UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR TOBACCO PRODUCTS

+ + +

WATERPIPES: A PUBLIC WORKSHOP

+ + +

March 18, 2016
8:30 a.m.

FDA White Oak Conference Center
Building 31, Room 1503
10903 New Hampshire Avenue
Silver Spring, Maryland

FDA:

CAROLYN DRESLER, M.D., M.P.A.
Associate Director for Medical and Health Sciences
Office of Science
Center for Tobacco Products

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

PUBLIC COMMENT SESSION

ARUNI BHATNAGAR, Ph.D.
University of Louisville
American Heart Association

ABRAHIM NADIMI
Co-founder, Social Smoke, Inc.

SESSION 5: WATERPIPE TOBACCO DEPENDENCE, TOPOGRAPHY, USE BEHAVIOR, SYSTEMIC EXPOSURE AND RESPONSES

WASIM MAZIAK, M.D., Ph.D.
Florida International University

CAROLINE O. COBB, Ph.D.
Virginia Commonwealth University

ELENA V. MISHINA, Ph.D.
Pharmacologist
Office of Science
FDA Center for Tobacco Products

SESSION 6: ACUTE AND LONG TERM HEALTH EFFECTS

KENNETH D. WARD, Ph.D.
University of Memphis School of Public Health

CHRISTOPHER LOFFREDO, Ph.D.
Georgetown University

ARASH ETEMADI, M.D., Ph.D.
National Cancer Institute

MARY P. MARTINASEK, Ph.D.
University of Tampa

MOHAMMED JAWAD, M.D.
Imperial College London, School of Public Health

ALSO PARTICIPATING:

MARIELLE C. BRINKMAN
Senior Research Scientist
Battelle Public Health Center for Tobacco Research

RAMZI G. SALLOUM, Ph.D.
University of Florida College of Medicine

M E E T I N G

(8:30 a.m.)

DR. DRESLER: Well, I have 8:30, maybe a minute after. Let's get started, please.

Welcome back to the second day of the waterpipe workshop. Yesterday, I thought, was tremendous and learned a lot; we had some good discussion.

One of the things that several colleagues and I were speaking about is that we know electronic cigarettes get a lot of attention and waterpipe hasn't had as much attention, so I think we learned a lot yesterday, that waterpipe deserves a lot of attention. So I'm just excited to have it, and thank you to

all the speakers yesterday and so very much looking forward to today.

So today we're going to start out with the public comment section. And so people were able to sign up online to give presentations, and they will have 8 minutes each. We try and spread that out some, depending on how many people have signed up to speak, so 8 minutes. And for the public speakers, you'll see you have the green-yellow-red. Green means go and you can keep going; yellow means, oh, better think about stopping because you're winding down, and when you're up here it will tell you how many seconds and minutes that you have; and red means you're done. Okay? So please let's try and stay with that. So it's just a really good guide.

So we will have the first speaker. Aruni, I think I'm not seeing others, and Caryn. Thank you.

Dr. Bhatnagar from the University of Louisville, American Heart Association, will be our first presenter.

DR. BHATNAGAR: Good morning, and thank you for the chance of speaking to you this morning. I'm from the American Heart Association and wanted to talk to you a little bit about hookah and why we're particularly concerned about the effects it might have on cardiovascular health. So we all know hookah is

complicated machinery.

It was invented, I think, somewhere in the 16th century in the court of Akbar, and the idea there is that it was initially to be used through -- to inhale hashish and opium, but it's been adapted for tobacco use. And in India it's been a very popular device and has been used for many centuries. It's a status symbol and a sort of sign of cultural upbringing. But in the United States, there's been a recent spread in the use of hookah, and it's become increasingly popular, especially among college students but also undergraduates who reported smoking hookah occasionally. And at least one in five American college students have used hookah, and the worldwide prevalence exceeds about over a hundred million. So this is not a trivial problem, although some believe that because it is occasional and that it is sporadic, that it might not have very serious health consequences.

So some consider that hookah is less harmful than cigarettes because they're not smoked routinely and there's something magical about the water that takes out all the toxins and therefore you're not exposed to much of that, much of these toxins, and that there are flavors that make the experience more pleasant and enjoyable.

But nevertheless, the hookah contains the hookah smoke, contains tar and nicotine and carbon monoxide, also a variety of different chemicals that we heard yesterday, and all these different types of chemicals are present, including nitrosamines, metals, as well as volatile organic compounds, fine particles, which the distribution of these fine particles is very similar to that that's found in tobacco smoke, and then there are aldehydes. So the question is why should we be concerned with all of this, and because you've learned a lot of what happens with these things with experience and studying the effects of smoking and other tobacco products. In particular, we're concerned about aldehydes, and the reason for that is that these aldehydes are relatively toxic and they're present in very high abundance.

And there are some listed here. You know, there's been a lot of debate about the contribution of these aldehydes in electronic cigarettes, in tobacco smoke, and therefore there is -- there could be some health consequences that we must be aware of and we must be cognizant of. This is the list of different -- some of the most abundant aldehydes both in cigarettes and hookah, and as you can see, in some cases the concentration exceeds those of cigarettes.

That has to do with the partial burning in cigarette. The more rapid and high temperature burning there is, the less aldehydes, so its partial combustion leads to development of these or the generation of these aldehydes. And so you can see that there is some of these levels here. Particularly, acetaldehyde and acrolein are much higher in hookah.

But so what? Does it matter? Are these concentrations high enough to cause any problem? We do not know. But from several experiments that we have conducted and others have conducted, that they had reason to believe that there might be toxicity associated with it.

In fact, if you do sort of theoretical evaluation of the contribution of different types of compounds and chemicals that are present in cigarette smoke, almost about 90% of the risk is actually just attributable to one particular compound, which is acrolein, and the reason for that is because the lowest non-effective dose of acrolein is 0.002 ppm. And so even if you exceed a little bit of this, the calculated harm is very high.

So we think that some of these compounds are particularly reactive and toxic, and then if there are going to be regulations about -- in hookah and types of things that we can do to it to minimize harm, that we should be aware that there

should be a minimization of the production of acrolein in these devices and ENDS.

But the main constituents of that, of course, of concern and the reason for smoking the hookah in the first place is nicotine, and there's this general belief perpetuated from the 1950s that people smoke for the nicotine and die from the smoke. That's apparently not very likely because at least from a cardiovascular perspective, nicotine is a very strong vasoactive drug. It increases heart rate and blood pressure and, as we all know, increases cognition and suppresses appetite. It can also affect the release of different transmitters such as dopamine, norepinephrine, and epinephrine.

And so it has profound cardiovascular effects, and I think it is important that we realize that some of these, of the effects, whether it's cigarettes, whether it's ENDS, or whether it's hookah, could be attributable to nicotine because that would have sort of very significant hemodynamic effects and those -- such hemodynamic effects may be important triggers for acute cardiovascular events. It may not be as profound for respiratory problems or cancer effects, but specifically for cardiovascular effects, these could be important.

And this is the possibility of different things that

nicotine can do. These are sympathomimetic effects increasing the heart rate, contractility, heart rate variability, blood pressure, but also disregulation of lipids. And so we need to be aware that nicotine is not an innocuous drug and could be used much like coffee. So not surprisingly, there are many direct acute effects of hookah that have been reported, and most of these could be attributable to nicotine. There's increase in heart rate, blood pressure, both systolic and diastolic blood pressure, changes in inter-beat interval, changes in heart rate variability. So heart rate variability is an important index because a lot of heart rate variability is a sign of good health.

Reduced heart rate variability is sort of -- portends disease. And so therefore it is -- the effects of nicotine on heart rate variability are particularly sort of profound. And this has been sort of -- been duplicated with just pure nicotine. If you just take a nicotine spray, you can get changes in endothelial function, you can get to changes in heart rate variability, and you can get increase in blood pressure as well as heart rate.

But there are also chronic effects of smoking hookah, and these chronic effects we'll hear more in the afternoon is sort

of, in general, it would convey the idea that there is increased harm, particularly for people who smoke hookah routinely and over many years. And these studies come from different parts of the world. Women smoking hookah, I know it's very common in India. My grandmother used to smoke a lot of hookah. And so there would be -- smoking hookah could be a big risk factor for cardiovascular disease as well as for all-cause mortality. And also, it increases cardiac stenosis, progression of coronary artery disease measured by the technique of the intimal. The coronary disease is also much higher in hookah smokers than in tobacco cigarette smokers, so there's particular concern about that. So I will end with some specific suggestions and not direct recommendations.

We particularly need to develop effective risk communication strategies, particularly those with college students who tend to believe that hookah is not really very toxic and that if you do it occasionally, you would not be addicted. We need to enforce some age limitations. I know this is a controversial issue, it's 18, but there's a big push to have it go to 21 years.

We have to enforce Clean Air Act, and I know this is also a very touchy issue, but most hookah is smoked on a social

basis, and so if there is stricter regulation on Clean Air Act, then it would sort of disperse these social gatherings and hookah smoking parties and the multiple hookah lounges and bars we saw yesterday. We need better warning labels on hookah and devices and a warning -- some things that we've done with cigarettes and so on. We need to label these products much more accurately. We need to monitor devices. We have many fancy devices now such as this, e-hookahs and other things that have sort of mushroomed and proliferated. We have to monitor what these devices can do. But more importantly, we have to study the potential for addiction, whether people who are smoking hookah occasionally can go into more nicotine addiction of cigarette smoking.

But all this could only be accomplished if we pay attention to the toxicity of the hookah and conduct well-designed, rigorous longitudinal studies that have been missing in this field and that have kept us from understanding what the real cost of smoking hookah may be.

Thank you very much.

(Applause.)

DR. ASHLEY: Can we ask questions?

DR. DRESLER: Yes. How could I say no to you?

DR. ASHLEY: That is a good question.

(Laughter.)

DR. ASHLEY: I'm interested in -- I apologize for not being here all day yesterday because others may have answered this question, but I'm going to toss it to you because you brought it up. So comparing cigarettes to hookah, hookah -- a typical person, I guess, now smokes about 10 cigarettes a day; it used to be 20 cigarettes a day, but now they switched it down to 10. I don't think people are smoking generally 10 -- they don't have 10 hookah sessions in a day, more than likely.

When we're comparing those, what do you think is a reasonable way to compare delivery of hookah versus delivery of a cigarette? Should it be 10 cigarettes versus one hookah? Is a comparison of one cigarette versus one hookah session fair? How should we be comparing this?

DR. BHATNAGAR: So I'm sure there are others in the audience who can answer this better than I can, but from what I understand, that each hookah session is equal to like three or four cigarettes. And so -- because it lasts for a certain amount of time, the exposure is almost similar. The cardiovascular studies were pretty good, if you're interested,

and other ones in which they are three to five sessions a day that people smoke hookah, which causes a constant -- and if you do that for about like 20 years or something and then the progression would be -- the risk is much higher than cigarettes. So it is not necessary that you do hookah 10 times a day, but even if a couple of times a day, that's a lot. But occasionally, there has been -- so people who do it like once a week or twice a week, which is more common of college students here, there have been very few studies trying to evaluate the toxicity of this.

