

## Intro

- CB: Hello and welcome back to The Med Thread where we discuss and relate, drugs and medications to history, society, and culture. I'm Cathy,
- MC: And I'm Mike
- CB: And today we're telling the story of weight loss, why there are hundreds of products out there for it, and our obsession with losing a lot in a short amount of time.
- MC: We're tackling the concept of using a silver bullet to lose weight and how the medications we had in the past work and what's different about the ones today.
- CB: Let's talk about what we mean by obesity up front. The Canadian Obesity Network defines obesity as is a progressive chronic condition characterized by abnormal or excessive fat accumulation that impairs health. It should be diagnosed by a qualified health professional using clinical tests and measures that assess health, not size.
- MC: Everyone has a different idea of what they're ideal body weight is, but obesity is often defined by BMI, or body mass index, which takes into account weight, height and sex. BMI is considered normal in the range of 18.5-24.9, overweight is 25-29.9 and obesity is defined by a BMI  $\geq 30$ . There is also another scale, called the Edmonton Obesity Staging System (EOSS) but I won't go into detail, we can provide a link in the show notes.  
(<http://www.drsharma.ca/wp-content/uploads/edmonton-obesity-staging-system-staging-tool.pdf>)
- CB: The BMI scale is controversial as it doesn't take into consideration percentage of body fat. It is a quick and simple tool to use but it isn't the only consideration. A true diagnosis of obesity should be designated by a healthcare provider who takes into account overall health and body fat composition. For example, younger adults tend to have less body fat compared to older adults at the same BMI. Also, muscular individuals will have high BMI due to their weight but very low body fat.
- MC: We commonly hear that there is an obesity crisis in North America, but how many people in Canada are considered either overweight or obese?
- CB: It is certainly affecting a lot of Canadians, millions in fact. 2/3 of Canadian men and over 1/2 of Canadian women are overweight or obese, which makes it a major public health priority.
- MC: There are a few reasons why obesity is considered a health priority, we know it is particularly burdensome in many respects. It is the leading cause of type 2 diabetes, and a major factor in high blood pressure, heart disease, stroke, arthritis, cancer and other health problems.
- CB: And don't forget that it is also a leading cause of non-alcoholic liver disease, sleep apnea, and osteoarthritis and back pain.  
(*Canadian Task Force on Preventive Health Care, 2015*)

- MC: There's also significant social stigma that surrounds obesity and weight bias is associated with inequities in employment, healthcare and education.
- CB: There is definitely a negative impact on quality of life. People who are obese were more likely to report poor physical health, mental health and activity limitations and BMI is a strong predictor of overall mortality.  
*(Prospective Studies Collaboration, 2009)*
- MC: And it isn't a simple cause and effect condition. There are a lot of different factors that have an effect on metabolism, energy input and expenditure including age, gender, genetics, hormones, skeletal muscle, and medications.
- CB: Energy requirements decrease with age as metabolism drops, the metabolic rate is estimated to drop each decade by 150 kcal/day. I'm definitely noticing that, having recently tried on my snowpants from a decade ago and not being able to get them on, despite not having any big changes in my diet.
- MC: I think we've all noticed this at some point and remember, females also have about a 20% lower metabolic rate than men. Part of this is likely due to hormonal differences as we know hormones play a role in our weight.
- CB: Genetics are a big player too; approx. 45-75% of the inter-individual variation in BMI is due to heritable factors.  
*(Sharma, 2010)*
- MC: And don't forget medications; drugs that affect hormones can affect weight, and there are others like beta-blockers which reduce metabolic rate and stimulants which increase it.
- CB: Also, the more muscle mass you have the higher energy requirements you have, meaning a higher basal metabolic rate. Conditions that result in muscle wasting can lead to weight gain.
- MC: Even our proximity to processed foods can increase our weight. As you can imagine, if we are closer to fast food outlets this can promote the overconsumption of calorie-dense, nutrition-poor foods.  
*(Sharma, 2010)*
- CB: Oh for sure! And a lot of the time, the healthy foods are unaffordable and much more costly than the \$2 menu at the local fast food joint.
- MC: With so many factors contributing to obesity it is important we, as clinicians, see the big picture and provide people with real-life recommendations and advice when it comes to weight loss.
- CB: Definitely, and it's important to set reasonable expectations for weight loss. Having unrealistic expectations that rely on willpower alone can lead to disappointment and frustration if they don't succeed. Setting SMART goals is important.
- MC: SMART is a mnemonic often used in goal-setting that stands for specific, measurable, attainable, [realistic], and timely. For example, a 10 lb weight loss goal over 3 months.

