A Practical Approach to Treating Smoking

Hilary A. Tindle, MD, MPH

Associate Professor of Medicine

William Anderson Spickard, Jr., MD, Chair in Medicine

Director of ViTAL: Vanderbilt Center for Tobacco, Addiction and Lifestyle

Vanderbilt University Medical Center

Nashville, TN

A Practical Approach to Treating Smoking

HILARY A. TINDLE, MD, MPH: Hello, my name is Hilary Tindle. I'm an associate professor of medicine and an internists and clinical investigator at Vanderbilt University Medical Center in Nashville, Tennessee. I'm very excited to be talking to you today about smoking cessation, and why it is important for our patients, and how we can do it well, even in our busy clinical settings.

We'll go over four major items today, including the epidemiology of smoking, and how it still is a threat to cardiometabolic health, and how smoking cessation improves health on a number of levels, how to screen and intervene, and future directions in treatment of smoking and tobacco use.

In the United States and many countries around the globe, smoking cessation has been a complete success story, in terms of public health. Back in the 1960, when the first surgeon general's report on smoking and health was release that linked lung cancer in men to smoking, 4-in-10 American adults smoked, more men than women, but 4-in-10. Now, we're down to much, much lower prevalence of around 13%. So, that is a major success story over past decades.

We see the same thing when we look at consumption of cigarettes over the last century. So, starting in about 1900, there was a steep rise to World War I and in to the 1960s in the consumption by each American adult smoker. In 1964, that first surgeon general's report was released that showed the ills of smoking, or at least started to demonstrate them, and that launched a very successful, multi-faceted public health campaign over the ensuing decades that resulted directly in the steep decline in consumption, and also in prevalence of smoking.

Despite all the ills of 2020 and the last years of the pandemic, there is one wonderful thing that happened in 2020, at least one, which is that we had our first surgeon general's report in 30 years that focused specifically on smoking cessation. We can draw a lot from this report, and I've pulled several highlights specifically for this group, which I found to be the most important in clinical care.

First, smoking cessation is beneficial at any age. That includes our 70, 80, 90-year-olds, even our centenarians. It enhances quality of life, as well as reducing risk of death. The sooner you quit, the better. So, one thing that's really important to tell patients is if they can quit, especially by age 35, they can expect an average of 10 years of life expectancy benefit. But, even at older ages, and even after 65, quitting smoking reduces risk of death. The years that one gains are far better, in terms of quality of life and also in terms of health benefits.

Smoking cessation reduces risk across every organ system. So, no matter who you're talking to, what age group they are in, what racial ethnic background, what region of the country, there is some benefit that the person in front of you is going to gain from smoking cessation. That's really important, because it's one of the many things we do in

primary care and prevention and preventing cardiovascular risk, and so there's a lot of competing things that we do in a small amount of time in a clinic visit or at the bedside.

In terms of statins, aspirin, other screenings, smoking is in really good company, smoking cessation. An individual healthcare provider, such as an MD, nurse practitioner, PA, respiratory therapist, dentist, you name it, anyone can give five minutes, three-to-five minutes, of brief advice, and only needs to treat 80 individuals, with a very small number needed to treat, to prevent one premature death. You can see that adding smoking cessation medication, which we'll go over today in today's talks, and adding behavioral support reduces that number needed to treat down below 20. So, it's in very good company with many other evidence-based interventions that we do to reduce cardiometabolic risk.

I want to focus on two benefits in particular of smoking cessation. They're familiar to you, but I may have a few pieces of new information that will be interesting. Our group looked at the Framingham Heart study, which we all know from all the benefits of knowledge that the study has given us since the 1940s, but what you may not know is that Framingham also collected data on smoking every 2-4 years for the entire participation of the subjects. That means that it has one of the most complete captures of smoking of any data set on the planet.

So, we leveraged this information, and we looked at people's smoking exposure over their lifetime in Framingham, and we looked at what is the risk reduction in cardiovascular disease when an individual quits smoking. First, we looked at former smokers versus those who continued to smoke on this bottom graph here in gray. What we found was that within five years, individuals had about a 40% risk reduction compared to those who continued smoking, so that's major, and that's in keeping with what you probably knew from other data.

In addition, what we found, when we compared those former smokers to people who had never smoked, was that they had to go out about 16 years since quitting, on the X axis here, to approach the risk, the same cardiovascular risk, as a never smoker. So, what that means is swift benefit in smoking cessation, in terms of reducing risk by about 40%, but the risk relative to never smokers lingers. What that says is we have to keep up vigilance with these individuals and do everything else we can to reduce their cardiometabolic risk, in terms of blood sugar, blood pressure, managing blood lipids, and healthy lifestyles.

A second major outcome and benefit of smoking cessation, of course, is a drop in lung cancer risk. From previous data, we knew that within 10-15 years the risk of lung cancer was cut in half after quitting smoking. So, our group also looked at the Framingham Heart study, the data that I showed you a moment ago, and what we found was within five years, lung cancer risk drops by about 40%. So, that's sooner than was previously known, for sure. So, that's a major benefit.

But, we also found, similar to the case with cardiovascular disease, that people who had quit smoking, relative to those who never smoked, still have elevated risk. So, on this top blue graph here, even after 25 years since quitting, there can be elevated risk of lung cancer. All this means is kudos for quitting smoking, but these individuals may be in

prime time for screening, continued screening, for both cardiovascular disease and lung cancer.