One thing I would say before -- if anybody else wants to join in, what we have learned from tobacco smoke is that tobacco smoke dose-response for cardiovascular mortality in particular, not cancer, not respiratory, is nonlinear. So the risks of smoking, say, two packs a day, 80% of the risk is transmitted by smoking three to four cigarettes a day.

So 80% of the risk comes from very, very low exposure. That's why secondhand exposure to tobacco smoke is so lethal because the risk is between one to three cigarettes. So if you go by that, if you are just vaping one of -- not vaping, but using hookah once a day, that's equal to three to four cigarette exposure, and you get the 80% of the risk of

cigarettes. So that's an estimate. If anybody else has anything else to add?

DR. DRESLER: You know, I think what I'm going to do is write down the question, and we'll ask that at the panel, too, because I think people on the first panel probably would like to address that too. So great. Does that make sense?

Okay, our next speaker is Abrahim Nadimi from Social Smoke. I don't know if you heard me before, but your timer's there. And then forward and then back.

MR. NADIMI: Awesome, thank you. Do I go ahead and start?

DR. DRESLER: Yeah, go ahead.

MR. NADIMI: Good morning. My name is Abrahim Nadimi, and I'm the co-founder of Social Smoke. We're a 13-year old hookah company based in Dallas. It goes without saying that we have a vested interest in selling hookah tobacco. However, we strongly believe that a relationship should and -- should exist between industry, the scientific community, and the regulatory agencies to ensure an educated consumer base for this and all adult products.

My time is really limited, so I'm going to briefly cover these topics today. But first I'm going to deviate from the agenda to address some of the points from yesterday's session.

Social Smoke agrees with Dr. King's statement that it is never healthy to combust something and inhale it. We also agree that labeling guidelines are lacking. There are some guidelines already provided by the ATF; however, they aren't strictly enforced, resulting in confusion in the marketplace.

Yesterday, much was said about the 0.05 nicotine and 0% tar numbers on labels. This is something that we have complained to our ATF field agent because these numbers appear made up. We have never posted these numbers on our products, but no one is enforcing these things, so the practice that has started with big and established Middle Eastern brands has unfortunately become an industry norm. It's not just these numbers, but there are other ways that labeling guidelines are already being violated. Whatever the labeling guidelines are, we will follow as we do when we export our product to other countries.

Another point that was brought up yesterday is the online sales of products. There are already some established rules for online sales of tobacco products, and the vast majority of credit card companies will not process payments unless the credit card data is verified with a matching form of ID. This isn't a cheap third-party solution, but we were happy to

implement it, and we used this process for years. But guess what? Even that wasn't enforced across the board. And as a side note, we have completely stopped selling online sales as of October 2015.

I find it particularly appalling that young adolescents are consuming hookah. Hookahs aren't pocket size, they are cumbersome to set up, and to do so without getting caught makes me wonder where are our parents? And if it's not hookah, what other harmful activities would our youth be doing?

So back to my presentation. Not all hookah smoking is the same. This was only briefly discussed yesterday but needs much more consideration because otherwise all hookah products are painted in an extremely broad stroke, resulting in an incomplete picture that is unfair to those that seek to base their decision on more than generalization.

Much research cites smoking in North Africa and the Middle East; however, the style of smoking and tobacco use is, in many ways, different from what is found in the United States. Much has been said about protecting the young adult demographic, so I'd like to be more specific and state that this demographic typically does not smoke hookah the same as what is found in the Middle East. As an example, when I went to Cairo in 2007,

I witnessed this style of smoking. Not only -- so it was the previous one there. Notice that these coals are placed directly onto the tobacco and are used to directly burn the leaf.

This tobacco is so strong, my Egyptian host joked that it wasn't like the sissy stuff they sell in America. And I tried two puffs, and I got lightheaded and an upset stomach. I'm not trying to say that all smoking in the Middle East is like this, but it is something to be considered when looking at the data from that part of the world. Our tobacco, like many U.S.-based brands, is meant to be heated and not burned.

This is not a subtle distinction. When the foil touches the tobacco, it causes the tobacco to burn, which is undesirable and causes the smoker to stop and tune the head or coals, as we heard yesterday. We learned a lot about smoking volume, but uncoupling smoking volume and combustion data from use frequency represents a very incomplete picture. A cigarette produces less smoke; however, who smokes one cigarette a day? A quick online search pointed me to a pack a day as common, which is 10 cigarettes -- today I heard 10. Either way, if this data -- if this is true, then all data for cigarettes should be multiplied by 10. And remember, this is

consumed every day.

The research also pointed out that a vast majority of users answered yes to being a hookah smoker when given the "rarely use" option, which makes perfect sense when coupled with the findings that show the vast majority of users smoking hookah at a friend's house, a hookah bar, or party. This is because users are socially smoking and sharing the hookah among multiple people; this is something that can be further researched. Or from experience, I can tell you that sharing with friends is an extremely common way of using the hookah.

I'm not trying to trivialize the health risk. My goal is providing some insight from my experience that might be able to enhance the quality of research being conducted. While some Middle Eastern-based hookah companies are very large, the vast, if not all, American producers are relatively small; factories producing small batches by hand. I noticed two big Middle Eastern brands cited over and over yesterday, which is especially unfair to domestic producers. I could get into more details about the differences, but time is limited.

This is a picture of the size of each set that we make, so it's 18 kilograms in each bucket. We do have a very big concern: If the FDA decides to regulate certain hookah

products based solely on their date of production while grandfathering in others, it will usher in a litany of unintended consequences. Not only will it close many U.S.-based producers, but it would also cement positions of competing, established Middle Eastern hookah tobacco manufacturers.

Further, there will be absolutely no positive health benefit as tobacco will still be on the market; it just won't be manufactured by U.S.-based businesses. We are also concerned about the cost of testing, especially if it's just to change flavors, because many of us are small businesses that cannot afford huge testing bills.

I will not deny that hookahs have brought with them a way for many of us to make friends and socialize. In an age where social media rules our lives, I see this fact as a positive. I know countless friendly and romantic relationships that thank the hookah for bringing them together. One such person was Spencer. I cried when I learned of his passing, and I think of him and his fiancée often. Spencer's life was tragically cut short by a drunk driver. I bring up this story so that you know that we care about our friends, about our consumers. Many are our friends and family.

And we would like to continue promoting a product that crosses generational and cultural lines but want to be responsible in doing so. I offer myself and my family to both the FDA and the scientific community if there's anything that we can do to help the efforts and results that we all seek.

Thank you.

(Applause.)

DR. DRESLER: So our other public speakers are not here, so we will move forward. And just to make sure nobody else in the audience had signed up to do the public speaking, I need -- okay, good.

So the next session is Waterpipe Tobacco Dependence, Topography, Use Behavior, Systemic Exposure and Responses. And our first speaker is Dr. Wasim Maziak from Florida International University, Dependence in Waterpipe Smokers.

DR. MAZIAK: Good morning, everybody, and thank you. It's a very optimal topic for a Friday morning. I want to acknowledge my team and my funding by Fogarty and NIDA of NIH. So we're talking about the hookah, reminding ourselves that this is a Middle Eastern tobacco use method that has become a global phenomena in recent years. And the reason why hookah smoking has become a global phenomena is because of the

increasing trends, the harmful effects, and addictive properties. And we heard several presentations yesterday about the intermittent use, the false misperception that this is not addictive, the filtering effect of water. And my goal is to convince you, based on evidence, that it's very addictive and is as addictive as any nicotine product can be.

Why people take up smoking: There are two different reasons or main groups of reasons that define different stages of smoking. So people start smoking because of social, peer influence, marketing, some cultural factors, while the continuation of smoking is mainly a factor of nicotine addiction.

How nicotine addiction develops: Very briefly, it's not a neuro-pharmacology type of session, but nicotine exposure changes the brain chemistry, and that change and those changes are revealed by behavioral manifestations that we usually measure, and by their measurement we define addiction or dependence in nicotine users. And these usual manifestations present themselves when people abstain from taking nicotine, and they can be in withdrawal, anxiety, craving, and so forth. And those symptoms are the same ones that we use to establish a diagnosis of nicotine dependence.

So the important questions to answer in terms of dependence and nicotine dependence of waterpipe smoking, I can identify three main ones. The first is does the waterpipe deliver nicotine to smokers? And that's an essential question because we know, from chemical neuro-pharmacology, nicotine is the substance of addiction in all tobacco products. And it's also the business model for everybody who sells any nicotine or tobacco product. That's why I'm very skeptical of the harm reduction model because the harm reduction model based on allowing hardcore smokers an option other than quit or die is a suicide business model for those who manufacture and sell nicotine because their model is to addict more people and sell more products. So if the harm reduction model works, actually they will be out of business.

Do waterpipe smokers exhibit signs of nicotine addiction? So this is now not the neuro-pharmacological, but the behavioral side. We want to show that -- to be able to convince anybody that the waterpipe is addictive, that actually if they go without smoking, waterpipe smokers, they experience withdrawal, craving, and the classical symptom of nicotine dependence that we know of from cigarette smoking.

The third question, which is very important, is what are

the differences in nicotine dependence between waterpipe smokers and cigarette smokers? Because this is -- has a very important implication on the way we measure nicotine dependence in waterpipe smokers and because of too many differences. Most of what we use are scales. The Fagerstrom and so forth are actually not suitable to measure nicotine dependence in waterpipe smokers. And the second reason, important reason, why we need to tease out the differences is that we cannot design tailored intervention or smoking cessation intervention for waterpipe smokers if we treat it like a cigarette, and then we will miss a lot of the symptoms and cues that are associated with waterpipe smoking but are unique to that tobacco use method.

I'll try to answer these questions quickly in this presentation. As far as nicotine, human studies, not tobacco smoke constituent studies, have shown that if you actually measure plasma nicotine before a waterpipe session and after a waterpipe session, you get high uptake of nicotine in smokers. And so the figure to the left shows that -- the yellow is pre-plasma nicotine level for the study we did, clinical lab study we did, in Syria. And the blue bar is after, nicotine level after the waterpipe smoking session.

The right-hand panel here is the comparison in cigarette smoking. So there's more even uptake with one session compared to one cigarette. The next graph, to the right, is actually the pharmacodynamics of nicotine absorption in waterpipe smokers compared to cigarette smokers.

This is a crossover design where the same person smokes the waterpipe and then outcomes after a couple of days and smokes a cigarette and we measure -- we actually sample -- this is a study done by Eissenberg and Shihadeh, and they measured the plasma nicotine at 5-minute intervals and just to show the differences in the pharmacodynamics. And then, as you see, there's a spike in nicotine plasma, nicotine for cigarette smokers, that goes down quickly while there's a gradual increase because of the length of the session in nicotine uptake in waterpipe smokers.

So this is the first answer, the question answered yes, and it's a strong yes because it's based on clinical data of people who are smoking waterpipe. And we measured that before and after smoking.

