Quick Takes
A PODCAST BY PHYSICIANS FOR PHYSICIANS
HOSTED BY DR. DAVID GRATZER

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The semaglutide era? Considering medication-related weight gain

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[Musical intro]

David Gratzer: Celebrities use it, politicians discuss it. And hey, our patients ask about it. Glucagon-like peptide-1 receptor agonists. Think semaglutide and other drugs of this class are much discussed. They're relevant across health care, of course. Maybe they're particularly relevant in our field. After all, so many people with severe mental illness struggle with obesity, in part because the meds we prescribe them. So, is semaglutide a game changer? What to make of sister drugs? What are the opportunities and the challenges?

Well, that's our topic today here on *Quick Takes*, a podcast series by physicians for physicians. My name is Doctor David Gratzer. I'm a psychiatrist at CAMH and we're joined today by three guests. First is Doctor Mahavir Agarwal. He's a psychiatrist here, a clinician scientist in the schizophrenia division, and he's also medical head of the Metabolic Clinic. He does CIHR [Canadian Institutes of Health Research] funded research as well as receiving grants from other agencies. Lisa Schaffer is joining us. She has a lasting commitment to Obesity Canada, starting out as a volunteer. She is now the new-ish executive director of that organisation. A belated congratulations, by the way! And Doctor Sanjeev Sockalingam, who doesn't need too much of an introduction here. He's a returning guest, having been on several times before. He is the scientific director of Obesity Canada and hey, he's got a couple of jobs around here at CAMH, including being the senior vice president, education as well as the CMO. Welcome all.

Sanjeev Sockalingam: Happy to be here, Doctor Gratzer.

Lisa Schaffer / Mahavir Agarwal: Thank you.

David Gratzer: Doctor Agarwal. Maybe we'll start with you. You've just co-written a really smart piece in JAMA Psychiatry talking about this class of medications. What are some of the opportunities here?

Mahavir Agarwal: I'll go back to your introduction, Doctor Gratzer, as you describe the lack of surprise when you think about the presence or prevalence of obesity in our population. That that lack of surprise is driven by the fact that a large majority of our patients are overweight and obese. And like you correctly mentioned in part this is iatrogenic. Our drugs which help our patients feel better, think better, be better, also contribute to them developing these metabolic side effects. And for a while now we have not had good answers. We have some answers. We have drugs like metformin and probably topiramate that can help. But we don't have answers that are universally effective. And these class of drugs suddenly bring about an opportunity whereby if they were available to all, if they were accessible to all, and if they are proven to be safe for all, they represent a game changer and that suddenly metabolic side effects can be managed effectively to the point that perhaps they won't be a concern anymore. And so imagine this world where you have all the effects of antipsychotics, but none of the side effects. How would that world look like? What would be the consequences?

What would be the upsides of that world? And suddenly we are able to somewhat sort of imagine that this world is, you know, actually possible.

David Gratzer: It sounds like you're excited.

Mahavir Agarwal: Oh, I'm very excited! I'm cautiously optimistic also, because, you know, it's a new group of drugs and there's so much we don't know yet. But this presents enormous potential, if not for the fact that it shows that this problem is addressable and addressable pharmacologically. And so it opens a new avenue of intervention. And I love solutions. So, this is a possible one.

David Gratzer: Doctor Sockalingam, of course you wear different hats. But speaking recently to *The Globe and Mail*, you've talked about the promise of this class, but you've also talked about some of the challenges, including with access. Do you want to comment?

Sanjeev Sockalingam: Yeah, I too share Doctor Agarwal's hope and optimism for the future. I'll just situate it by saying, you know, if you recall, we've designated obesity as a chronic disease in medicine, right? The American Medical Association and then the Canadian Medical Association since 2013 have adopted this. We haven't had much progress, though, in terms of treatments and our treatments across three pillars. So, we're going to talk about obesity medications like semaglutide, but we also have metabolic and bariatric surgery and also behavioural interventions. And so you know, the promise of this new class of medication is the early evidence that we know of its effect and impact and actually meaningful weight loss, but also help with, as Doctor Agarwal talked about, broader metabolic effects and health outcomes like sleep apnea, diabetes, diabetes prevention, cardiovascular disease and so on. The caution and the challenge is we have these treatments available and approved, but not everyone can access them. And I think particularly for people that we see in our clinical practice here at CAMH, for example, who probably are more often than not having challenges with working full time, having insurance coverage, um, are on social assistance, maybe precariously housed, access to GLP-1 agonists is quite costly and not covered under these insurance and the like. And so we have a lot to do about increasing access, despite there being hope and optimism about the effect of these medications.

