[MUSIC PLAYING]

SPEAKER 1: Yes, I will give a pretty general overview of the problem, and some of the difficulties, and an overview of providing treatment. But then Roy will really take over and give most of the rest of the treatment specific comments about dealing with this population as well. And really no disclosures.

I should also point out that I give an annual lecture to medical students on smoking. So some of these are taken from that lecture. This is the one I always start off with. Smoking is really a 20th century phenomenon that almost didn't exist before the 1900s. It was smokeless tobacco, pipes, cigars, or whatever, but not as much of a problem.

But you could see the rapid rise to normalize-- so the tobacco industry normalized smoking and pushed it on soldiers and everything else. And then finally, in the middle of the century, the health impacts really started becoming prominent. And so since then, it's been an effort to denormalize smoking with some success.

And so this is also a common slide that I use to show that there's been a steady decline. So 50 years ago, 42%, basically, was the prevalence of smoking. There really was no individual difference to speak of in terms of who the smokers were. Lots of people smoked. It didn't matter if they were rich, poor, or whatever. And since then, we've had a steady decline. But I always tell the medical students, this is actually misleading.

The blue line is the prevalence rate. And that looks like, well, we're really making progress. That's great. In a decade or two more, it'll be down to single digits, and pretty much no more of a problem. And that's really misleading for at least a couple of reasons. One is, the red line is the absolute numbers of smokers. And they have only recently started to decline. It's been steady since the '60s, basically, in terms of the absolute numbers, because of the growing population.

But the other reason that it's misleading is because there really are individual differences in smoking prevalence now. This is just an example for education. So some high schools-- they've had a little bit of a decline since the '60s, basically. But for the very educated, you can see it's over 80%. Then on the right, I just have some individual prevalences.

So for those with less than a high school education, a third still smoke these days. But if you have a postgraduate degree, you're under 5%. So clearly, there's been a disparity in who has had success in becoming smoke free. And then you can go into lots of other vulnerabilities. Poverty, access to medical treatment, basically, and then obviously, mental illness is an extreme case of this vulnerability.

The top right there is the prevalence. So this is just over the last 25 years or so. If you look at the top bars there for those with mental illness-- so they started 25 years ago, 40% to 45%, kind of like everybody was in the '60s. And they stayed there all the way through even today.

Whereas the lower bar there is the general population. They've just continued to show that gradual decline. And then the bottom right there is cigarettes per day. So the intensity of the smoking intake. And that's also been high, and stayed high with mentally ill smokers. And it's just gradually been coming down in the other population.

So there's really been this very extreme disparity in who has had access to effective treatment, and who has successfully quit. And that's shown here with this slide by diagnosis.

So this was actually 2007 data. So it's not as current as I would like, even though it just came out earlier this year on the right-- a cancer journal. So the general population then was about 20%. And you can see how much higher it is for various diagnoses. And then especially schizophrenia is one of the highest.

And so I looked for an updated slide to see-- and I couldn't find one-- but this is what I would anticipate that it would look like.

There'd be a decline in the general population of maybe another 5%-6% down to 15%-16%, but no change in those with mental illness. It just would continue to be flat and high like I showed you before for mental illness in general.

So this is from Roy. He put this together. Today, the majority of adult smokers in the US have a current or history of mental illness. So if you think about it, the invulnerable I guess, or the people who don't have a lot of the other concurrent difficulties aside from smoking-- they have been able to have a little bit more success in quitting. And so they are disappearing from the smoking population.

Well, who's left? All the people with the vulnerabilities-- poor, uneducated, and obviously, those with mental illness. So he put together this slide. And based on the data, the majority of Americans today who smoke have a current or history of mental illness.

This is another slide that a use with medical students. It's a little bit not widely understood that, while there are dozens of toxic compounds in tobacco smoke that can and will kill you-- heart disease, cancer, COPD, et cetera-- and there are thousands of constituents in tobacco smoke and general, nicotine is really not one of those toxic compounds. It's not benign, but it's not, generally, the constituent that causes these disease risks.

And that's why nicotine replacement is generally safe-- gum, patch, and probably-- and I'm always hesitant to talk about this with any conclusions-- but probably why electronic cigarettes are certainly not as dangerous as tobacco smoke. The jury is still out. There just hasn't been enough research on electronic cigarettes in terms of their health impacts.

But nicotine is really not the health problem, in terms of toxicity. It is why people smoke, obviously-- to get that rapid rush and bolus of nicotine to the brain that has its various effects that people find pleasurable.

So this shows the impact which Roy was getting to about the consequences of smoking. So this is all relative to someone without mental illness who has never smoked, in terms of years of life lost. So basically, these are additive impacts.

So if you're a current smoker without mental illness, you lose about eight or nine years of life. If you have not ever been a smoker, but you do have mental illness, you lose about six years of life. Well, if you have both together-- you have mental illness and you are a smoker-- they combine together, and you lose about 15 years of life. That's what the bars mean. And there's reduced risk if you're a former smoker. It's not completely eliminated, but it is less. But again, that also is additive. And so when you think about a consequence of what patients and anyone who smokes does, there's real consequences in terms of the predictable years of life lost.