- CB: Motivational interviewing can be really powerful in helping patients gain perspective on their obesity and their motivation to change. Asking a patient what they believe to be the barriers and enablers in their weight management journey is key to help them address challenges and to embrace success.
- MC: It is important to note that we don't need big dramatic changes in to make a difference. A modest weight loss of 5-10% of body weight has a significant impact on health.
- CB: So in the theme of our podcast, how did we get here? What have we used to treat obesity in the past, and where are we now?
- MC: Let's dive into the medications used, and where we started historically.

## History

- CB: The history of diet aids, or medications used to help people lose weight, is an interesting one. The most disturbing treatment I came across was tapeworms. There are reports that some people used to purposely ingest tapeworms to decrease the amount of calories absorbed and to lose weight. The book *Seabiscuit: An American Legend* by Laura Hillenbrand references jockeys using tapeworms to stay slim for the racetrack. I think this just shows people will go to extreme measures for weight loss.
- MC: Hopefully we don't see patients resorting to this in this day and age! Last season we talked about stimulants and in particular, amphetamines as study aids. One of the other uses for amphetamines such as phentermine was to lose weight, a popular practice in the 50s and 60. It did this in two ways, first by decreasing appetite and second by speeding up our body's metabolism. Unsurprisingly, these drugs, had bad cardiovascular side effects and several of them have been taken off the market in Canada. However, some of these products are still marketed in other parts of the world.
- CB: A similar drug that really should not be used for weight loss and is ephedra or ephedrine, which also increases metabolism and suppresses appetite. Similarly to amphetamines it also comes with a number of cardiovascular side effects, including increasing stroke risk. This prompted Canadian and US regulators to put restrictions and ban its use for weight loss.
- MC: There were a number of weight loss drugs approved in the years after amphetamine-based ones were no longer used. They targeted other neurotransmitters, such as the serotonin and the cannabinoid system.  
*(Rodgers, 2012)*
- CB: We know that serotonin plays a role in regulating diet, and one aspect that was interesting to scientists was its relationship with carbohydrate cravings. More serotonin seemed to decrease carbohydrate cravings and so a drug called fenfluramine was made and marketed and it does just that, it increases serotonin neurotransmission in the brain. Unfortunately, this one was associated with heart valve and blood pressure side effects, and it was taken off the market.  
*(Wurtman, 1986)*

MC: We also talked about cannabis last year and how it was used as an appetite stimulant for some patients. Well, the reverse could make sense and blocking the cannabinoid receptors could decrease appetite. The drug rimonabant, was born and this was marketed for obesity. Unfortunately, this one was taken off the market too because of bad neuropsychiatric effects like aggression or suicidal thoughts.