Another major point from the 2020 surgeon general's report is the quit ratio. So, more than three out of five U.S. adults who ever smoked cigarettes have quit. This is a major message of hope, because what it means is there are more former smokers walking around than current smokers. That means that your patient sitting in front of you in the clinic or in the hospital or in pre-op can also quit. So, I consider this to be one of the best pieces of information that's come out of this report.

For the 34 million Americans who continue to smoke, there are disparities. This is very important, and I'll show you several of the disparities from CDC data. There are certain disparities by region, and we see here from the BRFSS survey that there are very big differences in prevalence by state. The darker states in the American south and Midwest, also called tobacco nation, that's where I live now and practice, these tend to have higher prevalence, up to 27%. Whereas, the lighter states, California and Utah here, have much lower prevalence, 9-12%. The other states are somewhere in between.

I also want to put in a plug. When we're talking about smoking, yes, there are only 34 million Americans now. I know it's a big number, but it's a lot less than it was in the past, but there are another 58 million who are exposed to second-hand smoke. So, when you help one person quit smoking, you are helping others around them, including the elderly and children, who are captive, in terms of being exposed to second-hand smoke in the home and the car. So, you can really help a lot of people, just by helping one person quit smoking.

I like this CDC graph or visual, which demonstrates some of these disparities that we're talking about. I showed you the disparities by region, especially in the Midwest and south, but also individuals who are of lower socioeconomic status, education and income, as well as those with serious psychological distress, and that just means that the endure symptoms of anxiety and depression. To this slide, I would also add U.S. veterans, which are not on here, but do have a higher prevalence of smoking.

Finally, the major highlight from the 2020 report that I wanted to offer is that we have effective treatments. FDA-approved medications, which we'll review in detail today, do really help, especially when they are combined with behavioral care. So, we have good treatments. We just need to use them more, and we'll talk about that today.

Smoking Cessation: Screen and Intervene

How do we screen and intervene on our patients? Before we go in to some of the details of screening and intervening, it's important to take a moment to remind ourselves of the neurobiology underlying smoking and nicotine addiction. Nicotine exposure, especially through cigarettes, sets off a cascade, a neurobiological cascade, that involves release of multiple neurotransmitters, namely dopamine, but as you can see, many others, leading to changes in feeling and thinking, so changes in brain circuits of our patients. These neurotransmitter release processes further the reward of smoking, such that people want

to keep doing it. So, that's the process.

There are many receptor types, nicotinic receptor types, that are involved in nicotine addiction, but the α4ß2 here is one of the main ones. So, these receptors, nicotinic receptors, sit on dopaminergic cell bodies in the ventral tegmental area, and they result in dopamine release in the nucleus accumbens, shown here.

This schematic I also like, and I pulled this from the 2020 surgeon general's report, because it demonstrates not only that one receptor subtype, that α4ß2, but the many receptor subtypes throughout the brain that are involved in nicotine addiction, as well as the many regions of the brain, the midbrain and nucleus accumbens here, the VTA, projections to the prefrontal cortex, but also in memory, the hippocampus, and in feeling, the amygdala. Nicotinic receptors are everywhere, and they are affecting our patients.

I think that neuroscientist Eric Nestler wrote it best when he said, "at its core, drug addiction, "including nicotine addiction, "involves a biological process. This is the ability of repeated exposure of a drug of abuse to induce changes in a vulnerable brain that then drives the reinforcement, the compulsive seeking, and taking of drugs. These drug-induced modifications can be viewed as a form of cellular or molecular memory."

This is particularly important when we think about the patients who we're seeing in clinic and in all the different settings. Most of these individuals started smoking before they were 18, when their brains were still forming and vulnerable. They were targeted by very effective advertising campaigns. So, I think, taken in context, nicotine addiction and smoking, when we understand all of these layers of the behavior, it really helps us, as healthcare providers, to understand what a complex behavior we are dealing with. It is rooted in biological changes to the brain.

But, the good news is that effective treatments exist, and we have a wealth of guidelines, especially in the last 12 years, that have been published and are widely, freely available. The effective treatments include pharmacotherapy, and we'll go over this in detail, but that targets the nicotine addiction, those nicotinic receptors, as well as behavioral support. This targets behavioral components, and behavioral support can be delivered in a variety of modes. Combining these two is superior to either alone, and that's why combination pharmacotherapy and behavioral support are standard of care.

Finally, more intensive treatment is better, but brief intervention works. 3-5 minutes can double quite rates. So, you really can make a difference, just by taking a few minutes to talk to your patients and write them a prescription, if appropriate.

The Five As, which you may have heard about, are a wonderful framework to do this, and I'll show you some even more streamlined approaches than Five Steps. But, in essence, these are ask about tobacco use, advice your patient to quit, assess their readiness. And, you don't even have to ask the question, are you ready; you can make it a statement. Now is a great time to quit. Assist them. And, arrange follow-up care. The CDC encourages us to do this with every patient every time.

Some streamlined versions, for people who are incredibly busy, healthcare providers and patients alike, you can ask about tobacco use. Do you use smoke cigarettes or use

tobacco? Advise them to quit. An example, quitting smoking is one of the most important things you can do for your health right now. And, then, act, so act can take the form of writing a prescription, and we'll give you some details on that, brief counseling, and connecting your patient with free existing resources. Those include a network of state quit lines, 1-800-quitnow. Smokefree.gov is the National Cancer Institute website that 5 million people visit a year. It's very effective. And, become an ex is another newer website that was created and maintained by the Truth Initiative. Each of these, or all in combination, are excellent resources for patients.

