Dr. Duckworth:

This is the first time we've ever been able to have this conversation with a national expert, because there are some things that are available to attend to the pernicious and common problem of weight gain with antipsychotic treatment. And so, today's talk is called, Integrating Pharmacotherapy for Obesity into Psychiatric practice: This is Our Fight Too. Let's go to the next slide, please. The NAMI HelpLine is here for you. If you want to talk to somebody, if you want to connect with somebody, if you are lost and looking for help, we have about 300 fabulous volunteers with lived experience. You can call them 1-800-950-NAMI. That's 10 a.m to 10 p.m. you can text or chat. And we are here to help you. And we're very proud of our helpline and its wonderful work. Next slide, please?

We have a whole series of these on Ask the Expert. So, if you have other questions which are maybe very important to you, but not on today's topic, I just want to remind you, we have an incredible library of America's research and scientific experts on topics of great importance to people. And so, I just wanted to remind you of those things. Because we won't be taking up too many topics that are off today's important topic. We have an expert that's talking about lack of awareness of illness, updates in bipolar disorder, caregiving. We have put together all-stars to attend to those and we're very grateful for their donation of their time and expertise. Next slide, please? Today's speaker is Dr. Jonathan Meyer. Dr. Meyer is a clinical professor of psychiatry, University of California, San Diego. He attended Stanford as an undergrad, went to Harvard Medical School and has gone on to become one of the national experts in the metabolism of antipsychotics.

In addition to his work on the compounds we'll be discussing today, he's also written a book on Clozapine, a book on Lithium. These are two relatively underutilized pharmacotherapies that he is also an expert on. We're very fortunate to have him today. He's a distinguished fellow of the American Psychiatric Association, had written many book chapters and peer-reviewed articles. So with that, I'm going to get back later on in the questions, you sent in superb questions in advance. We're also going to take your questions in real time. I'll do my best to integrate them with the excellent questions in advance. So, take it away, and thank you.

Dr. Jonathan Meyer:

Thank you so much, Dr. Duckworth. Thank you all for sharing your afternoon with me on an important topic. I will have to say, I am a psychiatrist, and to the extent I have expertise, you might say it's lived expertise, simply because I've had to become knowledgeable about this area, because this is probably our best hope for many people struggling with weight-related issues, whether it's due to the meds or not. And so with that in mind, I'm going to go ahead and share my slides and we'll go ahead and get started. So, just give me one second here to share my slides.

Okie dokie. So, there I am. These are my disclosures. None of these companies as far as I know are actually making any of these new agents, but they make a lot of agents, which are important for people with severe illnesses. And these are our goals. We'll talk about the anti-obesity medications, we'll talk about some clinical guidelines and how we select perhaps some of these and some of the data and the mechanisms of action, especially safety. Well, I think most of you know that obesity is a problem in society at large, but it really accrues more acutely to our folks for a variety of reasons. So, here's an NIMH review that was published fairly recently. All the references are down below, looked at 57 studies, and this is data that was already more than a decade ago, but even back then, the prevalence of overweight and obesity among people with more severe forms of mental illness was substantially higher than that in the U.S. population in the same timeframe.

And not surprisingly, problems with obesity have gone up every year since then with one exception most recently, the last data point in the U.S. population, it looks like that may have leveled off. We'll see where that goes, that's one data point. But we know there's a couple of issues here, partly simply because the health-related consequences of being overweight and obese include all the typical comorbidities,

metabolic syndrome, diabetes, sleep apnea, cardiovascular disease. But our people who live with severe mental illness tend to have very significant reductions in their lifespan, 15 to 20 years. And a big part of that are a lot of these cardiometabolic problems, many of which do stem from their being overweight or obese.

This is a study which looked at a number of sources of data throughout the literature, and what they are looking at is the risk of having mortality from a specific cost. So, let me give you a way to interpret some of this information. You look at suicide, not surprisingly, the rates tend to be tenfold higher if you have a diagnosis schizophrenia than the general population. But admittedly, the most common cause of mortality in the population is not suicide. Yes, tenfold the higher risk is not good, but I want to focus your attention on the other red boxes, especially the one where it says cardiovascular or cardio and cerebral vascular, the number one cause of death in Western society is related to cardiovascular causes. If you have, in this case two times the relative risk for mortality, you have twice the standardized mortality for the most common cause of death in Western civilization. And that is where we tend to see the vast majority of the excess deaths among individuals living with schizophrenia is from cardiovascular.

Admittedly, early on the course of the illness, it may be suicide, because we don't see a lot of people who have heart attacks when they're 25, but assuming they make it past that point, the latter cardiovascular is where we tend to see most of the harms.

And it's not just a problem of obesity and cardiovascular disease. One thing we've come to appreciate more than anything, in case you didn't know, is your brain and your body are connected. And anything which causes inflammation in the periphery such as having diabetes or metabolic syndrome will affect your brain. And here is an analysis which is correlating components of the metabolic syndrome or having diabetes with cognitive impairment. We have come to appreciate that as much as anything when we can get people to lose weight, it improves all aspects of your life, including cognition. And I'll show you some of that data later on with the GLP-1 drugs. Well, this bidirectional relationship between health conditions and physically and mental health conditions has been known for a long time.

We certainly know that people who may have overweight or obesity, especially if it's distributed more centrally, tend to have a lot of inflammation. And this inflammation as you can imagine, impacts brain function. And we know that if of course you're impacting brain function, maybe you won't function as well, therefore you may not also eat as well. And if you have the circumstances where in your community there's not healthy choices, where you're on a fixed income, you don't have good choices or food, all of this contributes to these problems.

The beauty of talking about some of these new agents is they make a lot of things better. So semaglutide is one of what we call these glucagon-like peptide-I or GLP-1 agonists. And yes, its primary role initially was diabetes. Now it can be indicated for weight loss in non-diabetics, but guess what? It makes people feel better. Physical functioning, role functioning, vitality, mental health, all got better when you treated people.

And I stole this part of this slide from a colleague of mine, Craig Chepke, who I know has done one of these talks last year. He says, "There's no antidepressant that'll put a smile in your face like helping them drop a couple of pant sizes." That is part of it. But there's also direct biological aspects of this, which I don't want to minimize. The other thing when you're working with individuals who are living with schizophrenia is that nobody likes weight gain from their meds. And because of that, if they feel like the medications are a source of the weight gain, they're not going to take them. It's just human nature. And these are large, large analyses showing that non-adherence discontinuation has increased three-fold for people on antipsychotics, which have very high weight gain liability. But even in the ones which are moderate, you're still increasing this risk two-fold. A big part of what we try to do hopefully as providers, is to initially start people on medicines with lower risk for weight gain.

