizable to the population today. Patient demographics are an important consideration because differences in age, sex, body mass index and so on may have a significant impact on the weight changes that occur. Specifically, the weight gains associated with lithium are more severe in patients with obesity than their lower-weight counterparts (6.1 kg obese vs 1.1 kg non-obese[32]). Conversely, the weight gains associated with olanzapine are lower with increasing body mass index.[197] Further, this paper provides the mean ranges of absolute weight change, which may be useful for interpreting the impact of medication on weight change. However, these ranges merely reflect the results of available studies, some of which have small sample sizes (ie, n<10) and may not be generalizable to a heterogeneous population. As studies differ in treatment duration, dose, concomitant medications and intervention type, changes in weight observed in clinical practice may be different from the results presented here. For example, the duration of treatment has a significant impact on the weight outcome of patients for some medications. In one study, patients plateaued after 37 weeks of olanzapine treatment,[197] while another study observed that patients taking clozapine may persist in gaining weight after 46 months.[198] Given that weight gain is a complex and multifactorial issue, it may be possible that other factors contribute to the reported weight changes. Several of the studies examined did not account for potential confounding factors such as lifestyle changes. This may be especially pertinent in the case with glucocorticoids, where the results from a recent systematic review suggest that dietary intake is infrequently reported, making it difficult to assess weight changes.[179] However, as the course of pharmaceutical treatment does not occur independently of side effects such as weight gain, the estimates reported are still relevant to clinical practice.

Conclusion

Medication-induced weight gain can be frustrating for both patients and health care professionals. The increased use of pharmaceuticals in the past decade may, in part, contribute to the increasing rates of overweight and obesity globally. Excess weight has been shown to result in the development of many of the diseases treated by medications and to be associated with worse treatment outcomes. Further, due to the obesogenic effects of many pharmacotherapies, and poor long-term success in weight loss interventions, the assessment of the weight gain potential associated with medicinal treatment is of particular importance for individuals who already are overweight or obese and in patients with chronic disease.

This paper provides considerable options for selecting medications and summarizes the available literature on the effects of these common medications on weight change. Clinicians should select medications associated with more favorable weight profiles when first initiating treatment, or consider changing medications if patients are experiencing the weight gaining side effects, if clinically possible. When it is not feasible to change medications, adjunctive therapies or lifestyle intervention may help to combat weight gaining side effects.

Disclosure

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