[Theme fade into Restaurant noise]

CB: Imagine you're sitting in a restaurant reading the menu and your server approaches your table.

MC: May I take your order?

CB: You're looking at the list of items and they're using words that you mostly never heard of. So you ask, "What do you recommend?"

MC: Let's see… we have a cold GLP-1 agonist topped with a shot of insulin. We've got some really good alpha-glucosidase inhibitors in today, served raw and garnished with meglitinides. Our chef also makes a beautiful roasted glitazone which comes with a side of DPP-4 inhibitors. If you're adventurous, we just got delivered SGLT-2 inhibitors and chef fries them in a sulfonylurea batter. And as always, we have our signature biguanide. But really, you can mix and match. So what will it be?

CB: "Say that again?" "Never mind, I'll just have the prix fixe."

MC: This is The Med Thread restaurant, where we serve delicious pharmacy talk every month! I'm Mike.

CB: I'm Cathy, and today we have a full meal for you, appetizers to desserts, all about type 2 diabetes medications. We're joined by Jennifer Donnan, a pharmacist and PhD candidate from Memorial University to help us figure out how clinicians and patients make decisions about medications, because when it comes to diabetes, the choices seem endless.

[Restaurant noise]

Appetizers

MC: Starting at the beginning, our appetizer is a primer on what diabetes treatment looks like now compared to that of 50 years ago. A paper by White in 2014, outlined the history of diabetic medications. To highlight a few points, the first oral agents around mid 1950s. These were sulfonylureas like tolbutamide. Then we got the biguanides like metformin and they were introduced a little later in Canada. From 1959 to 1983, we had over 20 years of very little advancement in drug therapy, then we waited another 10 years before we saw a new type of medication.
(White, 2014)

CB: There are just so many medications on the market for diabetes now, and even since I graduated in 2011 there have been whole new classes introduced. Jennifer I'm glad you're here.

JD: Thanks, I'm so happy to be here.

CB: I'm interested in what you've come across in your research Jennifer, does the increased number of drug options allow for patient choice? And how so?

JD: Yes, you're right. If we look at what options were available to patients 50 years ago there were only a couple of medications in pill or capsule form and then very basic insulin options. Today,

there are 18 unique oral agents, 5 injectables, in addition to the numerous types insulin products. In the last 10 years alone, there have been 3 new classes including 12 unique medications approved for use in Canada.

Now, not all of these medication work in completely different ways. There are 8 classes or groups of medications that are taken by mouth and 2 that are injectable. But even so there are plenty of differences between these classes. They target different pathways that the glucose follows from the time it is ingested until the time it is eliminated from the body and therefore the side effects that they can cause are also different. For example, some cause weight gain while others cause weight loss. Some have shown to reduce the risk of cardiovascular events like heart attack and stroke, while others may increase or have no impact. Some drugs have a higher chance of causing blood glucose levels to go too low, this is called hypoglycemia which can be very dangerous, while others have very low risk of this event.

This does not even account for the differences in cost or frequency in dosing. There are lots of options with lots of unique characteristics meaning that choice can be overwhelming for both clinicians and patients.

First course

[Clips of various drug advertisements: "Talk to your doctor"]

MC: For our first course, the meat of our discussion today is really about patient choice. We always drug advertisements who prompt patients to "talk to your doctor" about this or that drug. What effect does this call to action have on patient choice?

JD: I think you bring up an important point here. I am really uncomfortable with advertising like this. Large pharmaceutical companies are trying to nudge the general public to seek prescriptions for their products.

Though this type of advertising is not allowed in Canada and most other countries around the world, it is legal to advertise directly to consumers in the United States. And therefore, we see a lot of these adverts on TV, in magazines, and through social media. Advertising like this can be very influential and, in my opinion, detract from an important decision that needs to be made between an individual and their physician.

Studies have shown that there is a disproportionate balance between the risks and the benefits presented in pharmaceutical ads, whereby benefits are over-emphasized and harms under-emphasized. It also promotes the use of pharmaceuticals over health lifestyle choices where they could be more appropriate first course of action.