The second question is do waterpipe smokers manifest behavioral symptoms of withdrawal, craving, adaptations to ensure access, failed quit attempts, and tolerance? And these

are the classical symptoms of nicotine dependence that we know from the cigarette literature.

We did several studies investigating those symptoms, and in one of these early ones that we did back in 2008, we brought people who were overnight abstinent from any tobacco use; there were only waterpipe smokers. And we asked them how they feel in terms of their craving, restlessness, urge to smoke, before smoking, and then we measured those symptoms after smoking, and we see a very high level of those symptoms indicating withdrawal before the session, and then these were all ameliorated by subsequent waterpipe smoking. So this is very simple clear evidence that actually even with intermittent use, most waterpipe smokers experience withdrawal and craving, the classical symptoms of withdrawal/craving that we know from cigarette smokers when they abstain.

How about testimonials or qualitative evidence that shows that people experience those? And I can read a couple of those. Some of them even come from not our research, but some of them even come from hookah clubs and so forth. The first one, "If I cannot smoke, I feel restless and tired. When I travel to visit my parents, I do not smoke. Their home environment is not encouraging, and I do not feel an urge to

smoke. I crave the narghile from 7 until 10 in the evening."

The second testimony that was done by Dr. Jawad's, who is here, research, "Sometimes it bothers me – if I want it [the waterpipe] I don't just forget about it – I'll do anything just to have it...I don't know why."

This is very, very familiar to us who have been working in the nicotine dependence business when the latest stage of nicotine addiction is that compulsive, you cannot get it out of your head. It's not about okay, I'm going to smoke if I can or not. If I cannot, this is going to become a so dominating idea that characterizes advanced level of addiction.

How about confidence in quitting and failure to quit? So we did an early study when actually people, according to their smoking level, whether it's daily or weekly or monthly, had -- those who smoked less frequently were more confident they can quit and more even successful in quitting compared to those who smoked daily, who are less confident to quit in their ability to quit and made quit attempts subsequently. So this is kind of very common in nicotine dependence where the more addicted, the more they're hooked, the more likely that you think it's really hard for you to quit.

How about drug-seeking behavior? We know from cigarettes

actually that if you're a cigarette addict, all your daily activity is planned to have -- ensure access at all times of the day to cigarettes. So you plan your day accordingly. And we see that even happening in waterpipe smokers with such innovations that, such as -- this is the portable waterpipe.

This is a soccer fan for the German soccer team in the World Cup, we got that in Beirut, who had a waterpipe on his motorcycle. Of course, it's not as accessible as cigarettes. People take it to parties and stuff. You can even share a waterpipe if you have a traffic jam. So it's very relevant to Washington here, your kind of guys. And this is even very interesting, because this is Tripoli at the time of civil war, and so these are things -- the blankets are to shield from snipers, and this guy is running with a waterpipe from somebody.

So behavioral adaptation to ensure access present themselves differently in waterpipe smokers than cigarettes because the cigarettes is a pack; you can put it in your pocket, go with it, and then access it. The waterpipe is a seated, prolonged behavior that is not as portable or easily portable. So we looked specifically at this issue to show what are adaptations people, waterpipe smokers, do to ensure access

given the non-portability and the time-consuming nature of the practice.

And this is one of the studies that we did, and we asked two questions: Do you carry narghile, which is the local name of waterpipe, when you go out, in case you need it? Is narghile an important consideration for you when you choose a restaurant/café to go to? And sure enough, the more daily -- the more hooked smokers are the ones who actually answered yes to both these questions because they want to have, ensure that they have access during the day to the waterpipe, while less frequent smokers were less likely to kind of plan their day accordingly to have access.

Some of the qualitative evidence about this behavioral adaptation that I can -- testimonies that I can read for you. This is actually from a hookah blog, another research that we did. "My cousin wouldn't go out and wouldn't go out to a party with his friends without having with him his waterpipe handbag, all its accessories, and all the tobacco-filled heads," apparently are in the handbag. So this kind of shows how kind of dominating practice, that people will make sure that they will go nowhere without making sure that they have access to the waterpipe.

Tolerance is another landmark of nicotine dependence where the same dosage does not get you the buzz or the effect that is required. And this is actually an important phase in the early stages of nicotine dependence because then people max out and then the aversiveness of the tobacco product becomes a bad -- and you cannot go over, like people cannot go over smoking 40 cigarettes per day no matter what they want because they cannot -- you cannot handle it. So this is -- and from also Dr. Jawad's research: "On holiday...I looked at my mum and said 'Can I try it?' Then I used to do it with my friends every once in a while, very rarely. When I got to university I started smoking it a little bit more. Then we got one in the flat and we started to do it a lot more."

Loss of autonomy. When you cannot control the behavior is also a landmark of nicotine dependence, and it's usually when you want to stop but you cannot stop. And this is also -- these are testimonials from waterpipe smokers, and I'm going to read only one: "I can't smoke before I play sports because I'm out of breath. If I smoke less than 4 hours before playing, then it really affects me. I can carry on playing but I'm breathing heavily." So this is a person who has contradiction between his sports. He likes sports but also his waterpipe

smoking habit.

So the second question is answered yes based on different lines of evidence from qualitative and quantitative and even lab work.

The last question: Does dependence on waterpipe differ from cigarettes to warrant specific approach? So there are unique features, and I've already talked about waterpipe is not accessible. It a seated behavior different from -- and it's a very social behavior that is very different from cigarette smoking, and these things affect how actually dependence manifests itself in waterpipe smokers. We need to tap into those differences to design effective intervention strategies and also to measure nicotine dependence in waterpipe smokers accurately.

And so I start with some qualitative evidence: "I usually smoke narghile once daily, but sometimes I smoke more. Because even when I have already smoked it, seeing or smelling narghile makes me feel that I need to smoke again, and I usually do smoke."

So these are actually factors that you don't see much with cigarettes because of the aromatic smells of the flavored tobacco and the shape, the appealing shape of the artifact. A

lot of that represents a cue for smoking the waterpipe that we have to tap if we want to understand and even treat nicotine dependence in waterpipe smokers.

I want to stop a little bit on this study because this is a current study that we're doing in Lebanon, and it's funded by NIDA. This is the only study that I'm aware of as the -- looking at the natural history of nicotine dependence development in youngsters. So we started with four groups, waterpipe smokers; they're all 12 to 13 at baseline. Waterpipe smokers, susceptible waterpipe smokers, cigarette smokers, susceptible cigarette smokers. Susceptible cigarette smoker and waterpipe smoker based on a question whether you expect yourself to smoke in the next 6 months or so. And we followed them when they were not smoker or starting to smoke and to see what are the first symptoms of nicotine dependence in both groups, or four groups actually; what are the nature of those symptoms and how soon and at what frequency of use they appear?

So if I can, like a couple of -- the results from that study that we've just analyzed and is now under consideration in *Tobacco Control*, we're in the 3R revision stage. If they ask for another revision, I'm going to have a fit, but I hope it's going to be published eventually.

So smoking onset -- from smoking onset to the appearance of first HONC symptoms. HONC is the Hooked on Nicotine Checklist, which is a very sensitive instrument to nicotine dependence at early stages, so it's especially good for adolescents, and it was extensively validated. So for waterpipe smokers, from the first use until the first HONC symptoms appear, you have a period of about 11 months. The same, for cigarette smoking is about 17 or 19 -- 18 months. So you see it's even a shorter interval between first use and the appearance of first nicotine dependence symptom. And in terms of frequency, if you add the time of appearance of that symptom, it's about 7½ waterpipes per month compared to 27½ cigarettes per month. So you can see at lower levels and in a shorter period, nicotine dependence actually appears in waterpipe smokers compared to cigarette smokers.

Some people criticize the HONC because it's not a kind of standardized, or not very widely accepted as a measure, so we looked at ICD-10 defined criteria. So this is the International Classification of Disease definition of nicotine dependence, and it requires three symptoms of maybe the last six, I think, to seven symptoms.

So from smoking onset to attaining the full definition of

nicotine dependence for waterpipe smokers, the period was 14 months. For cigarette smokers it was almost 30 months. Again, reaffirming that initial symptoms of dependence and the fully blown syndrome of dependence appears in waterpipe smokers earlier than in cigarette smokers and also at lower level of use. And this, perhaps, is explained by the length of the smoking session where you get a lot of exposure to nicotine compared to the frequency of smoking for short periods for cigarettes.

So this third question is answered yes. There are differences, and there are differences in the nature of the symptoms and in how they appear and at what frequency they appear.

The last thing I hope to cover is the gateway concept, and this has also been fought a lot because when we show that people start with waterpipe, move to cigarette, a lot of criticism arises that okay, these are young people; they're usually open to experimenting. Why this is a gateway, not a normal experimentation phenomenon.

So there are some ways that you can tease out those things, and there is a very, very nice lecture about the gateway and nicotine dependence and how this is a one-direction

biological process not related to experimentation in the *New England Journal of Medicine*. But we did a longitudinal study to assess that. So if we are correct, our assumption -- and I hope you can give me just 30 minutes, 30 seconds more because this is important. Our assumption that because waterpipe is less accessible -- the more dependent waterpipe smokers, because they cannot have access, they are more likely to start cigarettes.

So we wanted to test this assumption in a longitudinal study. We started with people who are waterpipe smokers/non-waterpipe smokers and follow them up to see how many of the two groups become cigarette smokers. And lo and behold, we saw that actually those who -- the waterpipe smokers at baseline were more likely to become cigarette smokers at 3 years follow-up. But for this, for our hypothesis about the access and dependence to become true, we need to show actually that this risk of becoming a cigarette -- or initiating cigarette smoking will be dependent on your frequency or level of dependence.

So we did an analysis where we compared the risk of later initiation of waterpipe smoking based on use frequency, and also we saw an increasing trend; the more frequent people use

waterpipe at baseline, the more likely that they will initiate cigarette smoking. So that kind of provides some indirect support of our hypothesis because the more you smoke waterpipe usually means that you're more dependent. And because of that, because your day cannot be manipulated to have access everywhere you go, people will go out and then probably start smoking cigarettes.

And our data was supported recently by the -- a similar study, similar study design from Brian Primack and colleagues when they compared waterpipe smokers and nonsmokers at baseline and show that actually for probability initiating cigarette smoking for those who are nonsmokers was about 20% lower than from those who were waterpipe smokers at baseline. And I cannot believe I'm going to make it on time.

And this is one of the push pads that you see everywhere in our work, that addiction is -- waterpipe addiction is one of the greatest fallacies in tobacco research, and this actually posts -- criticizes even nicotine as being the addictive substance where actually the tobacco industry is now acknowledging that this is the main addictive substance in tobacco.

Future questions to answer. This is the last slide.

What are the main components of tobacco dependence syndrome in waterpipe smokers? We hope that we'll be able to answer this question by continuing to follow up those young waterpipe smokers as they develop more symptoms and establish a full waterpipe dependence syndrome.