We understand that the meds play their own role. The patients themselves bring their own biology to bear as well. The biggest risk factor more than anything demographically for weight gain independent of the

meds is younger age. So, those who work with children or adolescents complain bitterly that this population is extraordinarily sensitive to weight gain. Your heritage plays a role as well. Being quite thin puts you a greater risk for future weight gain, gender to some extent as well as genetics. Now, I'm not saying we screen people for these genes, but there's clearly an association in the literature. And the last thing is, if someone's going to have a problem with the drug, you'll tend to see it right away. olanzapine is one of those medicines which has very high risk for weight gain, but not everyone actually gains weight on it. Most do, I will say, but not everybody does.

And those who are going to have a big problem, we usually see very early on in treatment. Well, if you're living with an illness like schizophrenia, antipsychotics are the foundation. They're not the be-all and end-all. There's a lot of other things which need to be done to get you to function to your maximum potential. But antipsychotic medications tend to be the foundation.

This is what's called a heat map. This is from a large meta-analysis of 18 antipsychotics indicated in adults for acute schizophrenia. In case you had any doubt, red is bad. So, what are the agents which tend to have more red? Well, sadly, there are also some of the agents which are the most effective. And really the poster child for that is clozapine. We have nothing for treatment-resistant schizophrenia that's going to be replacing clozapine anytime soon. And I include in that statement the latest muscarinic agonist drug, xanomeline and trospium.

The biology of resistant schizophrenia is such that I'm not so sure that this new muscarinic drug will ever replace clozapine. And so, sadly we still are wedded to some extent to certain medication which have high risk. But that doesn't mean I'm going to start somebody on day one with a medicine like for example, olanzapine when I might have other options. The patients will earn their right to take olanzapine once they fail other options, but I think we're starting to learn more and more as a field that's maybe not the place to start, even if it perhaps has a shade better efficacy than certain other medicines for schizophrenia. And this is another analysis just looking at the dose response as well. Sometimes you can see a very clear dose response relationship. What you don't see in some of these analyses are medicines like clozapine, because we tend to not put people on fixed doses. We continue to titrate to get efficacy.

There's certain medicines like lumateperone which goes with the trade name Caplyta, which only has one dose out there market 42 milligrams. We also will try to prescribe medicines in the way which we think can minimize the adverse effects. But our first goal, to be honest, is to manage the positive symptoms of the illness. Well, olanzapine is still used, not uncommonly, for people living with schizophrenia. And we do it because of the efficacy. It's a shade better. It's not clozapine by any means. It doesn't really work in resistance schizophrenia, but might be a shade better in terms of positive symptom efficacy than other antipsychotics, excluding clozapine. But olanzapine is associated with a fair amount of weight gain. The biological property pharmacologically is that olanzapine has a lot of histamine H1 antagonism, and when you do that, you cause sedation for one thing, but you also impair satiety.

And if people don't feel full, they continue to eat. The problem with eating is that it's also pleasurable. And so, here you're impairing satiety and you induce people to eat. But because the act of eating itself is pleasurable, it's rewarding. And as they say in the world of substance use, it's reinforcing. So, a smart company said, "Well, if we can block that reinforcement aspect in the reward center, people will still probably be induced to eat, but maybe not nearly as much as they would otherwise." And that's why olanzapine is now out there marketed as a combo drug. There's a combo drug separate from generic olanzapine, which is olanzapine plus samidorphan. The trade name is Lybalvi, but the whole point is to use an opiate antagonist to block reinforcement. People may still eat some, but they won't have the reinforcement aspect of eating. And here's the data which proves this.

You can see these were stable individuals with schizophrenia who are outpatients randomized in a double-blind manner. The green line is the olanzapine/samidorphan, the orange line is generic olanzapine. You can see the people in this study who were on the combo drug, their plateau on weight happened much earlier. They gained significantly less weight. And if you look at the proportion of people who

gained either 7% or 10% of their weight, it was about 50% higher on generic olanzapine. So, this is something the prescriber can do. If she or he feels like an individual needs the efficacy of a olanzapine, they can use it in the form of a olanzapine/samidorphan. People still gain some weight, but we reduce the risk of more extreme forms of weight gain by 50%.

Well, sometimes we can only do what we can do. People need medicines, which may induce weight gain. The patient themselves maybe has a lot of demographic risk factors by age, heritage, et cetera. What are some evidence-based options if you're not using olanzapine/samidorphan? Well, my form of exercise really rise to the fore, and these were the things we could always hang our head on before we had these new GLP-1 drugs.

This is graphics from a larger view. You look into this, you're thinking, "Well, how the heck do I make any sense of what this is?" Let me focus your attention right in the middle. This was a large meta-analysis which was just published within the past year, looking at meds for weight gain in people with schizophrenia. If you look dead center, you see that black diamond which separates out from that vertical line. This is an aggregate of these large studies looking at metformin versus placebo, and there's no question that it clearly makes a difference.

This is the one medicine that has repeatedly proved itself to be effective. And below is all the other junk that we'd studied, none of which really panned out. Or some of which if it had even a tiny effect like topiramate caused significant cognitive problems, and which people for the most part are not using so much anymore for that reason. Here's a prospective study done in adolescents, because we recognize younger patients are at much greater risk. The first author is Christoph Correll. They randomized people to lifestyle education by itself, switching their antipsychotic or adjunctive metformin. And they could people who were quite heavy based on percentile and who had also gained weight while they're on their second generation antipsychotic. And they had some weight-based dosing for the metformin. The whole point of this study is that they showed that people who switched to certain meds didn't always tolerate it, but metformin seem to do the best.

So, you could switch people if you can find a medicine they can tolerate, meaning an antipsychotic, but the body mass index or BMI decreased significantly in the metformin group. And for young patients you can switch their antipsychotic or you can add metformin. But the point is, metformin tends to work best when you start it early on in the course of therapy. And really what I want to illustrate here is it doesn't matter how young you are, you can see the mean age in this study was 13.7. Even if your loved one has an age of 14 and they're being started on antipsychotic for whatever reason, it doesn't have to be schizophrenia. It could be they have an intellectual issue and they have a behavior problem, whatever it is, metformin is the way to go and there's weight-based dosing to help you out.

This is just some basic info on how to use it and what metformin does, it does make you more sensitive to insulin, but the nice thing is, because it doesn't make you secrete more insulin, it doesn't have the risk for hypoglycemia like some of those older meds were that were developed. As I mentioned, it's best used at the beginning of therapy when there's a great risk for weight gain either because the person themselves is at high risk or using a high-risk agent like olanzapine. I gave you some titration. The big issue is you have to go slowly at the beginning because people can get a lot of GI side effects. The gastrointestinal problem that people really don't like is diarrhea. We have some target doses. I'm giving you some monitoring for people who have low renal function some concerns. For young healthy people that's not as much of an issue and about the only thing we really need to do is check your vitamin B-12 on a yearly basis, because it can impair your absorption.