The US Food and Drug Administration does regulate direct to consumer advertising, however it is really troubling how frequently ads to not comply with these rules. Just this year, Klara et al did a study to systematically assess adherence to these guidelines in ads aired in the US between January 2015 and July 2016. Of the 97 advertisements they reviewed, they found that the overall quality of data included was quite low. And while 26% of ads included quantitative information on the benefits of the medication, none included quantitative information on potential harms. But what was really shocking though was that 13% of ads promoted off-label

uses of the drugs, a practice which is actually banned by the FDA.

Not everyone shares the opinion that direct to consumer advertising is bad. In a survey conducted in the United States by the Food and Drug Administration, most physicians surveyed indicated that patients who had seen advertisements asked more thoughtful questions and were more informed about treatment options, making them more involved in their health care. Whatever way you look at, direct to consumer advertising absolutely impacts patient choice, but not in an unbiased, patient-focused manner which is the way we prefer to identify the best drug products for individuals.
(FDA, 2004; Klara, 2018; Parekh, 2018)

MC: So that's very interesting, but what about Canada. What are the rules governing advertising of pharmaceutical products in Canada?

JD: Well, like I mentioned, direct-to-consumer advertising about specific drug products is not allowed within Canada. However, advertisements that do talk to certain medical conditions that urge patients to talk to their physicians, those are more acceptable, and we do see more of that.

CB: And Jennifer, I'm actually surprised too that some of the ads actually promoted the off-label use, cause we that in healthcare as kind of a no-no. We don't often talk about off-label uses like that. So, it's interesting.

JD: That is definitely true. I was quite shocked myself and I guess it just goes to show that the rules and regulations that are in place aren't very well monitored.
(See Health Canada Advertising Regulatory Requirements: https://www.canada.ca/en/health-canada/services/drugs-health-products/regulatory-requirements-advertising.html)

CB: Another thing I'm thinking about is, I'm assuming that patients make choices that may actually be different than what a healthcare provider would choose for them, because in the limited time we get to actually spend with patients most of the time, we can't really weigh out all the pros and cons to each option. Can you discuss how clinicians, be it physicians, nurses, pharmacists, etc. how they make decisions and how this is different than how patients make decisions?

JD: Sure, there is research that shows that there are differences in the outcomes that patients prefer and the outcomes that doctors think they prefer. This is further supported by research that showed major differences in what physicians recommended or advised for their patients compared to what they chose for themselves when they became a patient, really demonstrating how physicians struggle to see healthcare from the patient's perspective until they are patients themselves.

In terms of how we differ in our decision making, I think as clinicians, be it physicians or pharmacists, we are trained to follow a very systematic approach. Physicians specifically are first concerned with making the correct diagnosis of the condition. Once they are certain they know what they are treating, they look to any existing guidelines to see what the most appropriate course of action is, and they go through various checks and balances to make sure that the choices they make are appropriate for the particular patient based numerous factors, like age, allergies, existing medical conditions, maybe previously tried therapies and medications. When

the choice is made and based on this process alone, it is a paternalistic approach. In other words, prescribers assume the authority to make a choice on what they feel is best for a patient.

Patients on the other hand make choices more on an emotional level. They are potentially dealing with any number of emotions. They could be scared or angry about a new diagnosis, happy that the diagnosis is better than they had anticipated, worried about impacts on family life, stressed about potential side effects or cost. They may also have lived experience that they are reflecting on, like a friend or loved one who experienced certain side effects or outcomes that are not desirable to them and this causes them concerns. Individuals also have different dispositions. Some may be risk takers, others very risk averse. Some patients may value quality of life over quantity, where others value quantity over quality. And all these emotions can shift based on the persons stage of life or personal circumstances and they all can influence choices, the choices patients make.

Therefore, in a typical modern healthcare setting, a patient-centered approach is strongly encouraged, whereby the clinician's disease and treatment expertise and balanced with the patient's values and preferences. The ideal that we strive for, I believe, is a shared-decision making model. Elwyn et al. proposed a model for shared decision making in 2012 which is summarized in three easy steps. The first step is introducing choice, the second is describing the options, and likely using the assistance of some sort of decision support tool, and finally helping patients explore preferences and making decisions. The model is built on the foundation that we need to respect what matters most to patients and individuals.