I also wanted to just show you, we will not go over this slide in detail, but in 2018, the ACC did convene an expert decision pathway, a panel to make this pathway, and it's basically a more detailed version of the 5 As, if you want to look at this to refer to it in the future.

So, smoking cessation pharmacotherapy, what are the guidelines and what's the evidence? Pharmacotherapy works, and we have seven options to us in the United States, as healthcare providers, five types of nicotine replacement. Three are over-the-counter, and two require a prescription. We have bupropion, which is a pill form, and varenicline. All of these medications work relative to placebo. The nicotine products, all five of them, are considered equivalent, roughly, and bupropion, these six, give odds ratios for long-term quitting, that means six months or more, that are about 2-times higher than placebo, so that's great news. Varenicline, relative to placebo, is even better, about three-fold increase in odds of long-term quitting, relative to placebo.

This is just another way of looking at the same information. Nicotine replacement, or NRT, monotherapy, meaning if you use one therapy at a time, like a patch or the lozenge only, that would give about a two-fold increase, relative to placebo, same with bupropion, varenicline about a three-fold. Another strategy, which is highly recommended now, is using combination NRT. So, that means using two forms at the same time, and there have not been many head-to-head trials with varenicline versus combination NRT, but in separate trials, it looks like these yield about the same great benefit, relative to placebo.

This slide shows some similar information, but it demonstrates, at six months or more, what the expected quit rates are for each of these individual seven FDA-approved meds. The slide also includes another medicine that's not FDA approved yet in the United States, but it possibly could be soon, which is why I've included it. That's called cytisine. We'll talk about that a little bit more.

Here are the five nicotine replacements, bupropion, and varenicline. You can see that the nicotine replacement forms are all about the same, in terms of efficacy, and similar to bupropion, and varenicline is a little bit higher when used as monotherapy. The other thing I want to point out is these blue lines, which represent the active drug, versus the red lines, which represent placebo, the blue lines are all higher, so any medicine you give versus not giving a medicine is a good thing. So, it's very important to connect patients with medicine.

In terms of national guidelines, regardless of the discipline that you look at, whether it's cardiology, cancer, a perioperative anesthesiology, or chest physicians, the American

Thoracic Society, most recommend currently starting with either varenicline monotherapy or a combination nicotine replacement.

For nicotine replacement options, I've introduced a little bit, but let's go a little deeper. Generally, we want to combine a long-acting form, which is the patch. That's transdermal nicotine delivery. It's very simple to use. The patient just puts it on in the morning, doesn't have to think about it. That yields a constant nicotine level that avoids withdrawal or at least dampens the experience of nicotine withdrawal.

The downside is the individual doesn't have control, like they did when they were smoking. So, it gives a very constant delivery of nicotine. That's why it's important to pair the transdermal patch with a shorter-acting and faster-onset, like the gum, lozenge, inhaler, or nasal spray, and that allows people to have some control back. It's tough to quit smoking. It's a major life event. So, you want to give people as much control as they can possibly have, and also as much comfort as they can possibly have. Using the combination of patch and a short-acting form of NRT gives them that control and comfort back.

This slide just demonstrates the differences in nicotine delivery. There are a couple points I want to make here. One is what I just described. So, if we look at this pink line, that is the nicotine delivery to plasma from a cigarette. You can see it's very rapid, a very high initial peak, and it goes down within about two hours. This is what feels really good to people and why they don't want to give it up. All of these other colors are the different forms of nicotine replacement.

The blue is patch. Here, you can see a very slow rise in plasma nicotine levels over two hours. Here's the gum in yellow, and nasal spray in white. If you combine patch in blue to any of the yellow or the white here, the nasal spray or the gum, you can see how a patient might be more comfortable with that, because they can dose themselves as needed.

None of these approximate the pattern, the pharmacokinetics, of the nicotine delivery in a cigarette, and that is important for our patients, just in terms of compassion towards them, to recognize. They're not getting what they want, exactly, when they are quitting smoking, even with nicotine replacements. So, we want to be very patient with them. But, using two forms can approach, at least approach, the pharmacokinetics of a cigarette.

The last really important thing to mention here is this slide explains why cigarettes are so addictive and also explains why medicinal nicotine is not as addictive, not considered addictive. That's because the medicinal nicotines have a much slower rate of rising, even the short-acting ones.

The products, whether they're gum, lozenge, patch, nasal inhaler, or oral inhaler are considered equally effective, and all do effectively treat nicotine withdrawal.

In terms of varenicline medication, again, this is a pill form. It's a partial agonist at the α4ß2 nicotinic receptor. This is what the medication looks like. Partial agonist just means that the medication stimulates the receptor, and thereby treats craving and withdrawal. But, it also antagonizes any lingering nicotine from smoking or from other sources, from

binding to that receptor, so it blocks the reward of smoking.

There are side effects with varenicline. The most common ones are nausea in about one out of three people, and about 12% of individuals can have vivid dreams. That doesn't necessarily mean nightmares; it just means very vivid dreams. But, the thing that I try to emphasize with patients in practice is most people do not stop varenicline because of side effects. Most people do well, if they take it with a full glass of water and a meal. Varenicline is not appropriate for pregnancy or in people who have unstable mental illness, and we'll go in to that a little bit more in future slides. It does also have to be dose reduced in renal impairment.

This slide is a very helpful cartoon for healthcare providers and patients alike. You've seen this bubble a few moments ago, looking at a sagittal slide of the brain and the nicotinic receptors and the ventral tegmental area in the mid-brain, with projections in dopamine release in the nucleus accumbens.