CB: It seems like each time we learn about what controls hunger, digestion, or metabolism, there is a tendency to consider those as targets for weight loss drugs.  
*(Rodgers, 2012; Wharton 2017)*

MC: That's true, capitalizing on weight gain as a side effect of drugs has led to development of other drugs that do the reverse! Just last year, a new drug called lorcaserin was touted by the media and scientists as a holy grail for weight loss. It acts by targeting a specific serotonin receptor in the brain, increasing satiety. Unfortunately, when you look a little closer, just under 40% of obese patients on the medication had at least 5% weight loss after a year. And even more important is that 17% of patients who got the placebo, also lost that much weight!  
*(Bohula, 2018; <https://globalnews.ca/news/4414557/weight-loss-drug-approved>)*

CB: And that's not all! We won't get into this in much detail, but last I checked, there were over 100 natural health products that claim to be appropriate for weight loss. Common ones are green tea or coffee extracts, apple cider vinegar, flaxseed, but also things like carnitine, conjugated linoleic acid or thyroid pills. I also remember seeing an episode of Dr. Oz which touted raspberry ketones, another natural product, as a 'miracle fat burner'. Overall, the idea is the same, these work either to decrease appetite or speed up the body's metabolism, but many don't have the evidence to support their use. Despite this, you can find these at your local pharmacy among with the multitude of dieting foods and meal replacements. And remember ephedra? You can still find that in products indicated as decongestants and in non-approved natural health products.  
*(Natural Medicines, 2019 – Obesity indication search)*

MC: There are lots of different therapies, but what do we recommend as pharmacists. Let's dive in to our current treatments.

### Current medications

MC: Treating obesity can help to control and improve arthritis, diabetes, sleep apnea, hypertension, and more. So what do we use to help our patients manage obesity?

CB: Canadian Clinical Practice Guidelines suggest that health professionals utilize interdisciplinary teams for behavioural intervention, medically supervised weight-management programs with meal replacements, anti-obesity medications, and bariatric surgery. The guidelines stress that the diagnosis and treatment of obesity must be delivered in a supportive, non-judgemental, and interdisciplinary environment.  
*(Obesity Canada guidelines: <https://obesitycanada.ca/resources/clinical-guidelines>)*

MC: It may be hard to access all of those components, but as the most accessible healthcare provider we have a role to play. Let's focus on the anti-obesity medications because that's our specialty.

- CB: Absolutely! We have 3 medications with approved indications for weight loss and weight maintenance by Health Canada. These are orlistat, liraglutide and naltrexone/bupropion combination. These agents are recommended to help adults who are not attaining or who are unable to maintain clinically significant weight loss with dietary and exercise therapy alone.
- MC: Orlistat came first, with Health Canada approval in 1999. Liraglutide got its weight loss indication in 2015 and naltrexone/bupropion was approved most recently, in 2018.
- CB: Ok first up, Orlistat. This medication works by inhibiting gastric and pancreatic lipases and decreases the breakdown of fat into free fatty acids and monoglycerides. Basically this means less fat gets absorbed, fewer calories get consumed, and weight loss occurs. If taken three times daily it can reduce dietary fat intake by 30%.
- MC: You may be thinking, if the fat doesn't get absorbed, where does it go? Well, it gets carried through the gastrointestinal tract and the side effects are usually related to this. Main side effects are fecal urgency, fatty/oily stool, fecal incontinence, and some more.
- CB: I love when things make sense, and the side effects here totally make sense. The fat doesn't get absorbed and gets carried through to the feces. Orlistat also interacts with medications, in particular fat-soluble vitamins. Orlistat also blocks their absorption, so it is important to take a fat soluble vitamin with beta-carotene at least 2 hours before or after orlistat.
- MC: Other important drug interactions include warfarin, as it decreases absorption of Vitamin K, and anticonvulsants, levothyroxine, and oral contraceptives.
- CB: Let's talk about how effective this drug is. In clinical trials, 63-69% of patients on therapy lost greater than 5% of their initial body weight after one year and over 38% of patients had a greater than 10% weight loss.
- MC: It is important to note that this was in combination with a mildly hypocaloric diet which means a deficit of 500-800 calories per day and it's indicated in combination with a hypocaloric diet today.
- CB: And speaking of indication, orlistat, brand name Xenical, is indicated in obese patients with a BMI  $\geq 30$  or 27 in the presence of other risk factors for example, hypertension, type 2 diabetes, dyslipidemia, or excess visceral fat.
- MC: Ok so that is orlistat, what else do we have?
- CB: Next up is liraglutide.
- MC: Liraglutide was initially indicated for diabetes, under the brand name Victoza. It is a GLP-1 receptor agonist and helps to lower blood glucose. When used for weight management it is marketed under the brand name Saxenda.
- CB: We've touched on this before, one medication being marketed for two different indications under two different brand names, and this is another example of a medication being marketed for what was seen as a side effect originally.