This is also a slide I routinely use with medical students to say, on the other hand, there is never an age at which it's just too late, and say, well, I guess I went on too long, and so I might as well just keep smoking because I've just ruined my health anyway. It really is the case that you can lengthen your life even after decades of smoking.

You can't quite see the top there, but the top one-- if you quit at around age 40-- so you've been smoking for 20 years, which you think, wow, that's kind of a lot-- of the curves there in terms of survival between the stopped smoking and never smokers are almost exactly alike. So you gain almost as much years of life as if you never smoked at all.

Down below, if it's about 50, well, it's a little bit less. But it's certainly much better in terms of years remaining than if you just don't quit at all. And then finally, at the bottom, that's 60 years. So you've been smoking for 40 years, and you still have years of life gained if you decide to quit at that point and you're successful than if you just give up and say, I'm just going to keep smoking. So there really is no age at which it's not worth quitting.

This is a very busy slide. But I always want to provide this because when I talk to medical students, they don't know what specialty they're going into. So they may go into pediatrics or something that they don't think they're really going to have that much to do with helping adult smokers to quit. But I tell them, almost no matter who you see, you will need to know what their smoking status is. Because it could impact the medications you're giving them to treat anything.

So this is a slide by very well-known clinical pharmacologist, Neil Benowitz, that shows a lot of the interactions between medications and smoking, in terms of how they affect the pharmacokinetics and dynamics-- so the efficacy of those medications.

So if you're giving a medication and you're monitoring the blood levels and they quit smoking, you may need to titrate down to the blood levels of that medication, because they may be having side effects or whatever. And then by the same token, if they relapse, that's going to change, again, the efficacy of those drugs. You might have to ramp up a little bit-- or more likely, really help them to get back on track and to stay quit from smoking in general.

And there are many psychoactive medications here that are affected. Alprazolam, chlorpromazine-- this is 20 years ago. I haven't seen an updated list-- Closzapione, fluvoxamine, insulin, Olanzapine, propanolol, tacrine, theophylline, tricyclic antidepressants, and benzodiazepines for the pharmacodynamics. So that was the pharmacokinetic and the pharmacodynamic-- just how the medications are affected. Beta blockers.

So all these, if you're treating any patient at all for anything, if they are smoker, you need to know what their status is. Because that could really impact the efficacy and the blood levels or whatever of the medication you are prescribing for them.

OK, so this is just a background to the treatment of smoking. And Roy's going to pick up and go into this in more detail. This is a handy mnemonic that providers use-- the five A's. So ask about tobacco use in every encounter, advise them to quit completely-- and just that alone, a provider who says, there's really very good evidence that quitting smoking completely really will help your functioning in general and years of life gained and all that-- that alone, a couple of minutes of very strict advice, can really make a difference in having somebody move to think about quitting, or even be successful.

There was a very good British study that, on a large scale, had just a couple-- 5%-6% alone-- but it really added up to thousands of quitters, just with five minutes of strict advice to quit smoking by their doctor. Assess readiness. And then the primary time that you would spend is to assist them in quitting, and to arrange the follow up. I left in the little question that I sometimes provide to medical students. So I didn't change the slides that much for you. Sorry.

But which of these is least likely to be done? I don't tell them until the end when I give them some other data. But I will tell you, the least likely of these to be done is to arrange follow up. And that is a mistake. Because this is a process. It's succeeding, failing, succeeding, failing, and then finally really making it successfully to stay quit. But it requires arranging follow up with the provider to check how things are going.

So what do you do if somebody doesn't want to quit? And that obviously is going to be a little bit more likely with smokers that you might come into contact with. So there is another mnemonic for the four Rs-- not quite as well known as the five A's, but it's just to try and remember how to address this. So you want to enhance motivation.

And you look for things that are relevant that focus on the risks that really mean something to them. You talk about the rewards, which I'm going to show you in a second, are things that you can bring up. And then you just repeat that motivational message all the time.

So in terms of motivating patients to quit, a lot of people say, well jeez, 20 years from now, I might not get cancer. All right, well that would be great. But who thinks about that long term? But there really are some things that can be improved right away within days or even weeks of quitting. And some of these are listed here. And what you want to do is find something that will really resonate with that smoker.

As part of the clinical grand rounds that Roy led, we had a patient who had grandchildren, I believe, who wanted to set a good example and didn't want to expose them to secondhand smoke. And that really resonated with her. And that's great. I had showed this slide, and I said, great. You just backed up the top couple of examples that I gave there. And so those are the things that you want to look for-- something that will really resonate, again, with that patient.

And then keep repeating that. Talk about them the next time. Well, how's it going? And then go over some of these additional possible rewards again. So assist is really the primary aspect of treatment. Behavioral counseling is absolutely essential. There is no medication that you could just give a prescription for. And I'll briefly go over some medications in a second. But Roy will do most of that. You can't just give a prescription and say, well good luck, and hope it goes well. You've always got to back it up with counseling.