But it's a relatively easy to use medicine if you titrate it slowly at the beginning and don't give people a lot of gastrointestinal side effects. One of the best drugs out there is exercise. The problem is I don't get a lot of people to take it, but as you can imagine, exercise does a lot of things on many levels that no one medicine does. And because of that, it really is perhaps the most strongly evidence-based therapy. The impediment is always getting people to do it. That being said, here's a review that was published

relatively recently and you can see that these individuals benefit greatly in a number of ways. A 2019 review talked about individualized lifestyle interventions showing large effects reducing weight, but the group-based approaches rather were not quite as effective.

A newer review looked at more specific aspects of symptom reduction and quality of live. And guess what? It all gets better. So, the PANSS is a Positive and Negative Syndrome Scale, which is used to look at schizophrenia symptoms in clinical trial context. If you get people to exercise it makes their total symptoms better, it makes their positive symptoms better, hallucinations, delusions, it makes their negative symptoms better. They have a little more get up and go a little more motivation, their depression gets better and their quality of life improves. It really does impact an individual far beyond what you might expect just for the impact on metabolic health more than anything. And guess what? You combine it with metformin, you really got a combo here. So this is from review of 2019, and shockingly combining metformin and lifestyle intervention, which includes both exercise and diet, really does help mitigate antipsychotic-related weight gain.

It's the kind of thing which we would like to give to everybody. Sometimes the formal programs are not always available everywhere, but whatever you can do to get somebody up off their backside and walking around and doing things and to control their diet is all to the good. But this is what you're here to hear about. I know, and you've all heard about this and the literature. I'm going to explain to you what these medicines are, what they do, and also what they don't do, because there's a lot of concerns. This looks very busy and very scientific. I want to say though that the Lasker-DeBakey award is the highest award in clinical medicine. Yes, there's the Nobel Prize, but for clinical medicine this is the highest award. And this was given this past year to these investigators for the discovery of not only GLP-1, but their development of sustained acting versions of this hormone, and specifically as a treatment for obesity.

The history of this goes back more than a century where people isolated this peptide, which they called in incretin, and they found that incretin was clearly implicated in controlling your blood glucose, but it wasn't clear what to do with it. And they finally understood that there was a certain polypeptide, this large peptide which was made, which got cleaved into different products, one of which was called GLP-I. So, GLP-I also exists in the intestine as well. And this is a cleavage product of this large prohormone, which also generates glucagon. So, the whole point is that all of this was implicated in control of blood sugar and insulin levels. But it only seemed to work when people were being fed. It didn't seem to have as much impact when folks were fasting. It did help diabetes as well. There was some evidence in the mid-'90s that they might get some weight loss, and this was really in rat models where they're injecting this stuff right into their brain.

But the conclusion was, GLP-1 clearly increased insulin secretion, which helps lower your blood sugar, and it also slowed gastric emptying, and most importantly, it seemed to decrease food intake via actions in the brain. Well, this is all well and good, but the problem with this is that the native peptide in the human body has a very short half-life, one to two minutes. It's degraded rapidly, and people really weren't sure what they could do about it. Well, around this same time, I'll just say, there were people who are doing some research with the saliva of the Gila monster and they found there was something that tended to act like GLP-1, and I'm serious about this. The lizard saliva had a compound, a molecule which acted like native GLP-1, but had a longer half-life. And from that there was a drug developed called exenatide, which was approved for diabetes, but it had to be injected daily and people were looking for other ways to extend the half-life.

The successor to that was another compound called liraglutide, and mostly what people were trying to do was make this thing more resistant to metabolism and give something which could reliably be dosed on a daily basis, which maybe was a little more effective than the first one that was discovered. The problem is, these medicines tend to cause a lot of nausea, and it took a while before folks could figure out that you can't just start people at the max dose, they're going to throw up. You have to sneak up on them slowly and have a built-in titration. Once it got to the point where it was studied in non-diabetics, we started to

see that there was weight loss, and people were losing on average with these early compounds 5% of their weight.

And the first of these agents, which were approved for non-diabetic weight loss was called Saxenda, and you can see the date, December 23rd, 2014. The problem is, 5% weight loss, wasn't great shakes. I mean, there was some other oral medicines which may have given you that, but at least it established the fact that if you can get something which resists metabolism, you can actually get weight loss in non-diabetics. And really a decade's worth of search for a molecule with even greater stability than half-life gave us Semaglutide. And that was initially approved for treatment of diabetes as Ozempic seven years ago. And most importantly, it was injected weekly. The average weight loss was six kilograms on the two-milligram-per-week dose, and 40% of people lost more than 10% of their initial weight.

They had found from the earlier research that if you want to just get weight loss in non-diabetics, you have to actually go to a slightly higher dose than you would use to manage the blood sugar in diabetes. And for that reason they studied a higher dose of semaglutide, up to 2.4 milligrams per week. Those people who were not diabetic, just folks who are heavy, wanted to lose weight, those people lost an average of 12.4% of their initial body weight compared to placebo. And that was approved as Wegovy three and a half years ago on June 24th, 2021. And for most people that really was the start of the revolution in these compounds. Because we had something which was indicated for non-diabetic weight loss. It was dosed to achieve that outcome, as opposed to the slightly lower doses used to manage blood sugar and diabetes, and it was injected weekly. And if you had not heard any buzz before that, that's why, is that the compounds we had just weren't quite as potent, weren't quite as effective, and semaglutide really was the beginning of the whole new revolution in this area.

And for 2022 until now the search has been among all these companies to look for even more potent activators of GLP-1, and also look at the contributions of other gut hormone receptors. We now have dual agonists, and there's a number of these receptors, by the way, which I'm just not going to get into, because it becomes very complicated. But you should accept the fact that there's a number of other these gut hormones which companies are studying. And the next one in line was the GLP-1 GIP dual agonist tirzepatide. Those people who were studied initially for diabetes got a product called Mounjaro, and they got 15% weight loss. When they studied at slightly higher doses for non-diabetics those people got an average 21% weight loss, and that trade name is Zepbound.

And now people are looking even multiple inhibitors. And the question is, where will it end? I think the idea is though that we really can expect multiple agents in the future, which may give us 20% or more weight loss, which is just remarkable. But this is now showing us the potential for all of these agents. So, here's a very, very complicated diagram showing you the interplay with a number of these. The GIP is the gastric inhibitory polypeptide. So Zepbound, which is tirzepatide, works on GLP-1, and GIP. Glucagon is also one of the ones which we make, which also helps raise blood sugar, that's its primary role, and you can see these have tremendous interplay. And we're still trying to figure out what's the best way to modulate this system to get the intended outcome of weight loss. If my goal is not necessarily managing blood sugar per se directly if you're non-diabetic, and that's why you'll see agents develop in the future, which will have varying combinations of activities like GLP-1, GIP, and maybe other hormones, which I haven't talked about, to give us exactly what we want.