Though I certainly believe this is an ideal we should strive for in the delivery of healthcare services, it needs to be said that it is not easy, not as easy as it sounds. There are many barriers in real life practice to make this reality all of the time. But I think there is a shift in healthcare culture and better tools and processes will be established to make this more and more feasible as we move forward.
(Mulley, 2012; Elwyn, 2012)

JD: Jennifer, I love the idea of having a shared-decision making. I can certainly appreciate that patients are different. Throughout the clinic I see patients that are very empowered to be part of the decision and want to know all of their options. I also see the flip-side where there are some patients that say, "well, my doctor knows best, I don't know much, so I'd be happy for them to make the decision for me." It is certainly something I'm interested in and getting really down to the nitty-gritty and what does that particular patient want.

[Clip from film: Ratatouille, 2004]

Second course

CB: For our second course, we're looking at how things are changing. As Jennifer described, our medication menus took a long time to change, with big gaps between new drug discoveries until a rapid change in pace in the last 20 years. A simple way to track these changes is to look at clinical practice guidelines which are published approximately every 5 years.

MC: So I tracked down the guidelines mainly from the Canadian Diabetes Association since 1992 and a few things pop up related to how we diagnosis and treat type 2 diabetes. We've always looked

at fasting plasma glucose and in 1992, higher than 7.8 mmol/L meant diabetes. In 1998, this dropped down to 7 and it's been that ever since. Also in 1998, we started looking at A1C, which is a measure of overall blood glucose control, but it wasn't recommended to be used diagnostically until 2013 because our laboratory standardization wasn't quite there yet. So instead, we started using it as a guide for treatment and we targeted a value of less than 7%.

CB: Talking about initiating medications, in 1992, we wouldn't start drugs until fasting glucose was higher than 10. And in 1998, we might be comfortable if our patient's A1C was between 7 and 8.4% even though 7% was the target. As we started getting more classes of medications, we could start using 2 or 3 medications at a time and our ability to lower the A1C got better. Insulin therapy began to be pushed further down the list of medications to use. By 2008, we were clearly recommending metformin as the first step in therapy if A1C was less than 9% and to use it in combination with another medication if it was above 9%. In 2013, we set the bar a little lower to 8.5%.
(CMA, 1992; Meltzer, 1998; CDA, 2003, 2008, 2013)

MC: That's a lot of changes over the years to the guides that clinicians use and this year, the Canadian Diabetes Association completely rebranded to the more succinct Diabetes Canada and issued a new guideline. So Jennifer, what's changed and why?

JD: There are several changes in the new Canadian guidelines as it relates to how medications should be used to help manage type 2 diabetes. Somethings that have not changed however are, the target for Hemoglobin A1C is still set at 7% and our first line of defense is the use of metformin. That is of course assuming the patient does not have specific medical issues that make it unsafe. The changes we see to these new guidelines, relate to the drugs we use once metformin is no longer working as it should. And unfortunately, most patients will require additional therapy over time.

In the 2013 set of guidelines, which was the last full release, recommendations for second-line, or add-on therapy were that any other available medication were reasonable alternatives. Though that is still really the case for many patients in the new 2018 guidelines, what has improved is that there is more direction on what drugs might be better in certain populations. For example, drugs like canagliflozin and empagliflozin, 2 of the SGLT2 inhibitors, which are the newest class of medications on the market, and semeglitude and liraglutide, 2 GLP-1 receptor agonists, have shown to reduce the risk of heart attack and strokes in patients who already have cardiovascular disease, and so now we're seeing recommendations for these types of agents over other ones in patients with underlying cardiovascular disease. So we're really seeing a more focused approach in certain patient populations.
(Diabetes Canada, 2018)

CB: I'm glad to see the guidelines changing, in that even though we have more medications, now it seems we have a more targeted approach to we go next.

JD: So, I think the new landscape for diabetes therapy offers a lot more options for patients. This allows physicians to provide more targeted treatments to their specific patients. But on the patient's perspective, there's also a lot more options for back-ups, maybe what's first-line recommended by the clinician really doesn't sit well with them, we now have a lot more options. We can discuss and discover, to see what really fits best for that patient.