I'm going to go over three scenarios briefly. These top neurons here are the dopaminergic cell bodies in the VTA, and the bottom ones here are the terminal axons in the nucleus accumbens. First scenario, ad lib smoking, smoking as normal, these nicotinic receptors here are on the dopamine cell bodies. Patient smokes. Nicotine occupies and stimulates those receptors and results in dopamine release here, at the bottom in these nice little yellow bubbles. If an individual goes cold turkey, meaning they quit smoking, and they do not use any medicinal nicotine or any other medication, that leaves all these receptors empty, and those receptors become hangry, like toddlers, and they get very angry, and this does not feel good to the patient. There's very little dopamine release, you can see here in the terminal axon, and this person is bound to be very unhappy and in high nicotine withdrawal.

With varenicline, or other medications that partially agonize those nicotinic receptors—here in this cartoon the varenicline is depicted in purple—it occupies those receptors and stimulates them, so you get a little dopamine release in the nucleus accumbens. It also blocks any nicotine that's lingering, so it blocks the reward of ongoing smoking. That's how it works, and that's why using medications, whether you're using the nicotinic agonist, like medicinal nicotine, or a partial agonist, like varenicline, why it's important to address the underlying neurobiology in treatment.

Now, there have been some safety concerns, and they linger, and that's why I want to take a moment to go in to this topic today. In July 2009, there was a boxed warning put on varenicline and bupropion because of concerns about changes in neuropsychiatric profile, like hostility, depressed mood, and suicidal thoughts. The FDA mandated a trial called the EAGLES trial. This was published in Lancet in 2016. So, why am I talking about it in 2022? Because, many of the very important points and pieces of knowledge that came out of this trial have not, unfortunately, made their way in to clinical practice, so it is important to review.

In a nutshell, this was the largest trial that has been conducted for smoking cessation. It was in 8000 or more people. Half of the did not have preexisting psychiatric disorders, half did. Of those with psychiatric disorders, about 70% had mood disorders. There were

20%, almost, with anxiety, and almost 10% on schizophrenic or schizophrenia spectrum disorder. The key is that all of these individuals had what's called stable conditions, so they had not had, for example, a clinic visit or an ED visit or hospitalization due to their psychiatric condition in the months prior to the trial, and they also had not had any medication changes. So, they had to be stable.

The composite safety endpoints included 16 neuropsychiatric symptoms, including depression, anxiety, even things as vague as feeling abnormal, which I think it's really important that these vague things that people tell us about that feel very real to patients were also included in this composite outcome. But, it also included suicidal ideation, behavior, and even completed suicide as an outcome.

The trial also looked at efficacy, which is biochemically confirmed, carbon monoxide confirmed abstinence, weeks 9 through 24.

Basically, what was found was that all of the medications that were tried, so this was a randomization to either varenicline, bupropion, nicotine patch, or placebo, so four arms, in the non-psychiatric cohort, there was no difference between any of these meds in achieving that composite risk, so no difference in neuropsychiatric outcomes. Same thing for the psychiatric cohort. So, while the individuals in the psychiatric cohort had a higher prevalence of adverse events, there was no difference by medication, including varenicline and bupropion. As a consequence of this trial, the boxed warnings were removed in 2016.

The efficacy results also teach us a lot. So, on this slide, we see the overall cohort of 8144 people, and I included the psychiatric cohort and non-psychiatric cohort here, just so you can see that they have basically the same pattern. So, while the quit rates are slightly lower in the psychiatric cohort, as you would expect, the same pattern is seen. Varenicline is in pink, bupropion in blue, nicotine patch in green, and placebo in lavender. What we see here is at weeks 9-12, as well as weeks 9-24, varenicline is the most efficacious monotherapy. About 50% more effective than patch alone, and then bupropion, and about three-fold more effective than placebo.

So, putting together the quitting that's going on and the quit attempts that are happening in the United States, I want to highlight an important disconnect. If we think about these 34 million smokers, adults who continue to smoke, most of them see healthcare providers. About 8 out of 10 of them see a healthcare provider every year. 7 out of 10 of them say that they want to quit. And, over half actually make a quit attempt.

But, here's the bullet that shocks me every time, and I know this information, but every time I read it or say it, I still find it shocking. Only 5% of these individuals who are making quit attempts are receiving the standard of care for smoking treatment, which is combined medication and counseling. So, only 1 in 20 people are getting the care they need. That's really important, because 95% of unaided quit attempts fail. So, quit rates remain low, because the people try to quit smoking without help, 95 out of 100 will be smoking at 6-21 months, so we really need to help these individuals.

Why is there such a disconnect, if we have such great evidence and treatment? I wanted

to offer a few insights from my own clinical care, as well as from the literature. I think it comes down to misconceptions and myths, and we, as healthcare providers, are just as guilty as our patients, as holding some of these myths. Now, some of them are not myths; they actually are true, like I don't have a lot of time. So, time is a big barrier. But, I'd like to illuminate some of these, and then actually go through them and see how we can address them.

We may think the patient is not going to quit. We've talked to them 10 times before. Why would the 11th time be different? The patient has too much going on right now. The patient is too high risk, or the meds are dangerous. I might alienate my patient if I bring this up. Or, we don't have a smoking program at my hospital or clinic, so what can I really do?