The whole point is that the combination has not been fully staffed of which one is ideal, and the fact that we now have 21% weight loss with Zepbound is wonderful, but we might get even more. This is the earliest one, liraglutide. Again, we didn't get nearly as much weight loss as we do now, but I just want to show you what the early data showed. It has been approved now for pediatric patients 12 years and older, as well as adults, as long as you have the BMI corresponding to 30. And I think that's the point, some people would ask, "Can you use these in non-adults?" Absolutely, and I'll talk about some of the safety data in a second. Those folks got 8% weight loss, and that was really wonderful. It's better than mostly what we had at the time. Some people even got 10% and some even 15%.

That number NNT is a clinical statistic. It stands for number needed to treat. And what that means is if you see an NNT of three is it means I'd only have to treat a few people in order to get somebody with 5% weight loss. If I wanted to get 10% weight loss or more, I might have to treat five people. And if I wanted to get 15%, 10. If you see numbers in the single digits like three or five, this is a very effective molecule, whatever it's doing more than anything. The 15% weight loss is a much higher threshold, and for liraglutide that's not something we would commonly see. Well, there are side effects, and you can see nausea is a biggie, then diarrhea, some constipation as well, because it does slow gastric emptying, and vomiting. Some people complain of decreased appetite. Well, no kidding.

To be honest though, you will hear folks complain about this, because in many instances they'd had somewhat of a, I would say an unhealthy relationship with food for a variety of reasons. And now food's no longer motivating and it's an aspect of their life which they actually miss. They miss sometimes the craving and the joy, even it was unhealthy, they got from eating. Dropouts to the adverse effects was about 6% more on liraglutide than on placebo, but a lot of people would put up with that because they were getting the results that they wanted.

Now, here's the good stuff, semaglutide, 2.4 milligrams is the max dose weekly and people lost in one Phase 3 trial almost 17%. It's approved for adults right now with obesity and BMI of 30, or if you have a co-morbidity BMI of 27, or for pediatric patients. And for those of you, again, who have people who are under the age of 18, as long as they're at the 95th percentile or above if below of age of 18, they will qualify.

Here's weight loss versus placebo. This is week 68. And the reason why they look at week 68 is there's a period of titration at the beginning, and so lot of weight loss. And that's exciting. It's hard to lose weight. There's a lot of things working against human beings in general. There's genetics, which we can't change. There's socioeconomics, that's where you live. There's lots of things. To have something which somebody can do on their own and lose this much weight is quite significant. What are the side effects? Well, nausea is a biggie. People will complain about it. We also saw some diarrhea and even vomiting, but discontinuations you see due to adverse effects was only 7% on semaglutide versus 3.1% on placebo. People will put up with the nausea, people will put up with some of the other stuff if they get the weight loss.

Also, what people have learned in clinical practice is that if a patient has started experiencing some of these things, you can just slow the titration. We're playing the long game here. This is a molecule we want to get to work. And if they have to go a little more slowly at the beginning, that's the way to do it. If people simply cannot tolerate it, then they're going to drop off and it's not going to be effective.

And now here's the latest one. This is the big guns. This is tirzepatide. The trade name for diabetes was Mounjaro. The trade name for non-diabetic weight loss is Zepbound. It's a duly acting agent. And look at this, more than 21% weight loss. Here we go. This is what people always wanted. And it just really shows you the hope that we're providing most of the country, to be honest, who are struggling with weight-related issues, including our own patients. And I'll show you data for people with severe illnesses like schizophrenia to really emphasize the fact that this is not a benefit which only will devolve to people who don't have chronic or serious mental disorders.

Dose-dependent benefits. You can see five milligrams gets you some, but 10 really gets you the most, but you can always go up to 15 as well. What do people get? Well, shockingly people get nausea and vomiting and the usual stuff. You can see COVID, they had to put that in, because the study was done during the period of more active COVID infections as well. Vomiting, it's higher than placebo, but I think they've learned also in doing these studies, if we slow the titration initially, things go better. Look at the dropouts, especially at the higher doses of 10 or 15. Those dropouts are somewhere between six and 7% versus 2.6% on placebo. It shows you that if you titrate more slowly, you get better tolerability and people will put up with some of the nausea, as long as they're getting the weight loss more than anything. And the whole idea of improving weight is that everything else gets better with it.

So, this is looking at the risk of certain types of comorbidities, depending on how much you benefit. You can see the risks for hyperglycemic and hypertension-approved even with modest weight loss of zero to 5%. But once you get to higher levels, you improve lipids. NAFLD is non-alcoholic fatty liver disease. This is what happens as people are insulin resistant they start to get fatty liver. PCOS is polycystic ovary syndrome. As you get even more weight loss, you improve reflux. If you have problems with your knees, it gets better. NASH is a more severe form of fatty liver, obstructive sleep apnea. And then once you get above 15%, you reduce mortality from cardiovascular disease, you reduce the risk of cardiovascular disease, you improve heart failure. And some people who previously had type 2 diabetes don't have it anymore, because their glycemic control has improved so much. This is just the physical manifestations of this more than anything.

Keeping people alive is a good thing. So, this is looking at the risk of major adverse cardiovascular events and people who are in these studies. Now, the first data I'm showing you here is a 12% reduction in people with type 2 diabetes and obesity, so this would be the highest risk group. If you have a diagnosis of diabetes, your risk for a future heart attack is almost as high as somebody who's already had a heart attack. So, this is the highest risk group, but even in people who had obesity without type two diabetes you're also reducing cardiovascular events. And that's wonderful. These medicines keep people alive, and you can see the biggest effect are on those which have the most benefit. This graphic on the left shows you a number of compounds, many of which you've never heard of. Many of those compounds also don't have large treatment effects. What has the largest treatment effect of all of them was semaglutide, and that had the greatest risk reduction.

This is really the most exciting thing I can think of related to body brain interactions. I already made the argument that systemic inflammation is not good for your brain. We often see it mostly as depression. I showed you some data on metabolic syndrome linking essentially the obesity and the systemic inflammation to cognitive dysfunction. Well, now we're looking at the risk of future dementia. So, here is what's called a retrospective emulation analysis. They get an EHR of over a million people. In this instance they looked at folks who had type 2 diabetes who had no prior diagnosis of Alzheimer's disease, and they looked at the future risk after starting semaglutide compared to a bunch of other anti-diabetic medications. Most importantly, among those people who were diabetic and obese, semaglutide decreased the risk of first-time diagnosis of Alzheimer's disease compared to all the other medicines with a hazard ratio of .29 compared to insulin, and even .59 compared to what the other GLP-1 receptor agonists.