So one of the first steps is heightening the motivation, which I just showed you. And then the single best thing that you can do-- and it takes 30 seconds-- is to have them set a quit date. That makes it real. If you say, well yeah OK, in the next couple weeks, maybe I'll try to quit, it just comes and goes and they never get around to it.

So you talk with them about when would be a good time. And really set a firm quit date. Because that really does increase their commitment and their preparation. And they should tell their friends to get social support. It also puts a little bit of pressure on them to follow through and quit like they said they were going to.

And then you also ask about their anticipated difficulties. I also tell medical students, if somebody says, well no, I don't think it'll be too tough. I haven't really thought about it. They're not serious. They will think about what will be the difficult times.

So you want to anticipate those, and go through-- what are some scenarios? What are some alternatives that you can do? And friends, for sure. Do you have smoking friends? Do you have non-smoking friends? Try to spend a little bit more time with your non-smoking friends. And tell your smoking friends, can you not smoke around me? Or I might have to not meet up with you at lunchtime or whatever, and smoke this time. I'll just have to come back to you and deal with you a little bit later. Or we can meet other times when we're not going to be smoking.

And then keep teaching coping strategies. And one of the things that you'd start off with-- you just make sure there's no cigarettes around in the house or whatever. Because it's very easy, if you have a craving, to just reach into the drawer, pick up a cigarette, and light it up, and that's it.

But if you have to get in the car, especially in this weather, go down to the store, pay your $6, $7, or $8 to get a pack, and then light up-- maybe before you get to that point, you'll say, my craving's kind of gone now, and maybe I can really deal with it. You won't do that. So availability is really the thing that you need to work on, making sure that they're just not easily accessible.

In terms of the medication-- again, Roy is going to go into this more-- there's still only three accepted FDA approved medications. Nicotine replacement, which has been around for a little over 30 years. The patch gum. And now there are other types of products. buproprion or Zyban, and then varenicline or Chantix.

Now as I said a moment ago, you can't just give a prescription and say, all right, well I've done my job. That's it. Good luck. Because no medication causes quitting if someone is not already motivated to quit. It's not like other medications that reregulate your system and you're fine then-- reduce your fever, and that sort of thing.

All it does is, it really attenuates the withdrawal severity, and takes away the craving a little bit, so that if you were already motivated to become a quitter, basically, it will help that a little bit. It'll lessen the chances that you'll have a lapse, and increase your ability to stay quit, basically.

So that's why the counseling has to come along with the medication. They are effective. They just don't completely eliminate your urges to smoke. I've done studies, not specifically for that purpose, but comparing these three medications in those who were already really interested in quitting versus, what I sometimes call, your generic smoker-- your smoker who's just not really interested in quitting-- we compared these active medications and placebo in a crossover comparison. And all the these medications were successful in those who were already motivated to quit, and did not work at all in anybody who was not already ready to start try to quit smoking.

So this was a short term test on each of the active drugs versus placebo. We were just looking at whether they would help people to initiate quitting. And they did not people who were asked to try. And we actually paid some of them per day of quit. And there was no difference between the active drug and the placebo for the people who are not already motivated to quit. But they both worked pretty well, significantly, in those who were already thinking about quitting-- not trying to quit right then, permanently, but saying, well, in the next month or two, I really want to try and quit smoking.

So we were looking specifically at their existing motivation to quit, and saw that the medications absolute were only effective in those already motivated to quit, and had virtually no effect on those who were not already ready to quit. So again, you just can't give a medication and just say, well that's it. That's all I need to do.

These are just some of the withdrawal symptoms. And I think Roy, again, will go into this. I've highlighted the two really critical ones for most people. They're the most common and they're often the reasons that people give for just saying, oh, I just couldn't stick it out. Negative affect, sad mood, and also the craving and the urges to smoke. But these usually only last for a week or a couple of weeks, as the system really does get used to not having nicotine on board, basically. So it peaks in the first day or two, and then it can last.

Now sometimes, some of these symptoms can be long lasting for certain people. But really, just two weeks is about the length. And then you are often able to readjust and become better, actually, functioning than you were before you quit.

And so some of the issues treating mentally ill smokers-- and Roy and I have talked about this. Sometimes he'll have others, I think. But many providers mistakenly believe that a patient's smoking aids their mental health functioning. This has been going on for decades. And even recently, we've heard people say, oh, I don't want to get into their smoking whatever, because they'll just fall apart and have so much difficulty.

Yes, withdrawal does occur, and it can be fairly serious. But as I just said, it lasts a week or two. So if you can get past that to the point where it's receding, often you will find-- and there is research showing-- that overall cognitive and mental health functioning improves compared to before they quit.

So yes, it's difficult at first. It may rise a little bit as a function of the withdrawal. But then, if you get through that period, you will actually be functioning better than you did before you quit. And that's also what the patient that we talked with a couple of weeks ago said. She reported that too, that she felt much better after having quit.

The second problem is, providers say, well, it's less harmful than the other things that they could be doing to cope. Well, I just showed you the years of life lost as a function of the smoking. And if you are able to quit, it does lessen the number of years of life lost. So that's a pretty powerful impact. And to say that's less harmful is not really good news, I would say.