How to measure dependence in waterpipe smokers in a way that is sensitive to the nature of dependence in waterpipe smokers? This is a big question that has had a lot of argument now, arguments whether what we use for cigarettes are suitable or not, and I think of course they're not because if you answer -- like, what is the first cigarette in the morning even, ask that, which is a main item in the Fagerstrom, ask that, waterpipe smoking is meaningless because this is an evening leisure-time kind of tobacco use method. Who can spend two hours in the morning to smoke a waterpipe and then go to work?

But anyway, how to make sure that waterpipe smoking is addressed in all smoking cessation intervention, because a lot of people, when they quit smoking cigarettes, they start waterpipe, and they're thinking okay, they quit, so that's okay. Usually, they go back to cigarettes. So we have to address waterpipe smoking cessation as a compensation method in

all cigarette smoking cessations and what type of interventions that we will need to effectively curb waterpipe smoking.

And thank you very much.

(Applause.)

DR. DRESLER: We have time because the public speakers, not all of them were there. So future speakers, you know, we'll work on being lenient, okay?

So our next presenter is Dr. Caroline Cobb from Virginia Commonwealth University, and I want everybody to know that we're staying in the Southeast still today. So Waterpipe Puff Topography and Toxicant Exposure.

DR. COBB: I'd first like to thank the FDA for this opportunity to present to you all. It's really my pleasure to present data from my research team. It's just a great honor to be here.

My acknowledgements first: I'd really like to call attention to Dr. Thomas Eissenberg and Dr. Alan Shihadeh. Without these individuals, I wouldn't be doing this type of work, and much of the data here wouldn't be here. But I'd also like to thank the other collaborators in this room who are part of this work. Many of you are here, are participants. And these are my current funding sources, and I have no other

conflicts of interest to report.

Just a little overview of what I'm going to be talking about today: We're going to really briefly talk about what is a waterpipe because by this time you guys all know very deeply. I'll talk about how waterpipes are used and specific means of how they're used, their smoking behavior, their puff topography. And then we're going to go through three different examples of how we can use puff topography and toxicant exposure data to really understand the interplay between these two things.

So this picture, again, I expect looks very familiar to you all, but what I like about the picture to the right is it's actually the waterpipe that we use in our clinical laboratory studies. Waterpipes come in many different shapes and sizes, but we chose this one because it's actually the same kind that's used in the waterpipe cafés in Richmond, Virginia. So this was a particular -- we wanted to make sure what we were studying was naturalistic. You can see that the waterpipe head has been deconstructed, and that's maassel or shisha, and that's typically the type of waterpipe tobacco that's used in waterpipe cafés in Richmond, Virginia as well.

So when you think of this question of how waterpipes or

hookahs are used, you might think of some basic questions like where they're used, how frequently, how intensely they're used, maybe how many heads per day. But I'm going to talk about another measure of waterpipe use behavior, and that's puff topography, a detailed measure of smoking behavior, and I think this is a really important measure for several reasons: one, it gives us a really intricate look into how these products are used, so characterizing patterns of use by individuals.

We can also use this information to understand exposure to smoke toxicants, which I'm going to spend some time talking about today. There is a body of work looking at cigarette smoke topography, as well, in a similar manner.

We also can look at changes in puff topography and whether products change the way people smoke. So if I give a waterpipe smoker a product with less nicotine, does that change their smoking behavior? Does that change the exposures that they have? Using tools of puff topography, we can measure that.

And then lastly, I think one of the really important means we can use puff topography is to understand what's actually in the smoke. So we can use puff topography to replay a smoking episode in an analytical laboratory. So that gives us a really detailed understanding of the smoke itself, and we can look at

toxicants that might be really hard to measure in the person; we can actually measure separately by using realistic smoking behavior.

These are just some of the main outcomes that I'm going to be talking about today, so these probably look pretty familiar. The number of puffs someone takes, how big that puff is, the total volume inhaled, the length of the inhalations, the time between them, and the forcefulness of that puff, so the flow rate.

Just a little bit more background on puff topography measurement. As I mentioned, this area of research is not specific to waterpipe smoke. We've used it to understand cigarette smoke, other types of tobacco products like cigarillos. And there's different ways we can do that. We can use direct observation, which has some limitations, but then we also have computerized devices which allow us more options in terms of the outcomes we can measure. CReSS is a typical one you might think of when you hear cigarettes. But all these techniques involve specialized devices like video cameras, pneumotachometers, flow meters, for example.

So this is the waterpipe puff topography device that we used in all of the following examples. This was developed by

Alan Shihadeh's group in 2005. And so you can see the picture; it's the same waterpipe I showed you several slides ago, but the main difference being is the integration of this flow sensor apparatus directly into the hose. That's the only difference. And you can see it's not integrated where the mouthpiece -- where the individual inhales from. It's located closer to the body of the waterpipe which also allows for a naturalistic use, so not interfering with -- as little as possible with their smoking behavior. And you can see this very small clear tube that connects the flow sensor device to the topography system where we can gather puff topography data in real time from that device.

So it might surprise you that actually the earliest reports we have of waterpipe puff topography are less than two decades old. Again, these reports were from Dr. Shihadeh's group in Lebanon. They used observation. This work was followed up with the development and testing of that computerized device that I just showed you, again, in a waterpipe café setting, which they were able to get many other measures.

So just to show you what that data actually looks like, to give you a sense of what waterpipe puff topography looks like,

you can see here the number of puffs from those 52 individuals; this is an average. It was about 171 puffs per episode, so many puffs. The puff volume was about 530 liters, which if you can imagine a liter bottle of soda -- not a two liter bottle, but a regular liter bottle, that's about half. It's a large volume of smoke. And that's per puff. Interpuff intervals are around two and a half seconds, 15 seconds interpuff interval.

Now, compared to cigarette smoking, obviously we see some major differences here. With cigarettes we get about 10 puffs on average or 10 to 13 puffs with much smaller puff volumes of 51 mL per puff and much shorter puff durations.

And these are studies using two different types of topography systems. So it gives you a sense of how different these patterns of behavior are. Very, very important differences.

So the next part of my talk is I want to discuss two examples using singletons. What I mean by singletons is this is studies of individual waterpipe smokers in the lab, and I think that's an important design feature to discuss because as we know, waterpipes usually aren't smoked by themselves, and most, as we see in the environment, they're smoked in group settings. So I just wanted to make sure that was clear. We're

going to talk about two examples with low and high frequency waterpipe users and then dual users of waterpipes and cigarettes.

So with our low- versus high-frequency users, this was a lab study. We had a pretty large group of individuals, mostly low users because we actually had a very hard time finding high-frequency users in Richmond. But the high users have to smoke almost on a daily basis to be in the high-frequency group, and they couldn't be dual users of cigarettes. They had to smoke less than five cigarettes per month. They each completed two double-blind sessions 45 minutes or longer. They were allowed to smoke longer if they wished. And they used their preferred waterpipe tobacco or flavor-matched tobacco-free alternative, which is the SoeX product. If you're familiar with the product, it's a sugarcane-based product with no nicotine. And the main outcomes I'm going to show you are from puff topography, plasma nicotine, and carboxyhemoglobin, which is a carbon monoxide measure that we get from the blood.

So moving straight into puff topography, into the data organized by frequency group and by condition, and you can also see some symbols as well. So the symbols indicate, for the asterisk, a significant difference between conditions for that

frequency group. And an asterisk means a significant difference between frequency group for that condition. So it's apparent right away that the low users have no symbols. These individuals smoked tobacco-containing and nicotine-free products about the same. They didn't really alter their puff topography at all.

For our high-frequency users, we saw a different pattern of results. So for the placebo product, they took significantly more puffs relative to the active condition. This resulted in greater puff volume, almost twice as much puff volume, total volume of smoke inhaled over the course of the session. That's 91 liters of smoke.

And remember back to this, a single cigarette is about one liter of smoke. The IPI was also significantly shorter, so they're taking more frequent puffs. And this data was also, for the placebo commission, was significantly higher than what we saw for the low users during that placebo condition. That's what that number sign indicates.

Moving straight into plasma nicotine, so these data are also organized by frequency group, and in this case the filled symbols indicate significant differences relative to baseline. As you see, we have -5 minutes prior to product administration

and 25 minutes post-administration. Again, we're seeing that the active condition is increasing plasma nicotine and we see no change in the placebo. But we don't see any differences between conditions at this time point. There's no number signs here. So although the high users got a little bit more nicotine at this time point, it wasn't significantly different, so about the same between groups.

When we look at carboxyhemoglobin, we see data that looks more consistent with the puff topography data. So for the low users, both conditions resulted in significant carboxyhemoglobin or carbon monoxide exposure. For the high users, the same story, but with the exception of placebo. So that smoke volume appears to be significantly increasing their carboxyhemoglobin levels greater than the active condition, and this was also significantly higher than what was observed for the low users for that placebo condition.

I'm going to move straight into the second study. This was the dual user study, similar environment in a clinical lab, but in this case we were looking for individuals that used both products. They had to smoke at least two waterpipes a month and at least five cigarettes a week. Again, they completed two sessions that were 45 minutes. In this case, we cut them off

at 45 minutes. And this was one single-own brand cigarette versus a typical waterpipe session, which might seem like an unfair comparison, but this was very strategic on our part because we actually really wanted to answer that question: What is one cigarette versus a waterpipe? That was the goal.

Main outcomes again were puff topography, plasma nicotine, and carboxyhemoglobin, but I'm going to be sharing. So puff topography, not surprisingly, we saw a dramatic difference in the puff topography behavior between these two products. Number of puffs were much higher and fairly consistent with what we see in other samples, about 84. The puff volumes were greater than what we saw in some of the earlier Beirut studies; remember, it was 520 mL. In this case, there was almost a liter of smoke per puff. It's pretty incredible. The total volume was slightly lower, and IPIs were also longer compared to cigarette smoking. You can see here, about 15 puffs on average and 71 mL for these individuals.

For plasma nicotine, you've seen this graph just a little -- a while ago. Dr. Maziak also utilized it. This is from the full sample, so this graph looks almost identical to what was presented in the preliminary data which Dr. Maziak presented. But as you see again, we see that nice clear spike

in nicotine levels from the cigarette, which declines over the course of this session, whereas for the waterpipe, which is about a 45-minute session, we see accumulation appearing, and at 5 minutes and at 30 minutes and 45 minutes, we see significant differences between these two products for those nicotine levels. But what I find most fascinating is that the peak levels are about the same. So in both waterpipe and cigarette smoking, they were reaching about the same peak level of nicotine in these two -- for these two products.

For carboxyhemoglobin, we see a much more dramatic difference between these two products. So again, you see the accumulation effects of carboxyhemoglobin over the course of the waterpipe session. And I know it's very hard to see in this graph, there was a change in carboxyhemoglobin for the cigarette smokers, but it was very small and it didn't -- was not a significant difference relative to baseline here.