And the same effect was seen in non-obese diabetics as well. So, we would say if you have diabetes, you have a lot of systemic inflammation when you get on this through something these medicines do, which is even better than insulin. You can see the hazard ratio was .29 compared to insulin, meaning they had almost a four-fold reduced risk of a future dementia diagnosis compared to insulin. And because semaglutide was the most potent GLP-1 agonist at the time, it was even superior to the other agents in the class. And this is really exciting news, because we've come to appreciate that a lot of people who we say, "You have Alzheimer's disease," it's maybe just not the classic Alzheimer's pathology. There's a contribution of also vascular components which are associated with having diabetes, metabolic syndrome and related aspects of inflammation, all of which are made better by semaglutide.

And we think the more potent agents would do this in even stronger manner. So, the potential signals are so great that there's now two large trials in non-diabetic populations, which we're hoping we'll get readout data in maybe the next year or so. They're actually looking at an oral form of semaglutide. So, you can see here they're double-blind placebo-controlled trial of either 14 milligrams of oral semaglutide plus SOC, a standard of care. Whatever they're doing they're doing, compared to placebo you can see there's a built-in titration. These people are followed over two years. But wouldn't that be wonderful? Imagine that you're heavy, you don't want to take a shot. So maybe have an agent which should not only help you with your weight but your future risk of dementia. This is one of the older drugs, liraglutide. Again, it wasn't the most potent in the class, but even in this small open-label study where people were only treated for a

month, we already started to see improvements in executive function and a composite battery of a bunch of cognitive tests.

So, there's something again, which these agents do likely centrally in the brain, which may be related to the peripheral effects, which may be related to the decrease in weight and inflammation, but may also be directly affected by the mechanism of action of the drug itself. And we're still trying to tease this apart, but the question is, how much benefit do we get from these newer drug like semaglutide in non-diabetics who happen to be overweight or obese? And that's really what we're looking for, because laryngotide wasn't the strongest molecule in this class. The fact that we saw an effect so early is wonderful, but I think for many people we want to see, can this be reproduced with an oral drug and can it be reproduced in people who are non-diabetic?

So, this is a double-blind study which is showing you as people were followed. Again, these effect sizes are significant. To put this in perspective, when I give medicines for depression or anti-psychiatry for schizophrenia, the effect sizes for both of those are between 0.4 and 0.5. The only medicine in psychiatry is a prescribed medicine which has a higher effect sizes than that might be stimulants for ADHD where we see effect sizes almost as high as 0.8 to 0.9. Here we have a medicine which is improving cognition, a double-blind study, and these effect sizes are quite significant. Digit span is one of those tasks that are given in a part of a cognitive battery, and here is a memory task as well. I think the whole point is that this clearly works. And again, just to bear in mind, liraglutide is not the most potent molecule in this glass.

So, what's coming down the pipeline? Well, for one thing, people like orals, a lot of folks just don't want to inject themselves even though the needle is small, there's just a lot of people who just don't like that needle thing. So, here's orals of semaglutide 50 milligrams and reduce body weight up to 70% in a Phase 3 study. They had to figure out how to get this stuff in an oral, 50 appears to be the dose. This looks pretty good, so just kind of stay tuned. They had to actually find what's called an absorption enhancer so they can get this molecule past the gut, essentially past the stomach acid and get it absorbed. But here we have a long-term study, again, 68 weeks, and people lost on average 70% of their body weight, very similar to what we saw with the injectable form. Obviously, very different doses to take account for the fact that you lose something in the GI tract, but that's it. That's what people want.

Here's discontinuations due to adverse effects. The one thing you do get from the oral route, yes, you got a fair amount of nausea, you got some diarrhea, but overall it was better tolerated. And if you look at the dropouts, see that last line, discontinuations due to AEs, which is adverse effects, only 6% for semaglutide-50 compared to 4% for placebo. I mean, they're getting real close. And I think this is really where the future lies for some, but maybe not all of these agents. If you can get into an oral form you can find the right dose. You really expand the population of people who may find this as an acceptable treatment. And you can also maybe improve on the tolerability by adjusting the titration. And here's some other investigational molecules as well. And these are ones which are more suitable for oral delivery than a larger peptide molecule as we call them. And so this is one which is in clinical trials, you can see the name there orforglipron versus placebo. So should we get about 15% weight loss at week 36?

Safety profile is very similar to what we're seeing with other agents in this class. There's another one, danuglipron. We should have data in theory, which will be coming out soon. We thought we were going to complete this over a year ago, but we will see where this is. But I think the point is that if you have individuals who you're working with, or loved ones who really are not big fans of the needle, even though the needle's tiny, they just don't like the idea, there is hope for them that there will be oral agents which can be used just through weight loss in non-diabetics, which will give you very similar and robust extent of weight loss as we saw from the injectable drugs more than anything.

So, here's another one, survodutide. Again, these are multi-mechanism agents. People are playing around with the recipe and trying to figure out what the best way is to modulate this system. Max dose you're getting almost 19% weight loss, so right in line with what we want. One thing they found, again, if you titrate it rapidly, people don't like it. And so the Phase 2 trial they had a fair amount of dropouts due to

adverse effects. They learned their lesson. I'm surprised they didn't really know that to begin with, because we've seen that for a long time with these types of medicines. But they learned their lesson, they're going to go even slower in Phase 3. And what was interesting is that even at the week 46 endpoint, the weight loss appeared not to have plateaued. And so, the studies of semaglutide and tirzepatide were 68 and 72 weeks, and they may even go a bit longer in their next studies.

This is the Phase 2 study and you could see the dropouts due to adverse effects were really high. The data I showed you earlier with oral semaglutide, the difference was 6% dropouts for oral semaglutide 50 versus 4% for placebo. Where here we have again a dropout rate of 4% for placebo, but it was many times higher for survodutide, so they're going to fix that in the titration, but we will see where that goes more than anything. And here's the one which is a triple agonist. Two's not good, three is better. Actually, two was very good, but three may even be better. So, here's a 48-week study. We're now even getting almost a 25% weight loss more than anything. And of course, it also looked like it hadn't plateaued. How does it look in terms of tolerability? Well, discontinuations due to adverse effects was almost zero for placebo. For the low doses it was like six or 7%. As you got to the higher doses it wasn't that bad.

And that's the beauty of this is that they figured out the titration, they figured out the recipe. Even at the highest dose, 12 milligrams, the dropout of the placebo was 16%. It's not as good as it could be, but it's pretty good for a lot of these doses. And I think as we have more of these agents studied, people will figure out what the best initial dose is and how to titrate this to mitigate some of these adverse effects and get people over the hump, so to speak, so that they can stay on it for 48, 68, 72 weeks and achieve that maximal weight loss. So, we used to think the gold standard for people with surgery, sleeve gastrectomy and other related surgeries and what people used to get on average, 25% weight loss, we're now bumping right up against that with these medications. And that is what is so exciting.