- MC: Certainly. GLP-1 is a hormone that regulates appetite and food intake. It is present in several areas of the brain involved in appetite regulation and works to increase insulin release and decreases glucagon release.
- CB: When talking to patients, I say that GLP1 helps make you feel more full by acting on appetite centers in the brain and slowing stomach emptying. This explains some of the common side effects as well, like nausea, vomiting, and diarrhea.
- MC: And unlike with orlistat, there aren't as many clinically significant drug interactions for liraglutide but there are some drug interactions caused by the delay in gastric emptying that should be considered.
- CB: And how well does liraglutide work? Well, in clinical trials, patients lost approximately 4-7 kg and the proportion that achieved at least a 5% weight loss was greater than with the placebo group. The participants on liraglutide also showed a favorable impact on metabolic parameters.
- MC: Now for the last officially indicated medication, naltrexone/bupropion combination, brand name Contrave.
- CB: This is interesting to me. I prescribe bupropion sometimes when treating clients for smoking cessation and now we see it here, combined with naltrexone for weight loss! Naltrexone is an opioid antagonist used to treat alcohol and opioid dependence, and bupropion is an NDRI, or norepinephrine and dopamine reuptake inhibitor, used for depression and quitting smoking.
- MC: The mechanism of this combination isn't fully understood, but there's evidence that the drugs act on two separate areas of the brain that regulate food intake including the hypothalamus and mesolimbic dopamine circuit. This can influence food intake and decrease body weight.
- CB: Simply, it works to reduce hunger and control cravings. But of course this isn't without side effects. The most common I've seen in practice related to bupropion component are sweating and sleep disturbances, and the combination is known for nausea, constipation, dizziness, dry mouth and diarrhea.
- MC: Most of the drug interactions associated with this combination have to do with bupropion and its inhibition of an enzyme CYP2D6.
- CB: And since naltrexone is an antagonist of opioids it is important to wait 7-10 days after using an opioid to prevent withdrawal symptoms in those who are opioid dependant.
- MC: And of course, not to use opiates while on this medication, because they just won't work. In terms of its' efficacy, weight loss with this combination was show to be 5-6% higher when combined with behaviour modification, so this is another medication that is recommended with lifestyle changes. The range of patients that reported a greater than 5% weight loss was 45-56% in the clinical trials. One study showed the 60% of patients taking Contrave lost 5% or more body weight and kept it off for 56 weeks compared to just 23% of patients taking placebo.
- CB: That is a lot of info on just 3 drugs!

*(Additional therapeutics information available from DiPiro Pharmacotherapy or CPhA, Compendium of Therapeutic Choices, or Drug Product Monographs)*

## Drugs that increase weight

CB: Before we forget, let's talk about some drugs that can cause weight gain.

MC: As we mentioned, there are a number of medications that are used to treat other conditions but are associated with weight gain and it's important for our patients to know that, so that we can work together to prevent or lessen it.

CB: Starting from the head and brain, certain antipsychotics, such as olanzapine or risperidone can increase weight by up to 10 lbs. With antidepressants, the older tricyclic class, like amitriptyline, are more prone to do so, and the more recent SSRIs seemed to have variable effects on weight. And with antiepileptics and mood stabilizers, we know that drugs like lithium and valproic acid can increase weight.