[Clip from film: SpongeBob Square Pants Movie, 2004] [Restaurant noise]

Dessert

CB: Now, dessert time, a time for good discussion. Something I'm all too familiar with is the patient handout that we give when dispensing a new medication. How did this become common practice? We seem to be walking a fine line between information overload, with every single possible adverse effect listed no matter how small the risk, and empowering the patient to be more knowledgeable about what they are taking. What does all of this text actually mean to patients?

JD: You're right Cathy. Pharmacists have a professional responsibility to inform the patient about their new medication, how they need to take it, when they should expect to see an effect and common side effects. This is typically done in a counselling session before the medication is dispensed. However, this information can be a lot to take in and can be easily forgotten by the time a patient gets home. Information handouts allow the patients to refer back to retrieve that information. This is especially helpful if there are special instructions, or if they suspect that they are experiencing a side effect of their medication and want to see if the handout provides that detail. The intent however was that they would help improve adherence to medications.

Like you say though, this patient handout can include far more information than a patient can digest and may include numbers to reflect risks and benefits and side effects that could be difficult for the average person to interpret. This all may in fact deter the individual from actually reading any of it, negating the intent. Also, the more detailed handouts also include more of the rare side effects, which could scare a patient and perhaps negatively impact adherence. I think that patient handouts are really important for keeping patients informed about the therapies they're receiving, assuming that it is prepared in a manner that the average person can read and understand.

Perhaps more important thought, and what we do not see very frequently, is information handouts that help patients engage more in the shared decision-making process. Handouts that highlight the risks, benefits and convenience issues, like cost, route of administration and frequency of dosing. That way patients can make trade-offs between these factors and help them make informed choices. It enables the conversations that patients have with their physicians be more meaningful, more productive and hopefully result in therapy choices that meet both physicians' and patients' goals and needs. There are many decision support tools out there that serve this purpose, but wide spread use is not common and greater uptake of these would make a big difference.

[Coffee pour effect]

Coffee or Tea?

MC: Coffee or tea anyone? To caffeinate or not to caffeinate. For medications, I often think about whether a particular drug therapy is 'worth it'. Jennifer, what do you mean by trade-offs and what are the trade-offs for diabetes medications?

JD: Well, examining the trade-offs that patients make between diabetes medications is actually part of the focus of my PhD work. I have had to learn a lot about the basics of the decision making process and the scientific approaches we can use study that process, called choice modelling.

It is convenient that this comes in the coffee or tea section of the interview. I often start by explaining how individuals make choices and decisions by giving an analogy to their morning coffee. Every time we make a choice we inherently think through the aspects of that choice that matter to us and we make trade-offs between the pros cons of that choice. For example, if you want to get a morning coffee, you are potentially faced with several options for where you might get that coffee. You could make it at home or the office, where it is free and saves time, but it may not be great quality and there certainly not much variety. You could go to Tim Hortons which may be better quality, has some selection for you to choose from, and is on your way to work, but it's going to cost you a couple of dollars. Or finally, you could go to a speciality coffee shop where the quality is great, there is lots of selection, it is slightly out of the way on your way to work, but it comes at a premium price.

As you can see, there is not obvious choice. You can sacrifice quality and selection to save money by choosing to make it at home; or you can sacrifice more of your time and money to obtain the specific product you enjoy the most. You make trade-offs for good performance in one category, for poor performance in another. It is also important to point out that not all categories influence choice to the same degree, and this may vary from person to person. For instance, once person may place a very high level of importance on the quality of the coffee, while another person might place a very high importance on cost. This have been where I have focused my attention in diabetes medication choices. I used a study design that allowed me to quantify how much each characteristic of diabetes medications influenced choice.