People are going to continue to develop agents in this class. We're really just at the beginning at the dawn of the era of these treatments. Yes, the current available ones are injectable, they're weekly, but that may change over time. And the extent of weight loss really will rival that of what we've seen in the past from the surgical approaches. This is one concern that people had had initially. When these drugs were approved for weight loss the FDA blanketed them with the same suicidality warning as they did for everything else, which was approved for weight loss even though there wasn't really a signal here. Over time, as these agents used more widely, the FDA really has modified its position, so the package inserts haven't changed. But here we have this drug safety communication, which was elaborated by the FDA almost exactly a year ago. So, they have their average event reporting system or FAERS, and their reviews did not find an association between the use of these GLP-1 receptor agonists and the occurrence of suicidal thoughts or actions.

They did say, "Look, there's a number of these events was actually quite small, but so possibly there's a very tiny risk." But they really wanted to go out and get in front of this and say, "We're not seeing this so far." We now have a subsequent review where they used a comparison of either metformin or an old drug called orlistat, which really impaired absorption of fat, had a lot of GI side effects, I would say. So, most importantly, the Guirguis Analysis looked at people with psychiatric disorders, because they really wanted to say, "Well, these people were often excluded from the clinical trials. Are we seeing something different?" Now again, you look at a large group of people, there are going to be some folks, regardless of what you're doing to them, will have episodes of suicidal thoughts or even self-injury. But the rates were lower with these GLP-1 receptor agonists that they were with metformin, they found no causality or link between suicidal ideation and these newer medicines.

They said, "Of course, there's no definitive conclusion because we don't have prospective studies and we should do more research in people with coexisting psychiatric disorders, but at least the datasets we have don't show an association." Here we have a retrospective analysis that was published by Kerem in 2024. They used a big U.S. electronic health record, over 100 million people involved of they looked at obese adolescents. This is analysis of adolescents in particular, age 12 to 18 who got a GLP-1 receptor agonist or lifestyle innervation within the prior year. So they found 4,052 who got this, and then the control group

was much larger, 50,000 people. Guess what? When you give one of these new agents to these obese adolescents, you actually improve suicidal ideation attempts dramatically, 33% reduced risk for suicidal ideation or attempts over 12 months of follow-up. And I think more than anything it really speaks to the idea that being obese has a number of consequences, one of which is mood and self-esteem, especially if you're in a period of psychosocial and physical development.

Treating this population gives enormous benefits, not only on metabolic health, but on all other aspects. The extent of this reduction in risk for suicidal ideation or attempts was more than anyone had possibly thought.

And then lastly, we have another study that was published just this past year, using again the same large database. They look at overweight and over obese individuals who are prescribed semaglutide or other obesity treatments, and they looked at people who are just obese and then they replicated those in type 2 diabetes. Guess what? Using semaglutide was associated with lower risk for either incident or recurrent suicidal ideation. This was consistent across sex, gender, your heritage. It is replicated in people who are diabetic as well. So, any concern that overall as a class these medicines increased risk for suicidal thoughts or behavior is really not seen.

Does that not mean that there might be individuals who will complain about this? Absolutely, everyone's different. As we know, some people when you give them a traditional antidepressant they say they feel worse. I think the point is though, as a class we're not seeing increased risk and in some instances dramatically decreased risk for suicidal thoughts and behavior. And here's the reviews looking at neuropsychiatric events in people with diabetes as well, and they look at the risks of 22 neurological and psychiatric outcomes within one year of the index prescription. You can see this is a laundry list of pretty much every neurological psychiatric condition you can think of. A big chunk of people on semaglutide, and they look at other diabetes medicines, sitagliptin empagliflozin, an old medicine glipizide as comparison. So, they try to correct for all maybe differences in their populations, but cognitive deficits improved on semaglutide compared to other agents. Dementia risk was better. And guess what? People even smoked less as well.

I know that one of the questions that was put forth was, "Might we use these GLP-1 agents for substance use?" Well, maybe not as a standalone therapy, because if you're thin and you're a smoker, I'm probably not wanting to give this to you. But if you happen to have people who may also be using substances who are heavy, there's enough data which shows there's benefit. Most of the data has shown risk and alcohol use disorders, I would say. It's just one of those unintended outcomes which is seen with these new medicines, which people are very excited about.

And here is the last thing I'm going to show you. The use of these agents for people with severe mental illness. These are predominantly individuals living with schizophrenia or schizophrenia spectrum disorders. You can see this literature goes back about a decade, and I gave you a summary table down below. I think the point is that it's very clear that these agents do work. They are tolerated in a very similar way in this population. Obviously, people have to agree to be on it. Most of the data is with the not so effective older medicines like exenatide and liraglutide. We had this one retrospective chart review that came out in 2023 of semaglutide from people in Toronto, and it was pretty clear that it worked, but it's just one of the only studies with the newer medicines. But the point being is that this is an acceptable treatment for many people with severe mental disorders, and we just look forward to having newer data with the more potent medications like semaglutide and even better tirzepatide in this population. It represents one of the great hopes for them.

What's the issue with practical access? Well, one thing, some people don't like the side effects, I'll just say that, and we've talked about what they are. There's ways to mitigate this. A big part of it's the early titration. You also have to convince people, "You can't eat what you used to." In talking to people who've been on these meds, they said, "Yeah, I overdid it and I really paid for it. In the past I could eat so many slices of pizza. Maybe it was the whole pie. And I was on the medicine for a while and I thought I could

do that. I was still a little hungry and it really made me feel not well." And people will learn and it'll help them modify their behavior. But the idea is we can manage most of these things by watching the titration. Just counseling people to watch their portion size, make sure that they drink water, stay hydrated, if they really get constipated we have stool softeners.

There's this old concern, this is based on animal models, about issues with pancreatic and thyroid safety. None of this has really been a clinical relevance. Look, we've had other drugs, which sometimes cause problems like valproate in pancreatitis, really didn't stop us from using it. And so these things haven't panned out. Again, these agents have been out in the world for over 15 years, so if there's any effect in these tumors, it's not been seen and these tumors are pretty rare to begin with as well.

This is the big thing more than anything, and I hate to leave on kind of a downer, but this is the problem, whoops, is that the coverage of these medicines through Medicaid is almost non-existent. And that's just sad. It is sad. It's such a huge problem in the community that very few states cover these in their Medicaid population.