David Gratzer: Ms. Schaffer, let me bring you in at this point in time. Two thirds of our guests are cautiously optimistic. Where are you sitting?

Lisa Schaffer: I will join them in that cautiously optimistic vote, for sure. I think it's a really interesting time. I think it's a very exciting time but I am concerned that we might be getting a little ahead of our skis in a more cultural narrative space, and that really, we're missing a big part of the conversation that needs to happen where we're really recognising obesity as a chronic disease that's going to require a continuum of care and maybe, you know, a more complex conversation than just here's a solution that we finally have that we didn't have before. I think there's a lot more in the conversation that needs to happen.

David Gratzer: And of course, you've spoken before about your lived experience. You don't speak on behalf of all patients in Canada, but what are your thoughts from that perspective?

Lisa Schaffer: From that perspective – I appreciate that you're kind of delineating the two worlds for me as well – because from that perspective, I can say this feels so exciting. This feels so optimistic in a place where people haven't had a lot of optimism before. So that's really exciting. I really wish for all patients that we can really solve some of these bigger concerns about access. But I also really want us to tuck in and do some work on what do we need to change systemically and from a policy level to support this, not just being a moment where everybody feels like they are having success because they're seeing weight loss, when we know that there are many other measures of success that people should be concerned about quite frankly, and that we hope people can start having healthier conversations about. So, it's really this moment of optimism, but I really hope we have the courage to stick in it and that we have the right conversations that go along with it. Because I often describe there's lots of tentacles when we're talking about the disease of obesity.

David Gratzer: Let me circle back to you, Doctor Agarwal. Let's look at things from a concrete perspective. So many doctors who would be listening, what would you think about in terms of a history that would lead you towards prescribing one of these medications? Which medication might you think about prescribing? What would be an opening dose?

Mahavir Agarwal: Well, that's an excellent question. And perhaps it also brings back to the point Ms. Schaffer was making about the larger perspective and larger narrative and taking in all the solutions. I think as physicians, when you're assessing our patients, the bottom line that one needs to remember is that if you're starting an antipsychotic, likely eight out of ten patients that you're treating will gain a clinically significant amount of weight. And so in terms of history taking and evidence around that, you would want to know about family history of metabolic problems, you would want to know about prior exposure to antipsychotics, the age of the person, the ethnicity and the racial cultural identity have a bearing. Sex has a bearing, it appears. And so based on those factors, you develop a risk profile.

We have evidence to show now that drugs like metformin can work very well when started early in prevention and early intervention stance. And so there are new guidelines would suggest that most patients, or most young patients who are started on antipsychotics should be offered metformin from the get-go. And if these interventions are not possible, or if they have not worked out and somebody has developed weight gain and obesity at that point, perhaps these newer drugs can come in. And at that point there there's the choice between semaglutide or tirzepatide or several of the sister drugs which will soon be on the market.

David Gratzer: Doctor Sockalingam thinking in terms of your role as scientific director, I mean, how much evidence is there? These are early days. There's some evidence. How persuasive do you find that evidence? And what are some research questions that are unanswered?

Sanjeev Sockalingam: So I think we have semaglutide and also with tirzepatide, we have pretty good results in terms of long term sustained weight loss. So, one-year studies that have shown pretty significant weight loss anywhere from, 13 to 15 to 18% and even higher depending on how much behavioural intervention you add on and the intensity of that. The benefits, though, as we've all been talking about and with these agents, is that they have been looked far beyond weight loss as the outcome. They've looked at health outcomes. For example, of sleep apnea, with studies showing, you know, 40 to 50% reduction, Reductions in cholesterol, pre-diabetes. And then those who have a history of cardiovascular events significant reductions in recurrent cardiovascular events. So, you're seeing the shift now to thinking about obesity as a chronic disease. So, this is prevention of other associated chronic diseases, which is so paramount when you think about that patients who have severe mental illness often die from cardiovascular disease and have a shorter life expectancy up to 20 years less than in a patient without. And so these are potentially game changing in this way. We have good results again, for, some of these long-term studies. And we have good side effect monitoring because they've been used in diabetes for many years before introduction in obesity.