In terms of other issues, as Roy said, the Zyban and Chantix had black box warnings until just a year and a half ago or so, maybe two years now. And so that was really keeping prescribers from going ahead and prescribing them. Because if there's this black box warning, they say, oh, I don't want to get sued or get in trouble or whatever. And I'll show you some of the data resulting from that. But Roy will really go into that in more detail.

I was on the drug abuse advisory committee, which Roy said, where we met in September of 2016, and looked at the data. And it wasn't unanimous, unfortunately, but most of us voted to say, hey, this is no longer warranted, basically. And I was very glad to see that the FDA said, yeah, I think so. Because I thought with a split decision, they could say, oh, too risky. We'll just keep the status quo. That's fine.

But a majority of us decided that it really needed to be removed. And so I'm glad that that was done. And hopefully, they'll be more readily prescribed, and now give mentally ill patients some of the armamentarium that everybody else who smokes has been getting all along, basically. And they'll be getting more effective treatment and start to see declines in that smoking prevalence.

So when they do get these FDA approved quit medications, and are adherent-- and I used to have a slide to show why it's important for adherence, because obviously, success goes up with adherence to the medication. But the quit rates are better versus placebo for anyone who gets it. They are lower in absolute terms for those with mental illness and with poverty and everything else. But the medications do improve quit rates over placebo.

So these are the EAGLES trials results. It might be a little bit hard to follow. But basically, what they looked at-- and this is a very large study-- 4,000 non psychiatric cohort, 4,000 psychiatric cohort, basically randomized to veranicline alone, buproprion, nicotine patch, or placebo. So all four groups-- 1,000 in each-- with each cohort.

You see the placebo rates are the lowest. And this is just from weeks 9 to 12 to the 6 month period. So it does go down with each. But you could see, for every single medication treatment, they are better than placebo. And even for those who were psychiatrically ill, they were better. They were lower in absolute terms, yes. But they did better in quitting smoking than they did versus the placebo.

And what Roy, I think, is also going to talk about-- there was no greater risk of adverse effects. And that's what the real meeting was all about. It was to address this issue. Is there a systematic reason that the medications cause some kind of adverse event? And what initiated this black box warning were the anecdotal reports around 2008-2009 of people-- violence and that sort of thing. Whether or not they were ill, that didn't really matter too much.

And they just started to put this black box warning, thinking, oh, there might be something wrong here. And that's just the cause of withdrawal from quitting smoking in general. So it was the fact that they quit smoking and went through severe withdrawal, and a few isolated people had these difficult reactions that they put that up there. There was nothing systematic.

All right, well, Roy is going to show the slide of the rates of side effects. And it's just flat, all the way across. Basically, it doesn't matter what medication you were assigned to. The adverse events were the same. It was a little bit higher for those who were ill, but it was due to the fact that they quit smoking, not because they were given one medication or another.

So other effective approaches-- and I guess Roy can talk about this a little bit more. And I'm not a physician, so I don't prescribe, and so I can't say, oh, go ahead and do this. But there are others if you have difficulty with one. If you come back, sometimes-- so if you change the medication prescription, if somebody truly uses it correctly and understands what to expect the first time and doesn't make it-- if you go on to another type of medication, very often you're more likely to have success.

So multiple NRTs are one way. So patch maintains a trough level of nicotine in the blood level to minimize withdrawal. And then you have gum, or lozenge, or whatever for those momentary acute cravings during the day. Nicotine patch combined with buproprion, until veranicline came along, that was considered the most aggressive form of treatment. And that is approved by the FDA, that combination.

And then there's been a few studies looking at combined veranicline and buproprion, finding some success with very dependent smokers. That has not yet quite been approved by the FDA, as far as I know. But there is evidence that that will be even more effective.

This is a slide that I use with medical students. I always include the bottom part of this, because I think they need to know what has not been shown to be effective-- acupuncture, hypnosis, whatever-- those get lots of attention, I guess, in the media. And people anecdotally say, oh, well that's how I quit. Well, that may be the case. But systematic controlled trials have not shown that those are effective.

So this is one other point that I emphasize with medical students. It might be a little bit less relevant here, but I always emphasize that you need to have biochemical verification of the quit status of your patient. And there's two ways-- carbon monoxide, blowing into a monitor, or getting a saliva or urinary cotinine. Cotinine is a metabolite of nicotine. So there are cut-offs of that.

This is a fairly recent study, but I now show this slide to show why I recommend that anyone who is doing this kind of work get some kind of a biochemical measure, so they can really know whether the patient that they're working with has had success. This was a very large multi-site study, in which they provided treatment for all quitters who were hospitalized for any reason. It was not just psychiatric problems. And so then they followed them up-- six months-- and said, OK, how's it going? And they either said they had quit or not.

For those who said, yeah, I'm quit. That's great. They were sent a tube to provide a salivary cotinine sample and to mail it back. So this is 822, so it tells you how many they started with quite a bit. So these are the cotinine results for everybody who said, yeah, I succeeded in quitting. Here's my sample. Well, you can see where the line is there. It's the cutoff, basically, for quit.