MC: It's important to know that even though these medications are typically taken chronically, weight doesn't continually pile on and seems to max out at about the 10 lb mark.

CB: Moving down, we know that long term use of corticosteroids can increase weight, which is one of the reasons we don't want people using them too long unless it's necessary. And this applies to oral steroids, NOT inhaled steroids for asthma.

MC: Moving down a bit further, a few of the medications used for diabetes can cause weight gain as well. Insulin for one, does, and again it's up to around the 10 lb mark. Therefore, other drugs that increase insulin can do so as well, particularly the sulfonylureas like glyburide or gliclazide, which can increase weight by up to 5 lbs. And one that is less used now, pioglitazone can also increase weight by that amount about 10 lbs as well due to its effect on how fat is stored and metabolized by our bodies.

CB: Something that I see frequently is the weight gain associated with quitting smoking, but this is similar to that of the drugs, usually only 5-10 lbs and usually right at the beginning and it doesn't keep going. And there are many more drugs that affect weight, so I think the bottom line is that if you think a medication is causing you to gain weight, it's a good idea to talk to your pharmacist!  
*(Wharton, 2018)*

## How to help

CB: I find it difficult to bring up the issue of obesity with patients so I found it intriguing that the Canadian Obesity Network recommends that healthcare providers use the 5 A approach. Ask, Assess, Advise, Agree and Assist. This is already a familiar process as we use this all the time in the world of smoking cessation to assessing readiness to change that lifestyle behaviour, so this can be carried over into obesity management as well.

- MC: We will have a link to this approach on the website. It is important that we meet patients where they are and ensure they understand that the short-term 'quick-fix' solutions that are often portrayed in the media are generally not sustainable.
- CB: Our patients need to know that success in managing obesity will require sustainable treatment strategies which can be challenging and frustrating but will reap the benefits in the long run. We need to act proactively and recognize that obesity is a chronic disease and not just a poor lifestyle choice in order to break down barriers in treatment.
- MC: The success should be measured in improvements in health and well-being, not just the amount of weight lost. The Canadian Obesity Network has guiding principles of their framework and they outline that the focus should be on things like better quality-of-life, increased self-esteem, higher energy levels, improved overall health, prevention of further weight gain, modest weight loss or maintenance of the patient's best weight.
- CB: One of their other principles is that a patient's 'best' weight may never be an 'ideal' weight. Like we talked about, there are multiple factors at play when it comes to obesity. Setting unachievable targets will set the patient up for failure, they note to help patients set weight targets based on the best weight they can sustain while still enjoying their life and reaping the benefits of improved health.
- MC: Yes, I think it is clear that pharmacists certainly have a role to play in the management of obesity. And here's the kicker, these clinical trials are looking at groups of people or a controlled and fairly short time period and even then, as we've seen, not everyone responds to the medication. On top of that, the number of people who do respond isn't that high, hovering around 2/3 of people taking them. As more research is done on the science of obesity, the more complex our understanding of it gets and we have to be cautious about a one-size fits all approach, and be cautious of the products out there that boast quick and easy weight loss.
- CB: Most definitely. From answering questions about the countless over the counter products marketed for weight loss, to helping with diet-related questions, to assessing readiness for lifestyle changes and advising on health risks and treatment options. There are a lot of points where pharmacists can intervene to improve quality of life here.
- MC: Well that wraps up this episode of The Med Thread.
- CB: We hope we've opened your eyes, or should I say ears, to obesity and that you've learned something from us.
- MC: Speaking of learners, our next series of podcast episodes will highlight our students! They've put together some short soundbites on questions about medications that interest them and will talk about how they found answers for them.
- CB: Make sure you don't miss that! And as always, let us know what you think and leave us suggestions for future topics. You can reach us at [medthread@mun.ca](mailto:medthread@mun.ca) or through Facebook at MUN School of Pharmacy.
- MC: As always, thanks for listening!

CB: Catch us next time!

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