What we don't know, and this is some work that Doctor Agarwal can talk about, but how do they work for antipsychotic induced [weight gain]? We have a few randomised controlled trials with liraglutide, some underway including a CAMH for semaglutide. The number one question patients ask, how long do I have to be on these medications? Right. It's not so different than, say, antidepressants or other medications that we are used to prescribing. But, you know, that is a question. And then I come back to the discussion of chronic disease. This is a chronic disease. Obesity is a chronic disease. And so that is something we have to talk about that there's an expectation you may need to be on these medications long term. And to Doctor Agarwal's point earlier we don't know in a range of different conditions and complex comorbidities what the impacts may be. And that's what we need to learn more about. And then I would say, the last plug I would say is in our pediatric guidelines, which got released by Obesity Canada just recently, we have some early results from one randomised control trial of semaglutide of its effects in adolescents. And that is a population we really need to understand about risk benefits and long-term outcomes if we really want to get upstream in terms of obesity management.

David Gratzer: Ms. Schaffer, what would you suggest to physicians who are thinking about prescribing this? What's absent from some of these conversations that doctors are having with patients that you think would be important?

Lisa Schaffer: Oh, I love this question! And I think, it's rooted in values. I think we really need to be able to invest in healthy and right conversations in those clinical settings as much as possible. But we also know we're not set up for success in that way. Our system has been designed around stigma from the patient perspective. And also, you know, we know our HCP's [health care providers] want to do right, but you guys are given very little amount of time. And right now, there are no billing codes for obesity. So, there's no way for us to really have these conversations in a fulsome way. But we'll put a pin in that over here for one second and just go I would love to see moments – and this is happening I'm so excited for this next generation of care as well – where we are talking about that whole person and really slowing down and having those kinds of conversations about the why behind this want, especially when we're talking about some of these GLP-1 drugs that have now kind of gotten away from us in a pop cultural sensibility. And so we have more people walking in and asking for a specific drug, which I think is kind of new, at least in Canada. I believe in having an informed patient, but by the same token, we need to make sure that our HCP's are set up for success, that our primary care doctors or those specialists that are interacting with more complex patients, also have access to education and understanding of what this moment truly means.

But just fundamentally, as a primary care person, if you're having that conversation, I really would love people to get more into the why. And again, let's root it beyond just that weight loss. We know we are not set up for success, because a lot of our research studies right now are dependent on those BMI outcomes. But let's start having those conversations and have the courage to have those conversations in the room and truly help people understand that this is bigger than just what we've thought it is so far about weight loss, that there's a whole bunch of other things that come as a benefit with this. But also this is a medication and a drug and a commitment to really understanding. And quite frankly, I think we need to help patients understand obesity as a chronic disease in the first place as well. Everybody wants a silver bullet, but there really isn't a silver bullet. So let's take that moment and transition it from a want for silver bullet to how can I get this person thinking about this differently and how we're in it together for the long haul.

David Gratzer: Of course, no medication is perfect. Side effects. Reasons to discontinue. Clinical consequences. What might one see with this class?

Sanjeev Sockalingam: Well, with GLP-1 receptor agonists, I think like any medications, there are patients and patient populations that we need to be concerned about. I think the most common side effect for these medications, I would just say are GI related side effects. And you know, that is one we have to educate patients on and also modify the titration of these medications. Right? These are weekly injections. But you may need to instead of accelerating the dose every month, you may need to start thinking about slower titrations if people are having those side effects, particularly with as we get to newer agents with more, you know, greater propensity for weight loss.

I will just say from a psychiatric standpoint, broadly, there were some initial concerns about suicidal ideation that came out with semaglutide, but there have been several studies now that have actually looked at large databases and comparison trials and actually have shown that the rate is not actually inflated by the GLP-1s themselves. That people seeking obesity [treatment] often have many comorbidities, and perhaps that might increase the risk of suicidal ideation. So nonetheless, I always tell patients that and we monitor that going forward, especially patients with concurrent psychiatric illness.