So, in summary, I think these two studies show a couple of things: One, certainly that we see dramatic differences in how these products are used by individuals, and these puff topography profiles result in very different toxicant profiles for these products. We also see this very interesting pattern of results for our high-frequency users, which I think ties in

nicely to some of the dependence data that Dr. Maziak just presented. I think for these high-frequency users, it's likely they are much more sensitive to nicotine effects and they could be compensating during the placebo session, looking for nicotine, which is resulting in greater puff volumes when they were smoking that placebo product.

The last study that I want to show to you is a very recent publication from our group that goes outside the singleton use design. So in this study we actually recruited groups. They had to be self-identified friends that wanted to come to the lab and smoke together, and they each had to smoke at least four waterpipes a month. So this is our dyad study. And for each individual, they completed a singleton session, so a smoking session by themselves, and one together. And this order was randomized. And they always smoked the same waterpipe tobacco in those sessions. And I'm going to -- the outcomes haven't changed except the carboxyhemoglobin levels are now expired air carbon monoxide, so just a different measure of carbon monoxide.

So starting with our puff topography data -- and I want to also clarify that in the dyad session, these individuals were sharing a single waterpipe; they were not using two waterpipes,

and we weren't collecting puff topography from each. They used a single waterpipe, and we collected the puff topography data from that single pipe, so we can't determine who's who in this study. All we have is the aggregated data from the two individuals.

So not surprisingly in the dyad session, greater puffs were taken, 110 versus 78. The total puffing time was also increased, and the IPI was decreased, so more frequent puffs were taken. Again, what I find fascinating here is some of the data that didn't change. So the flow rate didn't change, the puff duration was almost identical in both sessions. And also, to clarify, for the singleton data, one of the individuals from the dyad session was chosen at random to be included; it's not an average across individuals. This is a single individual. And the same goes for the next data I'm going to show you. And this was just an example to compare to the previous example I just gave you, the waterpipe-cigarette study, just to show sort of the similarity in results for that singleton data. You can see fairly consistently we're seeing these high puff volumes in the singleton data and similar IPI and total volume.

So for plasma nicotine, again, the singleton that was chosen at random to be included in the puff topography data I

just showed you, they were also compared to their data in the dyad session. So this is plasma nicotine data from one individual that's being used in their dyad session and in their singleton session. You can see both had significant increases relative to baseline, and while the dyad appears to be higher, this is the peak level at 45 minutes post-administration or longer. There was no significant difference here between these two conditions but still significant nicotine exposure.

For carbon monoxide, on the other hand, we saw a fairly different pattern. For carbon monoxide during the singleton session, the individuals had much higher carbon monoxide levels relative to the dyad, so lower levels of carbon monoxide when they were smoking with an individual, with a friend.

And so just in summary, we saw a little alteration of some of those puff topography variables during the group session. This is an interesting pattern of reduced CO exposure, which we think ties directly to that smoke volume differential. So in the dyad session, remember, two people were smoking the waterpipe and about 73 liters of smoke are inhaled. If exactly half of that smoke was shared between those two individuals, it would be about 37 liters of smoke, which equates to a lower exposure to carbon monoxide. But I think the biggest takeaway

message from this paper was that group use still results in significant nicotine and CO exposure.

By sharing this product with friends, you are not necessarily reducing your harm potential. And that was a real big criticism of all of our previous work, you know, this is uncharacteristic use in a lab, is this really true life? And so I think this was a great answer to that question.

And I want to close, actually, by showing off one more small story because you may ask, well, you didn't talk about any other toxicants other than plasma nicotine and carbon monoxide, and there's a host of other toxicants we know in waterpipe tobacco smoke. And the problem is, as I mentioned earlier, that these are often difficult to measure in a human during a particular session.

But what's great about puff topography is that we can use this data to again replay smoking episodes in the analytical lab. And Dr. Alan Shihadeh and Dr. Eissenberg did a really nice, I think, elegant way of looking at the relationship between the blood measures and the smoke toxicant levels, so the yield that we measure in the analytical laboratory. And there's a good, there's a fairly strong relationship between those two things.

So this gives us an opportunity to hypothesize, you know, if we measure this in the analytical lab, looking at smoke yield, we can try and hypothesize what this might look like in the person in terms of exposure. And so this is another way that puff topography is a great tool for us.

And so, in conclusion, I think these data really strongly support the availability of these instruments that we have to measure waterpipe-puffing behavior. We see differences in puff topography, and this is definitely related to the use experience, dependence level potentially, as well as the types of toxicant exposure profiles that we can see. And again, puff topography remains this really important tool that we can use in clinical and tobacco regulatory science to understand these behaviors.

And in terms of future directions, I know of at least one team that's working on means to measure puff topography and toxicant exposure in more naturalistic environments, so outside of the clinical laboratory. We also have the availability of other puff topography measurement devices and standardized equipment, but I think also will have utility to understand product characteristics, testing different flavors of waterpipes, for example.

And I really want to echo Dr. Maziak's discussion of this continued investigation to better understand waterpipe dependence. I think its relationship to puff topography is still an unanswered question, and we really need to work on these instruments available for that purpose.

And these are my references, and I thank you so much for your time.

(Applause.)

DR. DRESLER: Okay, our next speaker is Dr. Elena Mishina, who is a pharmacologist within our Office of Science, and she will speaking on Clinical Pharmacology Research on Waterpipe Tobacco.

Elena.

DR. MISHINA: Good morning, ladies and gentlemen. My name is Elena Mishina, as Carolyn said. I work for the addiction branch at the Office of Science. I'm going to talk today on clinical pharmacology and how it is related to waterpipe tobacco.

I will first talk about the major principles of clinical pharmacology and how it is related to tobacco studies. I will then present the systemic exposures to nicotine, carbon monoxide, and other toxic compounds. I will then discuss how

these systemic exposures relate to responses or pharmacodynamic and other biological effects. I will then go into some other issues and considerations and conclude.

This is quite a busy slide, but it is to tell you that clinical pharmacology is defined as a translational science. That means that the basic tools of pharmacology as receptor science and applied pharmacology as pharmacokinetics and pharmacodynamics, and how they're used to solve the real problems into individuals and populations. You see here the word "drug" several times. Since the middle of the 19th century when modern pharmacology has been established, pharmacology has been translated from Greek as a study of drugs. However, the word "pharmakeia" in Greek means not only drugs but has much more meaning. It also means poison or magic or -- and a matter of fact, any active, physiologically active compound.

In general, clinical pharmacology studies how this active compound moves in the body. It studies absorption, distribution, metabolism, and elimination, and how it acts in the body, how it interacts with receptors or the different pharmacologic effects. So this slide shows how the first studies of molecules in medical pharmacology -- then goes to

cells and tissues, then to organ pharmacology, the whole body and populations. And all studies translated from the bench to the bedside.

Here at CTP, we're at the front of systematic review of clinical pharmacology information related to waterpipe. During this review we have created several questions and try to answer to them. I will try to answer these questions during this presentation; however, I'm not going to talk about the systematic review. Instead, I will show just some examples.

So the questions are:

- What are the amounts of nicotine and other pharmacologically relevant constituents received during waterpipe use and through secondhand smoke?
- Is systemic exposure to nicotine relevant to addiction?
- How can we predict nicotine pharmacokinetics in vulnerable populations without clinical studies?
- And the last but not least, very important question, what are the clinically meaningful biomarkers that can be used as surrogate markers and later correlated with clinical outcomes in waterpipe users?

Now, thank you very much for the previous presenters, the waterpipe smoke composition have been thoroughly described. In

general, it's a complex mixture, and so far it has been identified about 400 constituents. Of course, it's nicotine, it's nitrosamines, nitric oxide, acrolein, phenols, and other compounds. It is important to mention the proportion of constituents in waterpipe smoke is different from cigarettes. It has more CO, more benzene, polyaromatic hydrocarbons than in cigarette smoke. All property of the instrument, like tobacco type and bowl size and temperature, liquid additives that affect smoke content.

Now, let's talk about systemic exposures to nicotine. As previous speakers mentioned, and as Dr. Ashley asked, it's difficult to compare waterpipe and cigarette depending on different volume, different puffs, and of course, different exposure. So in many studies it depended on study design, and the findings were conflicting. It depended on length and number of waterpipe sessions, type of tobacco. Also it depended on the experience of waterpipe or cigarette use. And the venue, was it done in laboratory or in the bar or at home?

I'd like to show here the example of the study which has approximated the waterpipe use and cigarette in real life. That was a study of 13 subjects. They were allowed to use, ad libitum, waterpipe and cigarette in crossover over 4 different

days with a washout period. On average, it was about three waterpipes used per day versus 11 cigarettes. This graph shows nicotine plasma concentration versus time of about 24 hours that was average for 4 days. The nicotine boost, which is probably around here, is similar. It is similar because these bars overlap, and this is actually standard error of means, so the bars would be higher. If we compare the area under the curve over 24 hours, it looks that 11 cigarettes produced more exposure to nicotine than in three waterpipe. It's about twice more.

Another study related the pharmacokinetic of nicotine pre- and post- of 30 minutes of active and passive indoor use. Passive means that somebody was not smoking a cigarette but was next to somebody who is smoking. It was found that plasma nicotine in active users increased to 19 ng/mL. That is about the concentration which is achieved with one cigarette. In passive users it was a change with high variability. In general, studies of nicotine exposure show that exposures were highly variable; they were correlated with number of puffs. The gender mattered; males have higher exposure than females. And also the experience with cigarettes all mattered as well; it was higher in dual users. From the exposure status we can

conclude that similarities in nicotine exposure in cigarette and waterpipe users is likely associated with similar changes at nicotinic receptors that would initiate and sustain addiction.

Now, let's talk about toxic constituents, and I'm not going to go only through CO but through others as well. Thank you for walking me through this, Carolyn.

CO is usually measured in expired air. This study compared the use of one cigarette over 5 minutes or 15 minutes of waterpipe. And the measurement of expired CO were done immediately after the end, 10 minutes later, and 1 hour later. You can see here how much difference it is in one cigarette and waterpipe in 5 minutes, and they were higher in 15 minutes. And it was sustained up to 1 hour.

The study which I discussed previously that compares 3 waterpipe sessions and 11 cigarettes, they also measured expired CO. This plot shows expired CO versus 24 hours over these 4-day studies, and the comparison of area under the curve indicates that exposure to three waterpipes, use of three waterpipes exposed people to about three times more of CO than 11 cigarettes.

Now, as a pharmacokineticist by training, I am interested

in pharmacokinetics of CO. It is very complex. After entering into the blood stream, CO binds to hemoglobin, and this is one of the measurements which is also performed in pharmacokinetic studies. The binding affinity to hemoglobin is about 200 times higher than oxygen, thus it causes decreased tissue oxygenation. Even small amounts of CO does it. It also binds to myoglobin and other hemoproteins, thus impairing oxygen-carrying capacity and oxygen transport to mitochondria. It eliminates through dissociation to pulmonary capillaries and expired air. I was looking for the pharmacokinetic model that described carbon monoxide kinetics in waterpipe users; I didn't find any.