And I don't care about the stuff to the left of semaglutide, it really didn't work very well. What we want people to have access to is semaglutide in the form of Wegovy, which is for non-diabetic weight loss. And then in the future it will be of course for Zepbound, which is tirzepatide for non-diabetics. So you think, "Well, why is this?" Well, for one thing, there's money issues if you have private insurance. A lot of these commercial plans just don't want to spend money, even though they'll benefit in the long run, but a lot of them are very short-sighted and they just look at the out-of-bottle pharmacy cost. But the big issue for Medicare and Medicaid is that Medicare itself was legally prohibited from covering agents used for weight loss. And I'll give you the quote there by the Modernized Medicare Act of 2003, and that was passed in the wake of the debacle caused by fenfluramine. Fenfluramine caused a lot of heart valve problems, and they said, "We're not going to cover these medicines." So they really damned the entire class based upon this.

Well, people have been trying to reverse this for a while. Now that we've realized the potential for these new ages, especially since semaglutide was approved for non-diabetic weight loss in 2021 in June, the Treat and Reduce Obesity Act was introduced then, and it's been reintroduced in each session of Congress since then. The whole idea is that Medicare Part D would cover this, but it's languished. And sadly, again, the current session of Congress just ended a few weeks ago. It wasn't signed in, and we hope it'll be reintroduced. I give you the link right here, and I really want to encourage you, you have a big voice out in the world there. Get yourself and your friends and whoever else to really write to your congressman and or senator or both. There's a petition that can be signed. I give you the link right here. Obesityaction.org/troa.

TROA again, it stands for Treat and Reduce Obesity Act. We need to get these medicines covered. They save lives, they help people. They improve quality of life. They do so many good things. They reduce future dementia risk. Yes, they may be more expensive right now than doing nothing, but people will benefit. Society will benefit by addressing this very important and prevalent problem, and whatever we can do to get access for the people that we love and care about is going to be to the greater good.

Lastly, I think we all know that this is a prevalent problem in society, especially with our loved ones living with severe mental illnesses. We started some of the old stuff like metformin, even with adolescents and adults, everyone should have access to that. It does what it does. It does it best when you start it off from the get-go.

But the new agents really offer a lot of hope, and they do tremendous things both on weight, metabolic parameters, cardiovascular events. There's cognitive benefits. There's no evidence for increased risk of suicidality. In fact, the exact opposite with a number of positive studies in people living with severe mental illness. Whatever you can do to advocate for passage of the Treat and Reduce Obesity Act, please do so. And at this point I'm going to stop talking, so I want to thank you all for paying attention. I'm going

to pass it back to our moderator, Dr. Duckworth, and hope you have some great questions for me. I think you will. Thank you.

Dr. Duckworth:

What an incredible covering the waterfront of these important compounds. Let's start with some basic clinical things. Some people ask the basic questions, "What is metabolic syndrome?" Could you just tell about that? And then I'm going to give a follow-up question. Why do people gain weight on compounds like olanzapine?

Dr. Jonathan Meyer:

Yeah, so metabolic syndrome is a syndrome where you don't have to be diabetical, or you could be, which is associated and the core aspect was central obesity. We've come to realize that some people who tend to put their obesity in the middle tend to have more problems with inflammation and other associated problem. So, metabolic syndrome, there's five elements to it, one of which is central obesity. Other elements include elevations of your triglycerides, having low levels of a good lipoprotein, which is HDL, want HDL to be high. Also, elevated blood pressure abnormalities of your glucose. So, people who have that may not be diabetic, or some are, but they're an increased risk for more cardiovascular events and other problems than folks who might be equally heavy but tend to distribute their weight below the equator, I'll say that. And to qualify for metabolic syndrome, you have to have at least three of the five criteria.

And we've really focused on this, because again, there's some people who may be looking equally as heavy as the other person, but depending on where they put their rate really makes a difference in their future risk. Now, the other aspect is, why do medicines cause weight gain? And I touched on it before, but I'll say it again. We think the common element for a lot of psychiatric medicines, which causes weight gain is histamine H1 blockade. So histamine H1 blockade does two things for you. It makes you sleepy, but it also impairs satiety. Meaning people keep eating, because they don't feel full. And it's not just antipsychotics. There's an old antidepressant called Remeron or mirtazapine, which has a lot of this. Any medicine which has this property tends to cause a fair amount of weight gain.

There may be other pharmacological properties on top of that, one of which is called serotonin 2C. If you block that it seems to give you an additive effect. But histamine H1 blockade really is kind of the necessary condition. And medicines which have a lot of that tend to be associated with a lot of weight gain. And sadly, even though it's one of my favorite medicines, clozapine, it has a lot of that, as does olanzapine and some others. Because it's part of the molecule we can't take it away. That's the way olanzapine was synthesized as part of the structure. I talked about a way of mitigating, at least for olanzapine, because there's a combo drug with samidorphan that doesn't exist for other agents. We just have to find other ways to try to mitigate the problem.

Dr. Duckworth:

Thank you. Many people asked how long you stay on these medicines. I know you mentioned long trials, many weeks. Is the expectation that you might put some weight back on after these?

Dr. Jonathan Meyer:

Yeah, actually, and it does happen. And there was a great editorial very recently talking about some of the ethics of this. It's that if you give people intermittent access, they may lose the weight and gain it all back. And we've come to appreciate that in fact rapid regaining of weight may be even more unhealthy than had you been at that same weight the whole time. And that's why we're really trying hard to see if we can get some of this legislation passed so you can actually get people on these medicines and then they'll be able to stay on them. I don't want to say forever, but I think that's the expectation is that this is a chronic

condition, like many things, like schizophrenia and you may need to be on your antipsychotic forever. That's really true for the average person. A lot of folks have a lot of genetic risks for overweight and obesity, and that may be compounded by the medicines that they're exposed to.

Well, that's not going to go away. Their genes aren't going to change, right? Maybe we'll be lucky and have medicine in the future with lower risk, but you can't bank on that. And maybe this is a person who needs a certain type of medicine like clozapine for resistant schizophrenia, which we may not be able to replicate in another molecule. So, we found that when you stop it the weight is gained back, and fairly quickly. At least for now, I think the party line is you want to commit somebody to it if you feel like they'll have ongoing access.

Dr. Duckworth:

Thank you. One of the other questions that come up is, "Should a psychiatrist prescribe this?" Again, we're going to talk about access in a bit. Is this something a generalist would do? Who should be prescribing this compound if you can figure out how to run the gauntlet to get access to one of these treatments?

Dr. Jonathan Meyer:

Yeah, so psychiatric providers have I think kind of gotten comfortable with prescribing metformin and when many of us who did research in this area used to talk about using metformin, many people say, "Oh no, that's out of my scope or whatever." And now we've come to accept that it's not a big deal. I think there might be still a little bit of trepidation among psychiatric providers, whether it's physician, nurse practitioner, PA, about these new agents. It's injectable. It's just a little unfamiliar like metformin was. I think over time you will see more and more, but the norm most commonly is it will be a non-psychiatric provider, the primary care. And again, all you need to do is have obesity. You have to have a BMI of 30 or BMI of 27 and one complication like hypertension to qualify. The big problem for many people, especially if a severe mental illness is it's not covered by Medicaid or Medicare, and that's just going to be the limiting aspect. Could you pay out of pocket? Sure, but that's not really feasible for a large chunk of humanity out there.