On the patient side, patients may be thinking I can't quit, or I'm too old, or the damage is already done. My lungs are shot. It doesn't matter. I have too much going on right now. Or, the medications don't work, or they're dangerous. This is a very common one, the medication us is just trading one addiction for another. Obviously, that's not true, but that's what some people think and why it's important to bust these myths, as we're trying to help people.

Another one is that using medicines is a crutch, but actually, we want to help people understand it's a tool, and it's a temporary tool. We're only talking about using these for usually 2-3 months at a time.

So, the 5 A's help us with a framework to address many of these myths and misconceptions, and that's why we really want to use them with every patient every time.

Smoking Cessation: Patient Case

So, let's go through a case and see if we can apply some of the evidence and principles.

So, you're seeing a 58-year-old man. He has hypertension. He has HIV, stable depression, and he's taking medication. Hasn't had any dosing changes or admissions recently. He drinks. He screens positive on the AUDIT-C for heavy drinking. And, he presents with pneumonia. He's admitted to the hospital with this pneumonia. He smokes 20 cigarettes a day since age 18, drinks three beers a day, more on the weekends. He wants to go out and smoke now, but he literally can't get out of bed. He feels too weak, and he tells you that he's tried everything to quit, including electronic cigarettes, or e-cigs.

So, your initial assessment is he's pretty high risk for smoking-related disease, given a number of factors. His age, the fact that he's male, his HIV status, his depression, his alcohol use, in addition to his smoking, all set him up for very high risk of a heart attack or CVD. He's high risk for other disease too, like lung cancer. And, he certainly meets criteria for lung cancer screenings, so if you have a program that you can connect him with, that would be a good thing to do as well.

So, you advise him, quitting smoking is the best thing you can do for your health right

now, and it's especially important as you heal from pneumonia. One thing you see that we did here with this case is tailor the advice. You gave a clear statement. Quitting smoking is the best thing you can do for your health right now, but also tailoring it, so this individual has a wound. The wound happens to be in his lungs, with the pneumonia. And, any wound you can leverage is potentially very concrete to your patients. So, even if they weren't thinking about quitting, or didn't want to, they may be willing to make an attempt to let themselves heal, and even if they'll only commit for three, or even six, months, or even less time, it's still helping them move in the right direction.

Further assessing your patient. He says he knows he needs to quit, which is great. He's making your job easy, as a healthcare provider. And, he says he's tried everything. So, you're wondering what exactly does this mean, and how much is he smoking now? He told you he was smoking a pack a day in the past. So, he says now I continue to smoke a pack a day, which is fairly common, and the national average is a little bit less than a pack a day. And, he tells you that he's tried a lot of things.

One is nicotine patch, but he only used it for a week, and he didn't use combination therapy. It was just the patch. He doesn't remember the dose. He also used bupropion, during which time he cut down smoking, but he never quit. He used an electronic cigarette for three months, but he continued to smoke during that time. That's the dreaded dual use, where people keep doing both behaviors. Eventually, he didn't like it, and he resumed smoking.

He also tried varenicline, and he quit with varenicline, but he relapsed after a divorce. Now, he's not so sure about varenicline. He says his neighbor told him this is the worst drug ever, but on the other hand, his best friend told him, no, no, it's the best drug ever. Now, he asks what you think. So, you're on the spot to answer him.

So, let's continue to assess a little bit more. He's motivated, and he's willing to consider medication. So, what should you do next? Well, ideally, we would want to set a target quit date within two weeks. There is evidence that people can set a target quit date within three months, but really, the sooner the better. If someone is hospitalized, I, and my team in our practice, always try to get them to carpe diem, let's make today your quit date. Let's just take it from here. You've already had several hours or several days of success, so the sooner the better.

We also know that we want to combine pharmacologic and behavioral support, and we reviewed earlier that most national guidelines recommend beginning with varenicline or two forms of NRT. So, what do we think about those recommendations for this particular patient?

Let's keep ourselves awake with a question. This patient's history of depression, despite what guidelines say, he's depressed, so it makes him ineligible for smoking cessation medication. What do you think of that? True or false?

Actually, it's false. As we reviewed, this patient can use FDA-approved medications. The EAGLES trial, in particular, is the largest trial and the most definitive trial that has shown us that's the case. So, for varenicline and bupropion and nicotine replacement, this

individual has stable depression. He is eligible to use these medications. 70% of the over 4000 participants in the psychiatric cohort in the EAGLES trial actually had mood disorders, including major depression.

You also may be wondering—I didn't ask it in the question precisely, but you may be wondering what about varenicline and HIV? There have been several trials, published trials, of varenicline and HIV, and it can be used safely in this population. And, varenicline has also been studied in people with alcohol use, including alcohol use disorder and opioid use disorder. So, it is safe for those individuals as well.

So, now, we're moving on to assist. You've helped him set a target quit date, ideally within two weeks, and you want to combine pharmacologic and behavioral support. So, that means writing a prescription, and that's very important. Writing a prescription for your patient for an FDA-approved smoking cessation med, even if you're going to refer them and connect them, it is important to write that prescription, assuming that they're medically eligible for FDA-approved meds, which this patient is.

So, what smoking cessation prescription should you write next? Let's think about the options. We could do nicotine replacement therapy only, like monotherapy, such as a patch. We could do a combination patch plus, meaning patch plus any one of the oral medications. We could do varenicline. We could done one of these only, or either patch plus B or varenicline, C. What do you think would be the best next option for this patient?