David Gratzer: Ms. Schaffer?

Lisa Schaffer: I would say from a side effect perspective, what we hear in our lived experience community is very much along the lines of what Sanjeev just said. And to me also is a moment for us to recognise what we

can see in these patient community groups or, you know, people choosing to titrate because they can't afford or they're trying to make their medications last longer, or sharing medications, which is truly haunting. And I know that's not a direct, actual side effect, but to me, that is a disadvantage in this moment that we're talking about. We know that they are not, covered largely across Canada today and that they are price prohibitive. You know, $500 a month isn't easy for many people to navigate. One in three Canadians is going to be living with overweight or obesity, and that means every single one of us knows somebody, or this really does impact all of us. And obesity isn't going anywhere. This is a chronic condition, as you said as well. So how can we set people up for success right from the beginning and not have to make those choices? It's heartbreaking when we see people get excited by being diagnosed with diabetes, because now it means their medication is being covered. And that's the reality of what we're seeing in our patient communities as well.

David Gratzer: Doctor Agarwal, you, of course, deal with a very specific population within the larger population of those touched by mental health. What are the implications for those with psychosis?

Mahavir Agarwal: Yeah, I echo what Doctor Sockalingam and Ms. Schaffer just mentioned. In fact, I have had people who have chosen to part with a large percentage of their ODSP cheque so they can be on this drug. And I've had people shed a tear and be happy that they were diagnosed with diabetes, because now the drug is free. And so those play out daily in in our clinics. And that's truly heartbreaking. Within the context of severe mental illness, there are a couple of particular ways in which these drugs can interact with our treatment. So, for example, constipation or gastric slowing is a common side effect with this class of drugs. Clozapine, which we use quite commonly in our psychosis population, that can also cause constipation. And we still don't know how or don't know enough about how clozapine and semaglutide can combine, and whether that accentuates these side effects. The other point is around ECT, which is largely a point around anesthesia. So, because semaglutide and similar drugs delay gastric clearing. So overnight fasting is sometimes not enough to ensure gastric emptying. And so CAMH for example, has a protocol where if somebody is on semaglutide, they cannot access ECT's. They have to be off the drug for at least 3 to 4 weeks for ECT to become available to them. So, there are times for my patients where they have had to choose between ECT or semaglutide. And depending on what was the most pressing problem then they have made, they have chosen one or the other. And I hope that going forward, as we get more experience with these drugs, we can navigate this problem a bit better.

David Gratzer: Well, let me ask you this. All of you have talked about stigma. Do you think part of the issue here is that, historically speaking, there's some things that doctors like to talk about: prescribing medications. Some things that doctors hesitate to talk about: obesity, sex, libido. And as a result, it's been a bit neglected.

Lisa Schaffer: I mean, I'm happy to jump in here, guys. To me, this is this is huge. And this is really important. I think, you know, our society hasn't made it easy to talk about obesity. When I first started volunteering seven years ago with Obesity Canada, just saying the word obesity felt like knees and elbows coming out of my mouth. Even though I was excited and proud of the work that I was doing, it still felt hard to even celebrate it. When I think about the obesity space right now, I look to you guys and think, this is what mental health must have looked like 15, 20 years ago when people truly, truly didn't understand it. And that stigma was really outweighing the knowledge that really was driving the solutions behind everything. We're in a very similar position, in my opinion, as it relates to obesity. And I think you're very right. And there's such a pervasive belief that this is about willpower, and this is something that somebody has done to themselves when that is the antithesis of the moment that we're in. And I think it's easy to just bypass that because it's a big, sticky wicket of a conversation. So that's my perspective. But open it to others.