So here is documented as having quit-- very low cotinine rates. So a couple-- maybe 10% are maybe getting pretty close, maybe they're slipping, whatever. And they're really low. But a third are nowhere near quitting. They're clearly still smoking. And yet they said, hey, I succeeded. So if you don't know for sure whether someone has been successful in their quitting, especially if you're dealing with other medication issues, as I showed you before that those are going to be impacted by their smoking status in terms of their pharmacodynamic and kinetics-- their functioning basically-- you really need to know, is this person truly able and successful to quit smoking?

That's why I always recommend-- for research, you couldn't get a paper published without carbon monoxide or cotinine documenting whether the treatment was successful. But I always tell providers, it really would benefit you to really know how things are going.

There are a lot of different reasons why so many might not want to admit that they failed. Or you have a relationship with, and they don't want to disappoint you. So there are lots of reasons that they might tell you something that's not quite identical to what the evidence really is.

So this is the arrange follow up. So I left on the little note there for medical students. It's the least likely of the five A's to be done. So basically, once you've treated-- even if you know that they have quit, you need to follow up. Because, again, it's a process where you're working with them and dealing with any difficulties. If they succeed in quitting, that's great. But I'll show you in a moment, you're not done yet.

So you want to schedule a follow up within about a week of the quit date, ideally. Because again, that withdrawal-- that's where it's going to be really peaking, and they may have the most difficulty. They may need more suggestions on how to cope with whatever's going on, and then continued follow ups.

And then that's my next question that I ask medical students. Why would additional follow ups, even if you know they quit at one week, and at one month-- well, isn't that it? Aren't you done? Well no, unfortunately. And that's shown here.

This was a study that had documented how long smokers have been quit, and then followed them systematically for the next two years. So over the next two years, those who had been quit for a little less than a year, the majority of them were relapsed within two years.

And what absolutely astounded me when I first saw this was two to five years-- even then you would think, all right, well they're in the clear. That's fine. Everything's OK-- even there, it's a small minority. But 15% at two to five years, and then 10% over five years.

So they had been quit for over five years. So you would absolutely think, OK, well they're fine. I worked with them. They're successful. That's great. Well 10%, which is not a tiny amount, 10% in the next two years-- this is not a lifetime. This is just over the next two years-- will still have relapsed.

So you're really never out of the woods completely. It does get easier, and you may need to maintain monitoring less often, less intensely. But following up and asking about it is never a bad idea.

SPEAKER 2: So my disclosures-- we've been funded for smoking cessation studies by the NIH-- two institutes within the NIH NCATS, which is the last of the centers that was created a few years ago-- and the NIMH, the National Institute of Mental Health.

So drugs and placebo for these studies were provided by Jansen, which was for an experimental study that Dr. Perkins was the PI, I was a Co-PI on it. The experimental drug didn't work. So we just published that. And Pfizer had provided an NIH study looking at bipolar smokers. I'll show you a single slide on that.

So the history of normalizing and denormalizing smoking-- I thought that was a really good one that Dr. Perkins put up. What I didn't realize was how much of a business proposition it must have been to change snuff and chewing tobacco to smoking combustible tobacco, and to literally create generations of people who became super addicted.

And as the US has been leading the effort, I think, to get to rid and denormalize it, and other countries a little behind, some of this has now spread the business model to countries that are emerging. Because there's money there-- China, India. So these are the new markets for the business of smoking. So it's interesting. We seem to have shifted some of this.

And I put this up because 50 years after the Surgeon General's report in the United States, JAMA, the Journal of the American Medical Association decided to take the first issue in 2016, and talk a little bit about smoking in the last century.

That's a doctor talking about Lucky's. And that's the physician saying, this is less problematic. I think you've seen maybe movies and ads of people in lab coats, doctors typically, with stets around their neck, smoking and saying, you stop smoking.

So from that to the tobacco hearings, the state's attorney generals around the country coming together, the tobacco settlements, which have come back to the states, these ads of people with head, neck, and throat ENT type cancers where they can barely speak-- you've seen them.

And you've seen advertising going every which way on cigarette packs around the world. Some are extreme. If you pick up a cigarette pack in Quebec or in Brazil, it's very, very in your face of what cigarettes can do.

So things like this have been happening. And it's a good thing, even though I might be redundant in some of the slides that Dr. Perkins showed, to remember a couple of stats that you can take away from this hour. One of them, as he pointed out, one in two smokers in the US of who still smoke has a psychiatric or substance abuse disorder. One in two. Every alternate person. So remember that number.

This is a slightly different slide. 14, 15 years of data from the state of California attributing deaths in people with schizophrenia, depression, and bipolar disorder. Now since it's over a decade, there's thousands of people. But if you take those three pie charts, you can-- I mean, it's a little bit on either side-- but it's literally half.

So just as one in two smokers had a mental illness, one in two deaths in the mentally ill occur because of one of 19 tobacco related diseases. So it's 50% of all deaths can be attributed to tobacco. Even though we've concentrated a heck of a lot on obesity because of what our drugs do, this is not even close to what smoking can do. Just remember that.