By all the guidelines, B or C is the correct answer. So, combination nicotine replacement or varenicline is usually the first place to start, but it's a little bit of a trick question, because, really, any medication that you give your patient for smoking cessation, provided they're medically eligible to take it, is correct, and will help them more than giving them nothing. So, any one of these is really the right answer, but most of the guidelines, because of the higher efficacy, recommend either varenicline or combination NRT.

Okay, so, we're continuing to assist our patient. We've set the quit date. We're going to give him either varenicline or two forms or NRT, do some brief counseling, and that can take the form of like what worked before, what rough spots did you hit before, how can we avoid those now on this quit attempt. And, you'll do a referral or connection to either the quit line or smokefree.gov. I'll show you a few slides of those in a moment. Or, if you have an internal program, such as a nurse or a social worker or nurse practitioner who specializes in smoking cessation in your clinic or your hospital, you could refer to that internal program as well.

Is there any advantage to varenicline or combination for this particular patient? So, how do you decide between these two firstline suggestions? Well, he's medically eligible to take either. Both are effective. But, if you're going to do monotherapy, varenicline is more effective. But, we've also said the combination NRT is probably just as effective as varenicline. What about his preference? Does he have any preference? Is the medication covered? What is his out-of-pocket cost? Does the alcohol use help us make our decision in this case?

I want to take this opportunity to show you some of the data that's been published in the

last two years on varenicline for smoking and alcohol. These two behaviors, obviously, co-occur. I'm not telling you anything you don't know. You've seen this a lot in your practice, undoubtedly. And, it would be a good thing if we could mitigate polypharmacy, especially for some of our patients who are taking many drugs, to treat with one drug, two conditions, alcohol and smoking.

So, we know that varenicline is appropriate for a daily smoker, and will it help with the alcohol at all? Well, I just want to say that this is continuing to be investigated in the literature, but there have been two published meta-analyses of varenicline versus placebo for alcohol. The first one took all comers, so the full spectrum.

The first meta-analysis looked at the full spectrum of individuals who drank in moderation and also heavy drinking, and it found that varenicline versus placebo did result in reduction in alcohol intake per unit time. It didn't improve heavy drinking or the number of drinking days, but it did reduce the number of drinks that people took. So, that's one potentially helpful benefit that varenicline could yield in this case. Again, we're not prescribing it for that reason; we're prescribing it for the smoking cessation, but this could be an added benefit.

There was a second meta-analysis that came out in 2020 that specifically looked at individuals with alcohol use disorder. That one found that varenicline reduced craving, but not consumption. So, in people with more serious forms of alcohol use, meaning disorder, they may benefit from reduced cravings. So, if they are a smoker, they may have an alcohol-related benefit, and these benefits could be potentially more pronounced in men and individuals who are depressed. That area is still under investigation.

So, really, either way we go, we'll be beneficial to this gentleman. We could start with combination nicotine replacement, so we would start with a 21mg patch, because he's smoking a pack a day. And, this is generally the dose that you would be starting with for an individual smoking a half a pack a day or more. We want to combine that with a short-acting oral. We usually treat for—guidelines give us flexibility in the number of weeks of treatment.

In our group, we tend to treat for three months, because it's a nice, round number, and I'll show you some neurobiology that supports that time duration. So, we would do a step-down, which is 21mg patch for one month, followed by 14mg for one month, followed by 7mg for one month. Really, this dosing is flexible, and if a patient comes to you and says I stepped down from 21 to 14, I'm really feeling more cravings, it's totally fine to go back up to 21 for another month. We really want to use this to comfort, because, usually, people are under dosed rather than overdosed.

If we go with varenicline, we'll also treat for 12 weeks, and we write a starter pack for the first month, and then a maintenance pack for two months, for a three-month duration. Varenicline is also approved for relapse prevention for an additional three months, for up to six months. And, on a case-by-case basis, individual clinicians can make a decision for their patients. If there's a risk of relapse, the patient is at extreme risk or very worried about relapse, or the clinician is, generally, any of the FDA-approved medications can be used for longer, on a case-by-case basis, again, to prevent relapse.

I also want to make a note about varenicline. In July of 2021, there was a global shortage. Patients could not get varenicline. Healthcare providers could not write a prescription for it. Because that shortage may persist for an unknown period of time, you may need to work with your pharmacist to investigate other potential manufacturers, and your pharmacist can help educate you what's available in your region.

Now, why do we generally talk about three months, or at least 8-12 weeks, when we're talking about pharmacotherapy versus a shorter time period? I just wanted to show this slide, which shows SPECT images of non-smokers on the left and then smokers of varying duration of abstinence on the right. So, here's one day, one week, two weeks, four weeks, etc., up to three months. The green that you see, the fuzzy green corresponds to availability of nicotinic receptors. You can see that the non-smokers do not have as much green here as smokers at one day, and especially at one week and two weeks.

So, what that means is, harkening back to that earlier cartoon we look at, when people go cold turkey, those receptors are upregulated. There are many of them throughout the brain, throughout the mid-brain, and they are hangry. This upregulation of receptors persists over weeks, and it corresponds to patients' self-report of craving. So, this biology and this changing biology takes a few months to reset back to normal levels. You can see that this picture on the right looks an awful lot more like the picture on the left, compared to these in between. Here, by 12 weeks, the nicotinic receptor levels have normalized, and the craving levels have normalized. So, during this in between time period, while patients are struggling to quit, they often need something, such as nicotine replacement or other FDA-approved medications, to help them through this process.