The first step in this process was quite hard because I had to identify what specific characteristics influenced choices. For any medication choice you are going to have to make trade-offs between the benefits, harms, cost, and convenience factors like injection versus oral, and frequency of dosing. But as we know there are many potential benefits and harms, some are minor, some are more serious and the likelihood that they will actually occur will also influence choice. This is what make the choice so complex. What we have found in our survey and from talking to patients, clinicians and reading literature on choices for diabetes medications are that trade-offs important in diabetes medication are:

- How well the drug works to lower blood glucose
- What impact it has on the risk for cardiovascular disease, heart attack and stroke
- What impact the drug has to reduce diabetes complications on the kidneys, nerve or vision
- Does it increase or decrease weight
- How likely is it to cause hypoglycemia
- Is it taken by mouth or by injection
- Cost

We also looked at some other characteristics like common but minor side effects, like rash or gastrointestinal upset, and rare but severe side effects like cancer and amputation. And while these did seem to influence decisions, certainly not to the same degree as cost or impact on blood glucose and cardiovascular events.

My biggest take home message from my research is that when given the opportunity, individuals do elicit preferences towards the varying characteristics of their medications. We just need to make sure that we give them that opportunity at the time the prescriptions are written.

CB: And I totally agree and if patients are given more of the characteristics and allowed to make their own choice, it certainly will make them feel more comfortable about the medication and know what their risk versus benefit is. And to cap the evening off, let's consider what is most important, the patient. How can we as health professionals more effectively present benefits and risks to patients?

JD: That's a really great question. I think there's a few of things that we need to consider here, when we look at providing information to patients. First, we need to look at how many options are we going to give patients. Secondly, we want to look at the numbers and how we present those numbers to facilitate comprehension. And finally, how we frame that information.

With respect to how many options to provide, you can imagine that with a condition like diabetes there are many options, and we've talked about that this evening. Allowing patients to choose between any number of them will be overwhelming. Rather starting with just 2 or 3 reasonable choices or best alternatives is a good place to start.

When it comes to numbers, common metrics of risk and benefit used in the medical literature between professionals are not well understood by the general population. Sticking to proportions that use whole numbers where possible and use easy to interpret denominators. For example, 3/100, or 7/1,000 or 17/1,000,000, these are easier ways for patients and the general public to understand proportions. It also helps if this information was represented in some sort of diagram so that patients can actually see what you are trying to say and this is where good decision aids can come in handy.

Finally, and probably the most important aspect, is the way in which information is framed to the patient. As we talked about earlier, patients bring more emotion into their decision making process. How we frame the information to patients will greatly influence their choices. Think about for example, encouraging an individual to give diet and lifestyle modifications an honest effort before they move on to drug therapy. If you frame the information by highlighting how much time they will need to dedicate, the sacrifice they'll need to make to their hobbies, and maybe never indulging in some of their favorite foods to be able to achieve the goals that you're looking for, then you're taking a loss frame approach, you're highlighting what they will lose as a result of this choice. On the other hand highlighting their improved energy and sleep, weight loss and the opportunity to explore new foods, you are then taking the gain framing approach and you're highlighting the benefits of taking that certain option.

The same is the case when framing information about the medications. You need to provide all the necessary information to make an informed choice, you can't avoid all the risks that patients might experience, but don't start with those risks. The patient will have already decided not to pursue that option before you even get to the benefits if you start by listing all those negatives. Clinicians need to use their expertise and knowledge of the treatments that will most likely benefit their patients and nudge those patients towards well informed choices that balances the

risks and benefit tolerances for the individual and that will take dialogue.
(Naik, 2012; Patel, 2018)

[Restaurant noise]

CB: Thank you so much for being here Jennifer. I've learned a lot about patient choice and you've really reiterated how important it is to have these discussions with patients and never to underestimate what a little knowledge and empowerment can do to help out patients make informed decisions.

MC: So, this is our 8th episode and the last of our first Series, so we wanted to take this opportunity to also thank our listeners, guests, and many others who have helped us create our podcast.

CB: Yes, thank you and we've learned a lot about podcasting and hopefully getting better at it! And we're looking forward to coming back to you in January with Series 2, with more guests and more interesting topics to share.

MC: Thanks for listening! And as always, you can find us on Facebook at the School of Pharmacy, and at www.mtsclinic.ca.

CB: Happy holidays! And we'll catch you in the new year!

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