And we keep hearing about the 19 to 20 years lost. The State Medical Directors Association commissioned the study several years ago. And Dr. Parks put this out-- 15 to 20 years of life lost. And you saw the slide from Dr. Perkins, what could happen with 15 to 20 years of life regained if you quit, and a little less if you quit a little later. So it's something to remind ourselves.

In these grand rounds, it was clinically oriented. So we pitched at mostly providers. So it may not easily appeal to this entire audience. And I'll try and shift it from two weeks ago. But I haven't had a chance to actually shape or edit the slides, because we literally came to know yesterday fairly late in the evening that we were going to do this. And so we just brought our slides along to replace Dr. Kane's talk this morning.

But just to remind ourselves, if we take the entire nicotine replacement therapies-- the patch, of course, and gum have been around. But the lozenge, the inhalator, and the spray-- really, the spray is the only thing that goes in through the nose. Even though we call it an inhaler, everything else is oral. It's important to remember that.

And then there's two medicines-- buproprion that, literally, GlaxoSmithKline got its idea to bring it on as a smoking cessation drug from psychiatry. Because psychiatrists at the VA hospitals were noticing people were quitting when they were using it for depression. It's why they tested it even. And they even managed to get a different name for it, simply because of the stigma attached to Wellbutrin and depression. They managed to get another name called Zyban.

And the biggest concern was, what if someone didn't know who was prescribing? They were one and the same. Would you get double the dose? Would you have a seizure? The FDA I think in its wisdom, decided it's OK to have a different name-- veranicline and Chantix.

So this is it. And to give you a sense of the timeline of when these were approved, as Dr. Perkins was talking, 1984, and the last one, 2006. Some of the biggest culprits of not prescribing this is many of us in this room. Psychiatry is one specialty that does not prescribe smoking cessation treatments.

Even though we full well know, many factors-- we can talk about it, perhaps, in the questions. But part of my talk two weeks ago was to be schoolmaster-ish, as I was telling my colleagues after, and to have a little scolding type of talk of why we don't do it often enough.

Something that Dr. Perkins discussed-- this is important for a couple of reasons. So you can see the delivery mechanism of tobacco for the brain. And so that's in seven to 10 seconds-- the delivery of a highly addictive drug that is legitimately prescribed, as is alcohol. These are two licit-- when we talk of illicit, we should remember what is licit-- not just our prescribed medicines, but alcohol and tobacco are licit drugs.

So there you are. In seven to 10 seconds, it reaches the brain. It's that good, the delivery mechanism of a cigarette. And each cigarette on average-- it varies, because genetically, they've been modified to deliver more nicotine, even, over the last few decades surreptitiously-- about a milligram is extracted from the 10 milligrams, in most average smokers. In the mentally ill smokers, about 2 milligrams is extracted.

And boom. In 10 seconds, it's in the brain. So there are few things that have been invented that are that fast. Very few medicines can work that fast, as we know.

And so when you drop, and you're suddenly saying, when I smoke again, I am calm, you're countering the withdrawal, and convincing yourself that's what made you calm. What's making you calm is you've brought the nicotine levels back up to calm yourself of your addiction.

So if you can overcome it over two to four weeks, and school yourself in those ways, you could. Otherwise, it's a theoretical conversation you've had with yourself from your pharmacology class, which has not translated to you writing anything as a provider. That's really what it comes down to.

And how do you manage those little peaks that the patch, which is fairly smooth. If you look at the patch there, it's a much more steady thing. So probably the spray-- it's almost the same sort of way that a cigarette delivers nicotine. Except, it's way less. It's like 30%, maybe, if we took that as 100%. That's like one third of the peak. Everything else is so much slower, that in the highly addicted smoker, they're waiting for that level to come up.

So you can't overdose people. The theoretical things that some of us continue to have built into our brains that don't allow us to prescribe go somewhat like this. Oh my God. He's going to overdose. He's still smoking. I can't put the patch on. And the patch and the lozenge-- you can't overdose. You'd have to take a kilogram before you did in the highly addictive. I mean, we are talking of one, two, three pack a day smokers who have dropped it, just because they can't afford it. So a patch, a gum with two milligrams, four milligrams-- there's no overdose.

The biggest problem with nicotine replacements for state hospital administrators who are trying to get this system wide is underdosing. Not overdosing, underdosing. Remember that. Even if you smoked, you'd have to do some serious damage to try and get an overdose on nicotine. Very pure nicotine will kill you in seconds. Thank God we don't have it. It's one of the most toxic things-- very pure nicotine.

What do they look like, for those of us who don't work in a pharmacy, don't have patients pull out things from their little bag, or don't allow them to, or don't always get things put into a Ziploc and bring them back to the clinic? This is just an image that Joan, my assistant chief somewhere here in the audience, pulled out from Google image. I have no shares, by the way. But it's sort of what they look like.

Just to remind ourselves when we go to the NRT lock box, and CVS and Rite Aid, it's what they're keeping there, because each of those costs $40 to $50 for a month's worth. So the patch-- you'll see with nicotine replacement, the quantity with which you start is how addicted you are. If you had to ask a single question-- I'm not sure Dr. Perkins mentioned this-- then a third fact you could take away from this hour-- you just need to remember to ask one question.