Seeing a picture like this helps us, as healthcare providers, field questions that we might get from patients or their family members, such as, well, the nicotine is out of my body within 72 hours. Why do I have to use something beyond that? This is why. Because, the neurobiology doesn't go back to normal in 72 hours. It takes much longer, on the order of weeks to months.

What role do electronic cigarettes have here? Probably many of you are fielding conversations about electronic cigarettes when you talk about smoking. So, this particular patient in our case said he had tried an e-cigarette. He smoked right along with it. And, he didn't like it anymore, and he doesn't want to use it now, so we won't necessarily offer it to him, but I did want to take the opportunity to highlight there is a Cochran review, published in 2020, looking at 50 studies and 26 RCTs in over 12000 people. There are some limitations to this Cochran review, and there's actually a lot of controversy in the literature about it. But, a few important key points.

The e-cigs with nicotine seem to increase quit rates at six months, when they're compared to e-cigs without nicotine, and also compared to nicotine replacement. But, again, very few large trials. E-cigs without nicotine increased quit rates compared to behavioral support alone. The main controversy here, there are two key points, one is that in the Hajek article, which was published in New England Journal a few years ago, the e-cigs were successful, relative to nicotine replacement. However, at 52 weeks, most people who were assigned to e-cigs were still using them.

So, that is a little bit concerning for some healthcare providers who think, well, the e-cigs are supposed to be just like FDA-approved meds. They're supposed to be used in a short duration to quit smoking and get off tobacco products all together. However, if people are going to be continuing to use them, that could be a problem, given that e-cigs may be safer than cigarettes, but are not "safe", because they still involved exposure to heavy metals and some carcinogens in the e-cig aerosol.

Then, the other really important key point for your patients who are asking about c-cigs, if they won't use FDA-approved meds, and they are just bent on using e-cigs as a first step, then you can encourage them to at least get off all of combustible tobacco. What is not healthy, what is not an improvement is to continue to smoke cigarettes or use other combustible tobacco, burnt tobacco, and use the e-cigs at the same time, the so-called dreaded dual use. That does not result in reduction in healthcare risks.

Also, a very important context, and this is different depending on what country you're talking about, but in the United States, e-cigs are not FDA-approved for treatment. So, even if you wanted to, it's not appropriate to write a prescription for them, at this time.

Moving on to the 5 A's, the arrange A, we want to connect our patient with ongoing support, and as I mentioned, we can do an internal program or an external program or both. The external programs, I'll show you some tips and resources. Through the modified 5 A's, ask, advise, act, so, ask, advice, write the prescription, do very brief counseling or whatever you're clinical visit will allow, and then connect your patient with 1-800-quitnow. Those are the quit lines. Smokefree.gov or become an ex. These are really incredible websites. I would encourage you to take a moment to look at them, the next free moment that you have.

The smokefree has something literally for every type of smoker, veterans, women, teens, Spanish speakers, people over 60, and it really takes them through all the 5 A's that you've talked about with them in your clinic visit, anything from I want to quit, getting prepared, what do I do on my quit day. Okay, I recently quit, now what? Then, maintenance, staying quit. It really offers incredible tools, including apps and texting, if they want to engage in those programs, and they are free.

Becomeanex, a joint initiative of the Truth Initiative and the Mayo Clinic, also has wonderful resources, many of which overlap with smokefree.gov. There's a lot more on electronic cigarettes here, and there's an opportunity to join the Ex community, become an Ex and get online support that way. So, either one of these or both of them are appropriate for a referral for your smokers.

One really important discussion point that I've alluded to so far, but I wanted to show you some data, is, and this really hits home with patients, they often feel better when they quit smoking. So, even if your patient doesn't care about heart disease, diabetes, lung cancer, wrinkles, impotence, whatever, you name it, they may care about feeling better. There's a very wide growing body of research demonstrating the impact of quality of life, especially mood and health-related quality of life when people quit smoking. A lot of this has been done in the outpatient setting.

Our group actually studied hospitalized smokers, and we found some interesting things that I wanted to highlight for you. Among individuals in three major academic hospitals who joined a smoking cessation program during their hospital stay and quit smoking versus did not quit smoking, the people who were abstinent actually reported greater health-related quality of life, and more of them reported excellent, very good, or good health, compared to people who didn't quit. This was even controlling for their baseline health-related quality of life.

We also looked at a short questionnaire for depression and anxiety, the PHQ-4. People who quit smoking, in the red bars versus blue, were less likely to screen positive for anxiety, depression, and psychological distress, even when we controlled for their baseline levels of those self-reported measures.

Finally, we looked at health-related quality of life on another commonly used scale, the EQ-5D-5L, and this demonstrated higher adjusted odds of self-care and lower pain and discomfort in individuals who quit smoking. So, they improved more on these important patient-centered metrics, self-care, pain and discomfort, and also anxiety and depression.

So, another thing you can tell your patients is evidence shows that most people feel better when they quit smoking.

Alright, what are some future directions in the treatment of smoking? I just want to highlight a couple future directions here. One is a drug that I mentioned earlier called cytisine. The reason I want to mention this is I've been interested in this, and many of my colleagues have been studying it as well. There's a large global knowledge and history of use with cytisine, particularly in eastern Europe. It is not currently approved by the FDA in the United States, but you may be seeing it in the future. So, that's why I want to just give a heads' up.