Mahavir Agarwal: Yeah, I agree with you, Ms. Schaffer. I think obesity if it's a chronic disease, we should perhaps borrow from other chronic diseases where things have been more successful. And I will start with diabetes just because I know that world better. And also diabetes has, you know, a new mechanism come up every decade or less, an entirely new mechanism that was undiscovered before that. And they have a whole

new class of drugs, right? Unfortunately, mental health has definitely not been lucky in that sense. We are still stuck with this sort of same group of drugs for the last 60 years, and neither has obesity medicine. And I like this, uh, this this sort of parallels drawn between mental health and obesity. And I think both of these fields have lagged behind in terms of progress. And when you combine these two in our clinics, that's sort of the epitome of where we have no answers. And so if we are starting to have answers, I think this is the time to have those conversations, because for once, we can show thanks to these effective drugs, that this is not about willpower. The person who was struggling with their willpower before this drug was introduced is suddenly a success story with the same willpower six months down the line. And so while you know drugs are not the silver bullet, drugs allow us to feel more effective or efficacious about all the things that we are doing anyway.

Sanjeev Sockalingam: And just building on Ms. Schaffer's and Doctor Agarwal's comments that, I do think there are very much similar parallels to mental illness, and we'll take depression to be even more specific. You know, SSRIs came out in the 1990s to offer biological approaches to treating depression. But it also enabled a narrative to talk about the biology of depression, as opposed to the fault or the inner failings of an individual who is depressed that this was something you could just get over. And we have unfortunately perpetuated that throughout history in obesity, where obesity is thought of as a lack of willpower, and not a disease. You know, "eat less, move more," that's the prescription that every physician, has been trained on except in the last few years. And so as we have more effective treatments and, in this case, pharmacotherapy, it allows us to re-examine our other ways in which people that this can influence someone's biology and their predisposition to developing obesity. And so, you know, what's been interesting is obesity has been reconceptualized as a brain disease as a result of these medications, which is quite ironic when we thought of it as, you know, it's about all these external factors, exercise and food consumption. Not to say that there are not environmental factors or food can, you know, food and its reward pathways etc. are not critical, they are critical. But it allows us to have a different type of dialogue as we go through this.

David Gratzer: A comment that, uh, that you made, Doctor Aggarwal at the end of your, uh, viewpoint piece in JAMA Psychiatry, is that these are forever drugs. In other words, that, you know, they don't cure anything, but they help people better manage their weight as long as they continue to take it. What does that mean in terms of clinicians and conversations? What does that mean for policymakers? What does that mean for the future of this class?

Mahavir Agarwal: Yeah, I think that's a great question, Doctor Gratzer. I think the short answer to that is, I don't know, and I would love to see how this all plays out. However, I think I think we are well suited to have those conversations because we are in the business of prescribing drugs for the long run. A lot of our drugs, while not forever drugs, are reasonably long drugs. Our patients do tend to stay on them for a while. And within the narrow context of metabolic health, within the space of mental illness, for as long as they are on the drugs that perpetuate these side effects, one could expect that they would be on the drugs that mitigate these side effects. And so in that sense, they will likely continue. However, this is not uniformly the case. We have data showing that when people stop these medications, the weight tends to come back. However, this is not universal. There are individuals who are trying an approach where, for example, this is used for weight loss, but weight maintenance is done through a holistic or, you know, more distributed means. And it is possible that we will arrive at a strategy where initial weight loss is driven by a certain velocity or certain intensity, and then weight management or maintenance is driven by a certain different strategy. And so there could be a future that way. I think overall, in terms of cost benefit ratios and what it means for regulators and insurers, I think prevention and early intervention has uniformly been shown to be more cost effective when it comes to chronic diseases, and that has already been shown to be the case with semaglutide. There are cost effective analysis that have come out in research, and most of them tend to suggest that semaglutide, even at its present cost, is cost effective, and one can only hope, like with other drugs, the costs will come down with time. That's my take. Incomplete as it is.