Most PK models were based on fixed exposure to CO and do not explain variable exposures with waterpipe use. What we are looking at in this model is estimation of physiologic parameters as clearance in -- distribution that can predict other situations. There was one study in chronic cigarette smokers which can be approximated to waterpipe use. It was a population pharmacokinetic model. They measured plasma carboxyhemoglobin saturation versus time data. They modeled, they described the data with the nonlinear mixed effect model with multiple covariates. And I'm sorry for this gibberish to

this audience, but this is the language of pharmacokineticists.

They estimated that their model actually has some flaws. The estimated terminal half-life was not supported by sampling scheme, and most importantly, as I mentioned previously, the physiologic parameters were not estimated. Why we are interested in modeling of waterpipe data for carboxyhemoglobin is that we can use special topography for waterpipe and subject characteristics as covariates to describe it and to have predictions for other situations, as for poisoning, for example.

So other toxic compounds which usually tobacco users are exposed are nitrosamines, and they're normally measured as metabolites of NNN, NNK, and NNAL in urine. In a study of 55 experienced waterpipe users, immediately after the use, NNAL increased about twice. Another study that was an exploratory study in rural Egypt, they measured in 300 households NNAL in urine of male smokers of cigarette or waterpipe, as shown on this graph. And they have wives, non-smoker, both having secondhand exposure. What is important here is that relative to nonsmokers, waterpipe users have higher NNAL in urine. Our passive waterpipe smokers also have NNAL in urine. The median value between waterpipe users and cigarettes show that the

median exposure was lower in waterpipe users; however, this was a high variability, and these data overlap actually. In several other studies that measured daily use waterpipe, NNAL was sustained. Of course, it's partially because of its long half-life.

Exposure to volatile organic compounds is very important with waterpipe use. In the study of 55 young subjects that went to waterpipe bars and have self-reported of use of waterpipe for 74 minutes -- this study did not have a control arm -- they measured pre- and post-waterpipe use urine. They found significant increase of metabolites of VOCs: acrolein, butadiene, ethylene oxide, benzene. All of them were increased.

One of the important things with waterpipe is a difference in polyunsaturated hydrocarbon exposure. Cigarettes usually -- cigarette users inhale mostly naphthalene and fluorene. Waterpipe has high intakes of phenanthrene and pyrene. These molecules have four benzene rings; they're heavier, and it's known that heavier polyunsaturated hydrocarbons have heavier effects of carcinogenicity. Benzene was also a highly toxic compound that is measured in waterpipe users. It usually measures a metabolite in urine, phenylmercapturic acid.

In the study of -- large study of waterpipe users versus nonsmokers or people who had secondhand, they were studied in the bar, and the exposures were increased three times after the use. In nonsmokers it's also of interest because it was quite saturated environment in the bars. And when it was done at home, the increase was less, and it was no change in secondhand people; however, they all had the baseline chronic exposure. The exposure to polyunsaturated hydrocarbons in benzene is a risk factor for lymphohematopoietic cancers.

Now, since we looked at the systemic exposures that waterpipe users have, let's discuss what acute and long-term responses are the results of these exposures. All active and passive waterpipe users, as has been discussed by previous speakers, have dizziness, fatigue, headache, and other subjective effects. Cardiovascular effects were measured as after 45 minutes use, 30 minutes use, as increase of mean heart rate, systolic/diastolic blood pressure, mean arterial pressure, and respiratory rate. These effects may be related to waterpipe delivered nicotine and/or carbon monoxide.

Acute exposure to waterpipe use has been reported to impact respiratory function or cause inflammation. In the study of 30 minutes waterpipe use, all the cytokines that are

derived from T helper 1 and 2 cells and gamma interferon were lower in exhaled breath condensate. These degrees of cytokines are associated with chronic lung inflammation and may lead to development of chronic pulmonary diseases.

Oxidative stress biomarkers were measured in blood. They were all isoprostane, malondialdehyde, and dehydrothromboxane. The study was done, the measurements were done after, immediately after the use, 6 hours later, and 1 day, and after 1 week and 2 weeks of exposure. All biomarkers of oxidative stress were increased, and the increase was more profound after repeated use. And other oxidative stress biomarkers, such as glutathione peroxidase, reductase, malondialdehyde, and alpha-Tocopherol were measured and compared between waterpipe users and cigarette smokers, and all smokers had higher values than nonsmokers.

Waterpipe use affects the endothelial function. The study measured flow-mediated dilation measured as vasodilatory response of brachial artery to increased shear stress, and it was found that waterpipe users have lower FMD versus cigarette smokers and nonsmokers. This may indicate the early sign of coronary artery endothelial dysfunction. Another study evaluated large airway obstructive ventilatory defect, and it

was found that FEV1 and FVC was reported below the lower limit of normal.

There are other various responses I found in literature related to cigarette smoking. It's increased albumin in urine showing renal injury, acquired secondary erythrocytosis, elevation of carcinoembryonic antigen, chromosomal aberrations in lymphocytes. However, none of the studies have information of plasma concentrations; thus, we cannot model pharmacokinetics and pharmacodynamics, and we cannot establish this relationship, so relationship between exposure and response.

In conclusion, I would like to say that so far pharmacokinetics and pharmacodynamics of nicotine and other toxic compounds have not been comprehensively studied, particularly in vulnerable populations. We have very sparse data on people with renal hepatic impairment, not much differences in gender and age. No information for these vulnerable populations is impairing this data. Potential serious adverse effects of waterpipe use include CO poisoning, oxidative stress that leads to acute and chronic cardiovascular and lung diseases, carcinogenicity, and development and maintenance of addiction.

Although I mentioned different biomarkers which were measured during these studies, however, there was no correlation; none of the biomarkers can be considered so far as surrogate markers and then translated to clinical outcomes, so we think that more data on the relationship between exposures to nicotine and other compounds and pharmacokinetic responses would benefit our understanding of waterpipe input on health.

Thank you.

(Applause.)

DR. DRESLER: Okay, we're going to have some panel questions, so if Drs. Cobb and Maziak could come up to the front, please. And you can -- people will have cards, so you can write on your cards and pass them over, and then we can ask those questions. And let's start out with Dr. Ashley's question that he asked Dr. Bhatnagar. So tell me if -- do you want to ask -- do you want me to try and rephrase it? Okay. So what I wrote down was how many waterpipes and how long equals how many cigarettes? Was that --

(Off microphone response.)

DR. DRESLER: Okay.

DR. MAZIAK: Well, I mean I know this is very intriguing and very -- a question that is on everybody's mind because it

makes sense in terms of trajecting or projecting what we know from the cigarettes into the waterpipe rather than getting into the intricacy and details of each tobacco's method. So it was on our mind from the beginning, but the problem is they're not really very comparable. So some constituents of the smoke are comparable between the two; most of them are not.

And also the context of smoking, the two methods and the factors affecting smoking. In the social, for example, they mentioned the sharing, all that. These are all very nuances that affect exposure and that affects the comparison. So it's really not -- I mean, it's unfair also to cigarettes, to compare one cigarette to one waterpipe given the amount of smoke is usually -- I mean, bigger volume you get with the waterpipe. But on the other hand, these are the unit of consumption that people relate to. And so it's tempting, but I think they're so much different that I would be very cautious in terms of these kind of generalized comparisons, okay? One waterpipe equals 100 cigarettes. Like based on what component? Usually it's true when we compare specific components and then we make those comparisons, but people are tempted to do them in a general manner, and I think it's not scientific in the way I understand it.

DR. DRESLER: So would you say stop doing it?

DR. MAZIAK: Not for you, but everybody else.

(Laughter.)

DR. ASHLEY: Because the reason -- actually, the reason I asked that question was I gave a presentation to SRNT. One of the slides I put up was a slide from Alan Shihadeh and Tom Eissenberg. If you're on that -- Caroline, you may have been on that where they compared cigarettes and waterpipes and the delivery, and I kind of went is this a good comparison or not? So I figured, hey, you guys are going to be here, I'm going to ask you the question about your study.

DR. COBB: I know that that table that you're thinking of where we compared machine-generated smoke, and it's 1.7 cigarettes of nicotine, 8.4 times carbon monoxide, and 36 times the amount of tar. I mean again, it depends on the constituent. They are very different means of administration or time, and it really gets blown out of proportion very easily in the popular media also. You hear there's 100 cigarettes versus 1 hookah when really they're just talking about smoke volume, which doesn't give you an estimate of the harm.

DR. DRESLER: So a question for Dr. Cobb. Plasma CO. So in your initial studies that you presented, you were looking at

plasma CO, I presume plasma venous CO. And why did you pick that instead of exhales, and how do they compare?

DR. COBB: Great question. So yes, carboxyhemoglobin is just a blood measure of carbon monoxide in the blood; expired air CO is extrapolated from carboxyhemoglobin. They have, I think it's like 0.98-0.99 correlation. The reason we looked at blood measures of carbon monoxide is because you can't take expired air carbon monoxide measurements while someone's smoking because you have to wait a certain number of minutes after they stop smoking to get an accurate reading. So with carboxyhemoglobin, all we had to do is take -- was walk in, take a blood sample, and walk out of the session room, and the individual could continue smoking as easily as possible. So we chose it so we could get actual readings of carbon monoxide during smoking versus afterwards, to see that pharmacokinetic distribution over the course of that session.

DR. DRESLER: Okay. So a question about steady state nicotine in waterpipe smoking. So the studies that we've seen have all been more acute studies. I think some that Dr. Mishina had went closer to 24 hours but still didn't look like a steady state sort of study. So when we do drugs, it's they're single dose and then steady state, and people are

smoking all day, and so you see differences of nicotine as people smoking cigarettes. What does a steady state waterpipe smoker look like? So if you were to take their nicotine levels on a daily basis, what does a steady state waterpipe smoker nicotine level look like?

DR. MAZIAK: I'm not aware of any work done in that.

DR. COBB: And I would ask you what type of waterpipe smoker you would want to look at. I think it would greatly depend on their patterns of use. We don't even know, you know, a daily waterpipe smoker, what their steady states would be. A weekly or less frequent user, again, I don't know of any data that speaks to that.

DR. MAZIAK: We did one study when we measured urinary nitrosamines in waterpipe smokers, but not related to their smoking. So we brought people in the morning, exclusively waterpipe, exclusively cigarette smokers, and exclusively nonsmokers, and we measured the difference, and we showed that that's the only, I think, study that we did in terms of these constituents. That was not a lab study of pre, post or crossover kind of study.

And then it shows a higher level than nonsmokers in terms of nitrosamines. But nothing in terms of nicotine, I'm not

sure. And that's a very actually good question for even any dependence research because at what level they are actually function. The major issue here is to get exclusive waterpipe smokers, and that's not easy. So whenever you have mixed methods of smoking, especially in the youth group that is most at risk, it's very hard to tease out those, and you need to have a population where you can have abundance of exclusive waterpipe smokers for that kind of study. Probably that's what's hindering that kind of field somehow. I mean, I'm expecting --

DR. DRESLER: Well, it just seems so complex between daily, weekly, monthly smokers, and they're all variable versus the average U.S. smokers. Ten to fourteen cigarettes per day, it's perhaps a little bit easier to get that. So a question that went along with that, so this is pulmonary delivery, right? And so most of the PK studies are done with venous blood, but when I was looking at your PK curve, that was more consistent with some different sites of absorption of the nicotine versus arterial.