It's a naturally-occurring botanic alkaloid. And, like varenicline, it's a nicotinic receptor partial agonist. So, here's the nicotine molecule. Here's varenicline. And, here's cytisine. So, very similar structure. But, cytisine is interesting in general, because of its lower expense, and it also has not been shown to have any of the neuropsychiatric concerns that were present for varenicline that we reviewed. So, it's possible in the future we may be able to add this to our toolbox to help our patients quit smoking. So, stay tuned for that.

The other major area that represents the future of treating smoking is incorporating genetics. So, genetics play a large role in every phase of smoking, including initiation, becoming dependent, the amount people smoke, their total exposure, whether they can quit, and whether they persist in smoking. The blue here is genetic contribution, and the red is environmental. So, there's really a lot of genetics in this mix, and yet, we don't treat smoking by incorporating genetic information at present. That will change in the near future, and that will change because of a lot of very important data that's being published in genetic genome-wide association studies, GWA studies.

This one was published in 2019, one of the largest to date at that time, in over one million individuals, demonstrating particularly strong associations with genes on chromosome 15 of the nicotinic receptor and chromosome 19 that govern nicotine metabolism. The real

challenge now is translating this information in to precision approaches, and we are not quite there for clinical care, although, we are poised to start getting some of this information into clinical care. This is one of the areas that I find most exciting, both for research and for clinical care.

The pharmacogenetics and pharmacogenomics of smoking cessation are important. There are multiple pathways, as you saw in the prior slide, associated with the treatment response and side effects, in particular the nicotinic receptors and nicotine metabolism. The goals of precision medicine, which are becoming actionable, but not quite there, are really how do we incorporate this information? Do we do genome-wide association studies on everybody? Is there a way to just use discrete biomarkers? How can we do this in a cost-effective manner? And, what types of improvements in cessation will this precision medicine yield? Those are all very important open questions.

So, nicotine metabolism is taken care of in the liver in humans, and nicotine, inhaled from a cigarette, you've seen this cartoon before in our talk today, it goes up to the brain rapidly, but it is also metabolized rapidly by the liver in to cotinine, the major metabolite, and 3 hydroxy-cotinine. This is taken care of by the cytochrome P450 enzyme CYP2A6 primarily, along with several other enzymes, and results in the nicotine metabolite ratio, or the ratio of 3 hydroxy-cotinine to cotinine, which is a marker of the genetic activity.

About two-thirds of people are faster metabolizers, such that this process occurs several hours faster, and about one-third of individuals are slower metabolizers. Several factors go in to metabolism, including racial/ethnic background. But, by and large, on average, it's about a two-thirds/one-third breakdown.

The faster metabolizers with higher CYP2A6 activity tend to have more difficulty quitting. They are of a slightly different phenotype. They smoke more per day. They smoke more intensely. They exhibit more pronounced responses to smoking cues, and they have greater availability of those nicotinic receptors that we've been talking about. And, consequently, they tend to have more difficulty quitting smoking, although they can still quit. We still treat them just like the slower metabolizers. They tend to have lower quit rates with nicotine replacement.

This is a slide from a very important trial that came out in 2015. This was a multi-site trial in the United States, run by Karen Lerman, Rachelle Tyndale, and many other distinguished investigators in smoking cessation. What they did was they found that normal or faster metabolizers quit about twice as often on varenicline, the odds ratio was over two, compared to nicotine patch. Whereas, in slower metabolizers, the varenicline was no better than patch. So, what we have here is an interaction by nicotine metabolism, suggesting that it may be more favorable for the faster metabolizers to obtain varenicline rather than patch for quitting smoking.

This has not made it into clinical practice yet, and is currently under study by a number of groups. So, what I'm saying is, is there a way to optimize pharmacotherapy based on nicotine metabolism, whereby an individual would take a blood test, measure this NMR. It costs about $25 in our hospital system. Determine if they're slow or fast, and that cut point is yet to be determined, but an NMR of around 0.22 to 0.31 is probably somewhere

around the cut point. Then, if they are slow, give that individual nicotine replacement. If they're fast, give them varenicline to start.

The reason this is important is, based on the slide I just showed you, in faster metabolizers, who represent about two-thirds of all smokers, we can push quit rates to double them, if we give those individuals varenicline versus nicotine patch, and that makes a difference for the number needed to treat. It's about five for varenicline versus 26 for patch, so that's a lot of people.

So, in summary, we've talked about many aspects of smoking cessation today, but there are a few key points to summarize. First, smoking is a chronic disease, and it can be successfully addressed in the healthcare system by applying the 5 A's to every patient every time. We've had incredible success in the U.S., and also in other countries, with a 50-year public health campaign. However, 34 million American adults still smoke, and 58 million are exposed to second-hand smoke every year.

One of the key points for this talk, and for healthcare providers, is just how many of those 34 million are trying to quit every year. They are making quit attempts, whether you help them or not, but we need to help them more. Because, only 5% of them are receiving standard of care, combined FDA-approved meds and behavioral therapy.

Another point is that residual smoking-related disease, such as I showed you from the Framingham Heart study data, for either CVD or lung cancer, as well as other conditions, this residual risk can persist for years after smoking cessation. So, even after people successfully quit, continue to think screening for CVD and for lung cancer.

Finally, new treatments are coming. We may have new medications coming down the road soon, possibly in cytisine, and precision medicine is coming. So, hopefully, in future years, we'll be able to effectively incorporate things like genetic risk scores or biomarker results in to our treatment plans for pharmacotherapy.

These are a few additional resources. We've touched on them. Surgeongeneral.gov, CDC.gov. Thank you so much. It's been a pleasure to talk with you today.