Lisa Schaffer: I think this is a really interesting topic and one that we've spent a lot of time talking about over the last year. Sanjeev was one of the authors of a paper that we recently published last fall. It was actually called "The Cost of Inaction," and it's about how much we're losing by not treating obesity first. So, this is obesity specific without the addition of the mental health component. But when we look at it that way, what we know is annually it's about $27 billion to the Canadian economy that we're talking about by not recognising obesity as a chronic disease and offering these kinds of solutions. When we break that down even further, what we know within that is 6 billion of that is direct health care costs. And we know that that system needs a lot of love and attention. But 21 billion of that is what we're losing to the economy just by not helping people show up fully by people not being able to contribute to society through their benefit plans, all of those kinds of things. So, it's a really interesting moment that I think we're in, and I love the way that you just phrased a lot of those things, because I think there is a huge challenge in front of us, but the opportunity is even bigger. We have a real opportunity to get this right. And as Doctor Sockalingam was saying, if we start looking at obesity as that upstream factor as well, and if we were to treat it first, we are removing the ripple effects of or potentially removing ripple effects of over 250 other conditions. But we still have this pejorative mindset that we don't want to cover those medications. But I'll cover your heart stent or your diabetes medication, or your liver condition, or your new knee, when really, if we could just help each other, reframe, give each other the space and grace whether we are clinicians, policymakers or everyday Canadians to understand obesity differently. If we give each other that space and grace, I think we could make a really big impact.

Sanjeev Sockalingam: And I would argue that treating obesity either concurrently or first, depending on one's history, may also mitigate some of the psychiatric sequelae. Because we know obesity is a bidirectional relationship with depression, for example. We know that for people with bipolar disorder, who are living with obesity they have faster rates of relapse and poorer response to treatments. And so there are ways in which, you know, as just this tangible point that we see in the psychiatric kind of field where treating obesity really could have tremendous impact on our mental health outcomes that we're targeting for many of our patients as well.

David Gratzer: Well, let me push you a bit on that. It's tough to keep up on all the literature with regard to this class of meds. Certainly, there's much research going on in obesity, obesity and mental health, but some papers are even suggesting there might be utility here in other conditions. Think alcohol use disorder. Hendershot in JAMA Psychiatry is a really interesting paper talking about alcohol use disorder and people who are using the glucagon-like peptide-1 agonists. What are your thoughts? Is this an early literature? Does this show promise? Are we getting excited, maybe prematurely, without much evidence?

Sanjeev Sockalingam: I mean, I'll start off just saying, it's another interesting area of discovery as well. We do have, large retrospective studies and smaller studies that have looked at, GLP-1 agonists, mainly semaglutide and alcohol consumption, for example, showing reductions in kind of binge drinking, outcomes in certain populations. And so there is an increased number of trials underway for nicotine dependence, alcohol use disorder, opioid use disorders that are that are exploring the effects of GLP-1 agonists. I think the jury is still out in terms of the actual research and data, but we have these early signals and we're doing the right thing by doing research in this area.

Mahavir Agarwal: And I wanted to add, there are parallels with what is happening with GLP-1 class of drugs, with what is happening with psychedelics in the mental health literature. We have a new potential tool, and we are now trying to figure out where or what, you know, uh, condition can respond to psychedelics. And the same seems to be happening with GLP-1 receptor agonists. Much of this is healthy because we want to really figure out where it works and where it doesn't.

David Gratzer: What's the one thing you'd like a clinician to think about with regard to this topic? Doctor Sockalingam?

Sanjeev Sockalingam: That obesity is a chronic disease with treatment options that we now have available that provide hope for patients.

David Gratzer: Ms. Schaffer.

Lisa Schaffer: That it really takes courage to challenge outdated beliefs about obesity. And it takes even more courage to seek help and be able to speak about it openly, and that we can do this together.

David Gratzer: Doctor Agarwal.

Mahavir Agarwal: I would like to highlight that managing metabolic side effects is within the ambit of the psychiatrist practice. Like you manage extrapyramidal symptoms and do not refer EPS to every EPS 2 neurologist. I think we should be able to manage first line metabolic side effects and not look to GP's or other physicians to help out.

David Gratzer: This has been a really thoughtful conversation. It's not about me, but I learned a ton and I took lots of notes. I suspect many of our listeners will feel the same way. I really appreciate your time and your enthusiasm and hope that we can do this again, maybe in a year or two when we have a little bit more data, a little bit more patient experience, a little bit more wisdom perhaps. Thanks, guys.

Sanjeev Sockalingam: Thanks. That was amazing. Thank you.

Mahavir Agarwal: Thank you so much.

Lisa Schaffer: Thanks all.

[Outro:] *Quick Takes* is a production of the Center for Addiction and Mental Health. You can find links to the relevant content mentioned in the show and accessible transcripts of all the episodes we produce online at CAMH.ca/professionals/podcasts.

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