As soon as you get up in the morning, how long does it take for you to reach? If you're still half asleep and reaching for it in 30 seconds, you are super addicted. Under five minutes is the cutoff. That's a single question. It also speaks to whether you need to start on a much higher dose, whether you need to be pretty intense in the counseling and help people overcome urges.

And it sort of gives you a sense. Two out of three mentally ill smokers meet that definition-- under five minutes. And moderate levels of addiction are up to 30 minutes. Beyond that, it's less addicted. Soon after waking up.

And where you put the patch, how you take it off, as long as there's no skin irritation, allergy type reaction to the patch, it's the most commonly used. And definitely, in hospitals where smoking is not allowed, and as state hospitals go into this mode, I imagine this and NRTs will be the most commonly used medications to assist with quitting.

But as Dr. Perkins pointed out, an institution, a setting-- the Commonwealth of Pennsylvania might decide for its state hospitals, smoking is not a good idea. Unless you're personally motivated, it doesn't matter what their agenda. You don't smoke temporarily. People come out of prisons 10 years later, the first thing they do when they stop at the gas station is run in and buy a pack of cigarettes. We know this.

So remember some of these things when things are instituted. It is critical-- someone goes into a ward at [INAUDIBLE] psych. It's smoke free. They stay there say, for argument's sake, with a particular diagnosis for two weeks, instead of, say, three days. They're not smoking. The Olanzapine and clozapine builds up fast.

They get discharged to where and Kim Klein, Bill, and I work at Pathways LTSR. We allow a little bit of smoking. Or they get discharged to a group home, a personal care home, a family where they may smoke a pack a day.

The blood levels fall. What does the outpatient doctor immediately think? They're not taking their meds. 50% of the time, that's probably true. The other 50%, they're smoking like chimneys. And the blood levels have dropped dramatically. It's no longer effective. That, we don't ordinarily easily think. Because it's not in our repertoire.

The other thing that's happened amongst prescribers-- we've become hospitalists, like in other specialties, and ambulatory care docs. And not that many cross. A few do. But in many settings, that has stopped. So the hospitalist does not think of some of these issues. The ambulatory person is not thinking the person on the patch has come out and is now smoking 20 cigarettes a day.

So these have to be considered-- Olanzapine and clozapine have been studied a lot in psychiatry. The older drugs, there were no specs. Nobody bothered. The newer drugs, they do 5-10 patients studies-- completely inadequate, in my opinion-- just to make it into the three lines of a package insert that the FDA will approve. There you are. So those are the issues when it comes to smoking.

Some of these slides are just to, again, point out nicotine replacement as nicotine replacement. You start at a lower dose if you're less addicted-- five minutes, or maybe 30 minutes in some cases-- this is what you take. You have to have reasonably motivated people setting a quit date. It is a process.

Typically, even in successful quitters, you have four or five times before the successful quit for, say, six months, one year, two years, maybe. In the mentally ill smokers, it might be seven, eight, nine times. And we can't quit. We have to be the purveyors of hope in addition to writing any medicine. And we need to keep at it. We need to school ourselves.

The spray-- Jill Williams at Rutgers, she's a big believer in this. She's been in the smoking cessation business in schizophrenia for maybe 20, 25 years. And she thinks the aversive aspects and the fact that it resembles the cigarette, unlike all the oral nicotine replacements, gives the best result in people with highly addicted schizophrenia smokers. She may be right.

[NAME], who is going to be talking to you about anticholinergic logic drugs soon, feels that a lot of people, in her experience-- on one-on-one in our clinic-- they just substitute it as if they are using some kind of addiction. Instead of smoking, they're just squirting it up the nose.

It's tough to know the right thing. Probably, both are right. But it's something to think about if you have to use. It's much harder to use. And learning to use these correctly and instructing patients is 3/4 of the trick. We're not good at it. We're not well schooled in it.

This is an oral inhaler, meaning through the mouth, even though it's called an inhaler. It's not like a puffer. I mean, it is a puffer, but it's truly not a spray in the nose.

Buproprion. So we have clear cut ways in which we can use it. A lot of people are taking buproprion. They're still smoking. So many of us in psychiatry feel it's already been used, but it's been used typically for depression, negative symptoms of schizophrenia. And people are still smoking. But they never set a quit date. We never went after smoking cessation. We went after depression or negative symptoms-- a completely different use.

In the person who's not allergic, and who wants to quit, and who wants to try something other than NRT, reasonable.

Veranicline-- the drug that was almost never used. Even though the black box was removed two years ago, as you heard-- the most effective. So for those of us who do clinical trials, this is an interesting study. So in that box, which Joan kindly boxed for me in blue, is placebo cessation rates. We worry about placebo rates in psychiatric disorders.

In anxiety, it's close to 50%. In depression, it could be 20%-30%. You don't have to worry about placebo rates in smoking. It's 10% to 12%, no matter what you do. We can do somersaults. Only 10% to 12% will quit, meaning, that is your willpower quit rate.