But if you have somebody who qualifies, get ahold of the primary care provider and say, "Hey, this person qualifies. Yes, they have to do paperwork, yes, it's a pain in the neck. But if they have the type of insurance which will allow them access, then it should be pursued."

Dr. Duckworth:

Everybody who gets registered is going to get a slide set, a copy of this report recording, you did cover a lot of material. I want to point out that we had a series on cognition last year, cognitive enhancement therapy, cognition. So, your conversations about the potential prevention of dementia, also very important, probably more than we can talk about in this aspect. So, let's talk a little bit about advocacy. As everybody knows, nothing gets done in American mental health without NAMI. What would be the most effective way? Because there's pharmacy committees in all 50 states, so no Medicaid state has paid for Medicaid yet through their pharmacy and therapeutic committee. Is that true?

Dr. Jonathan Meyer:

Yeah. I think what we have to do is really try to get Medicare on board.

Dr. Duckworth:

Medicare.

Dr. Jonathan Meyer:

Get Medicare on board. A lot of the states will follow. Now, there's a few states, I believe, who are just on their own, are doing it through Medicaid. I don't think it's very many, but once we get Medicare on board once on the federal level, because what happens, a lot of states are financially dependent on what happens with Medicare. Once we can get that on board, and so my feeling is, bug your congressman, get her him on the horn, tell them how important this is, that these new agents save lives. They're not like fen-phen back in the day where it was harm, and be honest, the weight loss wasn't dramatic either. This is a very different era. This is a very different set of molecules. Think of all the things, it's not just people with mental illness. The broader population struggles with this. And here we have agents with dramatic effects on weight loss, on future risk for cognitive impairment, future risk for major cardiovascular events. You're going to save the system money in the long run.

Dr. Duckworth:

Yes, big time.

Dr. Jonathan Meyer:

I hate to say it, some people are cynical and think, "Well, if the guy dies of a heart attack, I don't have to pay for him anymore. He is off the payroll." Hey, guess what? But maybe he's not going to now he's going to be incapacitated with his cardiac problems and you're going to pay for him for a long time. Don't take the cynical route, take the bigger view and say, "Look, people live a lot longer now. If we can reduce future dementia risk, it's totally good."

Dr. Duckworth:

I'll follow up with our policy and advocacy team about what we're doing about Medicare, but I would encourage everybody to talk to their state NAMI, we're in every state. And having, I was the commissioner of mental health a very long time ago before I had gray hair. And the Pharmacy and Therapeutics committee, they make decisions on drugs. And it happens every month, every three weeks. And they review the data, and I think it's really important to do individual advocacy. But I will look at the Medicare angle.

Dr. Jonathan Meyer:

I was going to say, use this slide set, I'm happy to. I've reviewed the data, as recently it's available, especially the data we have in people with serious mental illness, which to be honest are typically excluded from trials. But now we have retrospective data looking at suicidality and adolescents and people with SMI. It shows that there's no unique problem there and there's benefits.

Dr. Duckworth:

Fantastic. Let's talk just a little bit more about the advocacy angle. Though private sector payers pay for this.

Dr. Jonathan Meyer:

Some. It's hard. You can get to it. There's hoops to jump through, there's no question. They're going to make you take some junk and they'll torture you a bit, but.

Dr. Duckworth:

They're going to fail first. Would you include metformin in the list of compounds that's hard to get?

Dr. Jonathan Meyer:

No, metformin is dirt cheap, everyone can get it. And that's why I say, if you have a loved one who is going to start on a medicine, which itself causes a lot of weight gain or if they're higher risk, and typically that's people who are younger, say anyone maybe under 25, I would want them to start on metformin day one.

Dr. Duckworth:

And that is available. Because I prescribed it and didn't have any trouble doing it.

Dr. Jonathan Meyer:

No problem. Yeah, for sure.

Dr. Duckworth:

And that is available. So, I agree that's kind of version 1.0, but it does help with some of this.

Dr. Jonathan Meyer:

It does.

Dr. Duckworth:

I want to thank the audience. We had 650 people, more than 550 are on now. I want to thank you for your attention, your questions. This is an important area. I hope we can have you back in the future as this literature evolves. This is an important topic and I just want to thank you, because we've never had solutions for this. We do have an access problem. NAMI is very good at advocacy. If it wasn't for NAMI there wouldn't be a 988. So, I just think we can work on things. I just want to say thank you very much. Hagen, let's go to our last couple slides please?

Our upcoming All-Star team continues. Dr. Maurizio Fava, who's the youngest person in Harvard medical School history to become a full professor has written and forgotten more articles than I've ever read on depression and treatment resistant depression. Maurizio is a lovely human being as well. Clozapine updates including the battle around REMS. Deanna Kelly and I were at the FDA hearing, Deanna is really a national treasure in approaching the problem of access to clozapine, and the REMS recommendations for it to be closed down were heard quite clearly. So the question is, what will the FDA do, and how does that then relate to package labeling? This may help people make their own choices, which is a core NAMI value. People should be allowed to assess their own risks. You get on a plane, you fly to the FDA hearing, you took the microscopic risk. This is the example, we want people to have information and make a risk. These are two important talks coming up in our brief pharmacologic run. We had a cognition series, now we're having a pharmacology series.

Okay, next slide please? NAMI has two books. Isn't that fun? We ask real people who use their names what they had learned. If you've lived with something, you may have learned something. And that's the radical secret in our two books. They're NAMI's copyright, all royalties go to NAMI, and that was a really fun project.

Let's go to another slide please. We have sponsors, which means we take checks. They have nothing to do with our content. We invite America's All Stars, and nobody has any input into that.

Let's go to the next slide, please? You are not alone. This is an educational series. Obviously, this is not to give medical advice. And if you're moved to make a donation to NAMI, we accept money, because we're a non-profit. But essentially it's the generosity of our experts like today's speaker and our lovely staff who put on these productions that I just really want to thank.

Let's do the next slide, please? Thank you. You can reach me. My name's Ken Duckworth. My email's ken@nami.org. I have an agreement with the HR department, nobody named Ken can be hired at NAMI. And I'm not an expert on this, I have to be a generalist, but I will do my best to find the answer for you. Ask the Expert is a website email address expertly run by Hagen. And we look at the topics that you want to talk about. This is a community we treasure and we'd like to give you the information you want. I want to say thank you again, great speaker, great session, and have a good evening everyone.