So if you're doing that pulmonary delivery, your curve should be approximately the same unless your nicotine is different or this question from yesterday with the pH. And so

I'm just wondering, has anybody done any sort of arterial look at how does this pulmonary delivery of waterpipe smoke, what does that look like and how comparable is that to the pulmonary inhalation of a cigarette?

DR. COBB: Yeah, I'm sorry. I don't have a better answer for you. I don't know of any arterial studies done for waterpipe smokers. We've had that question before, I want to say, in one of the manuscript reviews. You know, could you answer that question, could you address that? And unfortunately, I don't know of any arterial --

DR. DRESLER: Has there been any discussion about that PK curve? Because that PK curve for pulmonary delivery is starting to look like a mucosal absorption, you know, or a very high-dose nicotine patch. It's still too fast for that, but maybe mucosal? Nobody's tried to tease out site absorption, okay.

DR. MAZIAK: I mean, I made a comment yesterday, and based on how people smoked the waterpipe, we can have some expectation, because, for example, if you try like with the puffing of cigars or cigarettes, if you try to mouth waterpipe smoke, you cannot. If you suck and do not inhale, the waterpipe does not even go.

So there will have to be deep pulmonary -- this is a dominant, I mean, need of absorption here, because unless you have a deep breath, and that's why you see those big volumes of puff compared to the cigarette, there's no mouth here smoking. Everything goes as deep as possible to actually overcome that volume of the instrument itself and the tubing, to get the air going.

DR. DRESLER: It makes total sense to me. Then why aren't you looking at the higher PK profile? So anyway, I was just wondering.

DR. MAZIAK: Good question.

DR. DRESLER: Okay. Are there no established standards for machine smoking? How did you choose the puff volume duration interval? Also, is the puff profile a bell shape, like cigarette, or more like a square profile of an e-cigarette?

DR. COBB: Yes, I think Dr. Shihadeh's presentation yesterday did talk about the shape showed some actual puff topography data, that physical data, and you could see -- to me, it looks somewhat more like a box, but you see variations due to the bubbling of the water.

But the first question about the machine, the puffing

parameters, so those parameters came from real smokers. Those were averaged. The first data I presented from Beirut, those were averaged across those 52 smokers, and the puff topography profiles that we got from the clinical lab, again, were from real individuals. We didn't generate those data other than just using individuals themselves.

DR. DRESLER: Does the puff profile vary between genders or age?

DR. COBB: You know, I was sitting in the audience just considering that question because now we have so many -- these three studies. We could actually look at -- we have the power to look at gender, I think, definitely, to see, look for differences. But you could see some of the consistencies, at least in our studies, between singletons who used the cigarettes and waterpipes alone, in terms of the low frequency users, were fairly, I would say fairly similar. But I think that's a great question.

DR. DRESLER: How about between the U.S. and Lebanon?

DR. COBB: Definitely haven't been directly compared, at least in a published manuscript, but you can -- as you saw, the Beirut data from 2004 show very different -- or not very -- slightly different profile, smaller overall puff volumes. And

that could be reflective of the device, the waterpipe tobacco, so many things.

DR. MAZIAK: I'm expecting the gender, as much as population kind of differences, will be influenced by the size of the lung capacity. So I would much expect that women probably would have lower puff volumes and so forth, and that's actually, I think, one explanation why Lebanon data has lower levels than the U.S. I think it's more of the size of -- average size of the population rather than any pharmacodynamics. But again, this is here only.

DR. DRESLER: Okay.

DR. MAZIAK: Yeah.

DR. DRESLER: In the dyad study, were there two hoses or one share of a hose? Are the participants allowed to smoke at their own frequency in the dyad study?

DR. COBB: Great question. And yes, there was one hose that they shared, so that single hose was hooked up to the topography instrument. So again, the topography data were aggregated; they were free to smoke as they wished during that 45 minutes or longer. They could smoke longer also, if they wished. But that design characteristic made it difficult to parse out individuals, so maybe sometime in the future we might

use two hoses because that is commonly used sometimes in hookah cafés.

DR. DRESLER: Okay. The issue is not about differences in composition or exposure, but in terms of risk. What is the relative risk of smoking cigarettes versus hookah?

DR. MAZIAK: This is like asking a computer what's up.

(Laughter.)

DR. MAZIAK: I really don't know. This is a very complex question because, again, there is no one dimension that you can compare the two, and even the cigarette literature, you have people who smoke cigars or cigarettes. Do you compare them? There will be increased risk for mouth, for example, cancers in one instrument, lung cancer in the second instrument because of the differences in the pH and all the other nuances.

So in terms of health risk between the one waterpipe, the one cigarette, you can measure it in the acute effects, like on the lung function and those kind of things, but long-term effects is just impossible to traject, okay, what would that one cigarette compared to one waterpipe will do to the body. That's like a very complex question.

(Off microphone comment.)

DR. DRESLER: This afternoon.

DR. MAZIAK: Yeah, good.

DR. DRESLER: Has anyone looked at the impact of flavors on topography of waterpipe use?

DR. MAZIAK: Well, this is the grant that we submitted to FDA, so -- and it's a very important question to fund.

(Laughter.)

DR. DRESLER: You tried this yesterday, you know?

DR. MAZIAK: Yeah, I cannot argue about -- this is a tough question, and we hope we can answer that.

DR. DRESLER: Okay, nice response there.

DR. MAZIAK: I keep repeating. I keep repeating.

DR. DRESLER: What's your hypothesis? I know you tried yesterday too.

DR. MAZIAK: Yeah. We're expecting -- I'm expecting that we'll have a big difference in actually the topography, the exposure, and the satisfaction that you get from the waterpipe if you remove the flavor, like unflavored sweetened variant compared to a flavored variant, because we know, from variety of evidence, that actually flavor is a major component that attracts people to the waterpipe, and it's actually a shaping factor in the waterpipe experience. Remove that, I'm expecting dependence measure of satisfaction, even with withdrawal,

amelioration, all that will be different. Even puff topography, the deep, the depth, and frequency, and all that will be affected by comparing these two: non-flavored with the flavored. And it's also a prime probably target for regulation because it's apparent it's targeting youth. I mean, we know that. Everybody knows that. It's just we have to act on it based on evidence.

DR. DRESLER: Yeah, that overlaps with one of the other questions that I have, but it also makes me think what -- in the public session that we heard about the flavors and how it's -- the flavors are dominated by some of the larger companies. And we showed yesterday, if I'm not mistaken, Two Apple is one -- is that a brand? Or is that -- because that was also in one of the studies, the apple flavor. I heard that a couple times yesterday too. Is Two Apple an apple flavor? Or is that the brand?

DR. MAZIAK: Well, it is a brand and a flavor because it originated and was very popular from one of the manufacturers of the -- because what is Two Apples? I mean, you can have an apple flavor and you need one apple. Why two apples? But it was popular at one point, so they carried it away, and probably other manufacturers started to emulate that because it's an

apple flavor and actually it smells like green apple.

(Off microphone comment.)

DR. DRESLER: Red and green, correct.

(Off microphone comment.)

DR. DRESLER: Yeah. There are different types of apples.

DR. MAZIAK: Well --

(Off microphone comment.)

DR. DRESLER: More flavor, that's what I'm hearing. Okay, all right.

Do you see individuals switching from flavored to unflavored waterpipe tobacco as they become more dependent?

DR. MAZIAK: We haven't noticed that. In our longitudinal studies, people who smoke it with flavored, they continue with flavored. And the problem is, in a lot of settings it's difficult to access unflavored variants nowadays because the market is dominated by flavored waterpipe tobacco.

So I'm not sure, even if you wanted -- the old-fashioned Middle Eastern way of using it was unflavored, but even in that market, I think people are going more -- even those who are used to the unflavored and raw tobacco, because you cannot find it anymore. The flavored products have just washed out everything else and dominated the market.

DR. COBB: And just to add to that, the high frequency user study -- so the individuals that were smoking daily in Richmond did not smoke unflavored? They all still smoked flavored varieties?

(Off microphone comment.)

DR. COBB: Good question. I think that group did skew slightly older, but most of our -- a lot of our individuals -- I couldn't tell you exactly.

DR. DRESLER: It makes me think of another question yesterday when the older was greater than 40, so when you're saying older population, is it closer to my age with gray hair, or is it around that 40 age?

DR. COBB: I want to say younger than 40 was the average.

DR. DRESLER: Younger than 40 is the older?

DR. COBB: Right.

DR. DRESLER: It would be closer to 40?

DR. COBB: Yeah.

DR. DRESLER: Just checking.

DR. COBB: Older than college age; that's what I should've said. Older than college age.

DR. DRESLER: Okay, thank you.

DR. COBB: Because that's our typical -- those were --

that's our typical population that we get.

DR. MAZIAK: I hear you.

DR. DRESLER: I know. Okay. Okay, Dr. Maziak, in your discussion, you mentioned the "quit or die" abstinence view versus harm reduction. Can you discuss your views on the communication of relative risk to adult users?

DR. MAZIAK: So I'm not sure what --

DR. DRESLER: So is it, you know, quit or die and you need to quit view versus it being a harm reduction view?

DR. MAZIAK: Yeah, okay.

DR. DRESLER: So how do you -- so for adult users who --

DR. MAZIAK: Yeah.

DR. DRESLER: -- have chosen to do a --

DR. MAZIAK: Yeah. Okay. I understand now. So the main tenets of harm reduction is that -- and they always make a similarity with the injections, clean syringe approach, by giving those to drug addicts, and you will reduce their harm without requiring abstinence. And I think the comparison is very unfair because the syringe is not part of the dependence in drug addicts. There's no industry behind the syringe. And drug addiction and drug injection is a covered, not exhibited behavior. So it does not promote that behavior, where with the

harm reduction, whether it's with e-cigarettes or a waterpipe, you have a public behavior, you have an industry behind promoting that behavior, and you have actually no evidence of reduced harm. So what I'm saying, in short -- I don't want to go -- I feel kind of emotional about this issue.

So basically the harm reduction model is why we are only requiring abstinence from hardcore smokers, give them some options other than total quitting. And that assumes that this can happen without uptake by young people because that would be a bad thing to happen. And their approach, usually they said okay, you can tailor regulation and then policy somehow surgically, only promote that product to these adult hardcore smokers and prevent everybody else from uptake. First, it's a science fiction-based model because this has not happened. We live in the same society, and it's promoted to some slice and -- if my dad would smoke a cigarette, I'll see it as a youngster, and I'll probably imitate it. It does not happen this way. And the second, the industry does not abide by this model. They want to sell to young people because that's how they can make the profit.