What do the drugs do? They double it or triple it. NRTs, buproprion, and veranicline-- veranicline is usually the best in terms of potency as well as efficacy. They double or triple it. But what about the 70%-80% that still haven't quit? So this is always a trick. It's a process. You have to remember, just having done it once doesn't take care of everything.

So this is just another way of putting it. We use slightly different ways of thinking about, what are the odds of quitting? If you're more like a gambler, you would like the odds of quitting-- is it double the odds from just willpower? Is it triple the odds? That kind of thing. But essentially, using NRTs doubles your odds. Buproprion, maybe a tad more. Veranicline or Chantix, maybe triple the odds-- short term.

What about in schizophrenia? Most of the studies that we've been seeing have been not in schizophrenia or bipolar, other than the EAGLES trial. So if you look at this study done by Tony George, who spoke at this conference a few years ago-- he is in Toronto now, but this is I think when he was at Yale. In fact, it was. In 2002, he was still in Connecticut.

So if you looked at, say, short term quit rates, half the people quit in 10 weeks on treatment. You stop the treatment, and you see what happens? Everyone almost relapses.

What about bipolar illness? That was a study we did here just up the road. And almost identical to Tony George's studies, close to half the people quit. Placebo, as I had mentioned to you-- willpower is tough to try and quit with mental illness and smoking. And then you stop the drug, boom. So clearly, three months is not enough. We need to keep going, sometimes, for six months, if not a year.

A larger study-- and Eden Evans at Mass General did this-- openly gave veranicline to many people with schizophrenia. Those who quit then were assigned to CBT, as well as to Chantix or placebo. One interesting thing about this slide-- CBT stops and the placebo literally-- so whatever was holding them by way of therapy just drops completely. So counseling therapies are just as important.

The EAGLES study-- the largest smoking cessation study, to my knowledge, ever done. 8,000 people, five continents, more than 100 sites. And the point was, how do you get a rare thing like neuropsychiatric side effects that were reported anecdotally that led to the black box warnings on Chantix-- buproprion already had one for depression and suicide because it was an antidepressant, if you remember-- how do you get that off? You do a massive study to show rare events don't occur, or don't occur more than if you just got the placebo.

And this was the study that helped do it. And Dr. Perkins was on the FDA commission that voted-- many of them voted for and a few voted against. But the black box was removed.

If you look at, say, the efficacy, it essentially shows-- maybe I should have had John box this too-- essentially, low rates, double the odds with buproprion, almost triple the odds with veranicline. NRTs also doubled.

And if you looked at, say, slightly longer things for the psychiatric cohort-- a little like what Dr. Perkins showed-- lower rates than people who didn't have psychiatric illness of quitting-- but somewhat exactly the same in terms of which class of drug did what.

Side effects that were the big concern that stopped us in our tracks from prescribing the most efficacious drug we've had for schizophrenia and smoking, or anyone in smoking-- and here is an interesting one. So that is the non-psychiatric cohort of about nearly 4,000 patients, the psychiatric cohort of just over 4,000, 1,000 in each arm-- veranicline, buproprion, nicotine patch, and placebo-- the rates of something serious happening are higher, but sort of the same across any smoking cessation.

And in fact, on placebo, much lower in the non-psychiatric cohort. You would expect that. Because the base rates of these things would be higher in psychiatry. And this is essentially what led to the removal of the black box.

The clearances of drugs-- we have to remember this-- when people are smoking more, cutting back, cutting out, drug levels go up and down. So in addition to behavioral acting out and such labels that we commonly use on the wards in the clinic or in ambulatory facilities, we have to remember it is entirely possible drug levels are going up and down and causing the mental status to go up and down also. We have to school ourselves in this. This is critical. Also, drugs that can be pretty dangerous could get affected. So we have to.

And as [NAME] always wishes to point out, caffeine, which often substitutes instead of nicotine, shoots up when you quit. And you could have caffeine toxicity heading to the withdrawal symptoms, and everything begins to look crazy at that point. And we have no idea, is this smoking? Is it the caffeine? Or is it the withdrawal that's causing some of these anecdotal things that we've often heard about?

We have to remember each of these classes of drugs, even though the black box warnings have been removed, still have issues. We have to be vigilant. And that's why we are trained. That's what we do. And so we should remain schooled in that. But it doesn't mean we don't prescribe clozapione, we don't prescribe lithium. These are amongst the most dangerous drugs. So relatively speaking, who else would do it if not us?

So an approach to smoking cessation-- you have to be ready to quit. That video showed it-- trying to get at the quit date, trying people to commit, not just to please you, but are actually motivated inside is the key. Setting a quit date is the key. It's a process.

And more specifically, not only do we need to know it theoretically, we actually need to prescribe and get experience in it. Otherwise, it remains a theoretical proposition in your head, which doesn't translate to your prescription pad. That's really what it translates to.

Amongst therapies, motivational enhancement therapy, using motivational interviewing techniques is usually the best in the mentally ill smoker, even better than CBT. CBT has issues already with people who have psychoses. But CBT for smoking is even harder. On the other hand, MET, motivational enhancement therapy could get them ready, and get them moving along the right path to quit.