So I'm not sure, by offering waterpipe or e-cigarettes, we're even helping those and giving them a better option who

are hardcore smokers. In essence, they're not actually quitting, and in essence, they're kind of increasing addiction and also tobacco use in society.

So sorry for the long answer.

DR. DRESLER: Okay. It is one of those controversial questions.

DR. MAZIAK: Very.

DR. DRESLER: Dr. Caroline Cobb, would you please reiterate the takeaway from the plasma nicotine slide where you compared the peak in nicotine level of cigarettes with that of waterpipes? Did you intend to convey that the cumulative plasma levels are equal? So the plasma nicotine slide where you compared the peak in nicotine level of cigarettes with that of waterpipes.

DR. COBB: Sure. What I was trying to convey was the peak level achieved, not the area under the curve. The cumulative amount of nicotine delivered to the user is obviously very different for a single cigarette and a 45-minute session. My point was at 45 minutes, the peak level that you got within 5 minutes of smoking a cigarette you got at the 45-minute time point for smoking a waterpipe.

So you still reached very high levels of nicotine exposure

over the course of that session. It wasn't just a slow and low delivery over 45 minutes, like someone might make a comparison to a nicotine patch. You did reach a high, a similar level as what we saw with a single cigarette. So I apologize if that wasn't clear.

DR. DRESLER: Dr. Maziak, it appears that your presentation was based on research among Middle Eastern waterpipe smokers. Presentations have also been given that the type of waterpipe tobacco and usage pattern in the U.S., especially among younger consumers, is different. What research in your presentation was based on U.S. consumers and their dependence based on U.S. consumption patterns?

DR. MAZIAK: We actually did both, and the response even for the gentleman in the beginning, nowadays actually everybody in the Middle East -- and I'm talking now in the vast majority of youngsters -- smoke the waterpipe exactly the same way as they smoke it in the U.S. And that's based on research done -- we did ourselves in the Middle East and in the U.S.

So I don't think that this is the assumption that there are different patterns now among youth and different -- even the method itself, is different in different -- at least, as far as the Middle East and the U.S., it is accurate or based on

evidence. I lived in the Middle East until I was 47. I did research there, and I did research here, and they use it exactly the same way.

I mean, the college students in the U.S. use the waterpipe nowadays as the youth that we studied in the Middle East. The same type of tobacco, same type of foil, and the heated, not the burned variant. The burned variant, as I said, is now only seen in older people in the Middle East, but we're talking here about the epidemic among young people, not people who have been smoking hookah for decades and older males in the Middle East.

DR. DRESLER: Okay. And any other questions coming forward, because I'm getting down to -- I have one for Dr. Mishina. You have on your slide the number 400 for waterpipes, and so I'm thinking this is chemicals, 400 chemicals, for waterpipe smoke. Cigarette smoke contains approximately 8,000 chemicals. So where did the 400 come from?

DR. MISHINA: There have been 400 constituents identified in waterpipe smoke. This is what I know from the literature. There are much more in tobacco, but only about 400 were identified there.

DR. DRESLER: Well, let me push that a bit. Is the number 400 measured to date?

(Off microphone response.)

DR. DRESLER: So that's how many have been measured to date. So perhaps an approximation is we're in an early phase for this research maybe? Yeah, probably. Okay.

All right. Do we have any other questions from anyone? Any other questions you guys want to ask each other?

(Laughter.)

DR. DRESLER: No?

DR. MAZIAK: I have to apologize to Caroline for misquoting her study.

(Laughter.)

DR. DRESLER: Okay, so we have 15 minutes for a break and that we're a tad bit ahead of schedule. So that means we are not going to have a lunch break today, so therefore we might finish around lunchtime, which will be good for everybody's stomach. So let's come back in 15 minutes, let's say 20 of.

(Off the record at 10:25 a.m.)

(On the record at 10:40 a.m.)

DR. DRESLER: Shall we gather back together to start? That was sort of like a rhetorical question. I figured I'd start with my inside voice and then I'd go to my outside voice. It is cool to see the discussion though, so --

Okay. We're going to start with our last session, which is on Acute and Long Term Health Effects. And our first speaker is going to be participating remotely, Dr. Ward, who is often from the University of Memphis School for Public Health but is currently calling us from Dublin. And he's going to be speaking on Cardiovascular and Pulmonary Effects of Waterpipe Tobacco Use.

Dr. Ward, can you hear me? Dr. Ward, are you on mute?

DR. WARD: Hi.

DR. DRESLER: There you go.

DR. WARD: I can hear you now.

DR. DRESLER: Welcome. So you can go ahead, and we're ready for you, and let us know when to advance the slides and we can go. Thank you.

DR. WARD: Okay, great. Can I have the next slide, please?

Okay. And I don't have any conflicts to disclose. And the next slide.

Okay. So I'm going to talk about both cardiovascular and pulmonary effects of waterpipe smoking. I'll spend a little time on the acute effects, and then I'll spend most of the time on the knowledge base we have so far about more long-term

effects.

Next slide, please.

So we've already heard quite a bit about toxic exposure, and I won't reiterate that now. But it's worth just briefly reiterating that many of the toxicants that we know are delivered from waterpipe are relevant to both cardiovascular disease and pulmonary disease, and that includes carbon monoxide exposure, which has relevance for both of those disease classes, and nicotine. We're usually concerned with nicotine for its dependence-producing potential, but it also has acute cardiovascular effects. And volatile aldehydes and other organic compounds have profound effects on lung functioning.

Next slide.

So there is now a wealth of data from acute studies indicating that waterpipe produces several effects on the cardiovascular system. So we know that a waterpipe produces acute elevation in both heart rate and blood pressure. After a typical waterpipe session, we'll see heart rate increases of 4 to 16 beats per minute and increases in systolic blood pressure increased by about 6 to 16 beats per minute, and the diastolic blood pressure, 2 to 4. Not beats per minute, as you

know, but we do see consistent increases in those indicators.

We also see CO intoxication and syncope -- I'll discuss those in a minute -- in the context of pulmonary effects, but CO intoxication is also relevant for cardiovascular disease outcomes. It causes carboxyhemoglobin levels to change, and this can have dire consequences, especially for users who have underlying cardiac disease. Also, because of the high levels of carbon monoxide produced from waterpipe smoking, there have been reductions seen in exercise capacity caused by impairment of vasodilation in exercising muscles. In addition, waterpipe tobacco has been shown to impair baroreflex control of blood pressure, one of the homeostatic mechanisms that help maintain blood pressure at or near constant levels.

Some work by Caroline Cobb has shown heart rate variability after acute waterpipe use, the measure of cardiac autonomic dysfunction, and that predicts coronary artery disease as well as mortality. And we also know that waterpipe use is linked to platelet aggregation, which is involved in thrombus formation. And also, as we heard in an earlier talk today, it's linked to endothelial dysfunction. So these are some of the major acute effects.

May I have the next slide?

Okay. So I'll turn my attention now to evidence for some long-term cardiovascular effects. There's evidence that waterpipe smoking is linked to at least two important risk factors for cardiovascular disease, namely, metabolic syndrome and obesity. And these are data from a cross-sectional study of about 2,000 adults in Pakistan that found an association between waterpipe use and metabolic syndrome. This particular analysis excluded current cigarette smokers. We're only looking at exposure due to waterpipe, and 16% of the sample currently smoked waterpipe. And current waterpipe users had about three and a half times greater odds of metabolic syndrome than never smokers, and they were also more likely to have several other components of metabolic syndrome.

As you can see here, the odds of having low HDLs were 1.75. There's also increased odds of having elevated triglycerides, elevated blood glucose levels, and there's a trend for elevated central obesity, but that is not significant.

So this is an epidemiological study, and they couldn't examine pathways, but there are several potential mechanisms by which waterpipe use could affect metabolic syndrome, including how nicotine impairs lipids and stimulates abdominal obesity to

HPA access activity. And the study had some limitations as, I'll say, for all of the studies that I'll show you on long-term effects. But they excluded current cigarette smokers, but we don't know anything about past cigarette smoking use, which is it could be a problem in this study.

May I have the next slide?

So in addition to metabolic syndrome, waterpipe use also may be associated with higher weight and risk of obesity. These are data from a study that we did in Syria, and the data are from a representative household survey of adults. And to get to individuals who had never used waterpipe, daily smokers had nearly three times the odds of being obese, and that was defined as a body mass index of 30 or greater. And these associations were independent of demographic characteristics, as well in cigarette smoking and number of chronic conditions that participants had.

So this slide shows obesity, but daily waterpipe smokers also had greater body mass index when we examined it as a continuous variable, and it translated roughly into about 12 extra pounds of weight for daily smokers compared to never smokers. So these associations of waterpipe use with both metabolic syndrome and obesity demonstrate some potential

pathways by which waterpipe use could influence cardiovascular disease outcomes.

May I have the next slide?

Okay. So there's growing evidence of the effects of waterpipe on long-term outcomes, but it's still a very small literature. When the first meta-analysis came out back in 2010 that examined health effects of waterpipe, there are actually no published studies on coronary heart disease that could be published. So that fortunately has changed, though again it's still a pretty limited literature. So this shows all the literature that I'm aware of, to date. So there's been a few community-based cross-sectional and case-control studies. There's also been a few hospital-based cross-sectional studies. And there's just one prospective study in the literature that came from Bangladesh, but unfortunately, they looked at tobacco use in general, and virtually all of the waterpipe smokers also smoked other tobacco products. So they weren't able to isolate the effects of waterpipe. So we have to rely on cross-sectional evidence, and I'll show you a little bit about that.

May I have the next slide?

Okay. So these are data from a study out of Iran, and they looked at cumulative exposure of waterpipe tobacco smoking

and found that it was related to self-reported heart disease. So this is a study of more than 50,000 adults. They were 40 years of age and greater. And outcome again was self-reported history of heart disease that included both ischemic heart disease and heart failure. And they measured exposure by waterpipe-years. And this is similar to pack-years for cigarette smoking in that it captures intensity and duration of use, and it's calculated by multiplying the number of times waterpipe is used per day by the number of years that the person has smoked.

So in this slide you can see trends in the odds of having self-reported heart disease according to waterpipe-years. And waterpipe-years goes from never, as the reference, to less than 50 waterpipe-years, 50 to 100, 100 to 180, and greater than 180. You can see the adjusted odds ratio increasing. It's only significant in this analysis.

In the top group, the p-value for the trend is significant, and the adjusted odds at the high level of waterpipe-years is 3.75. Now, the caveat here is that 180 waterpipe-years is an extraordinarily high level of exposure, and that translates into smoking four times a day for 45 years, and there were only 25 people in the group. So you have to be

very cautious in interpreting that. They also broke up waterpipe exposure in other ways, too, which are not shown on the slide. So there were significant results when they compared ever waterpipe users to never, and when they also stratified exposure at 50 waterpipe-years, so comparing people who had less than 50 waterpipe-years compared to people who had higher than 50 waterpipe-years.

May I have the next slide?

So a limitation of that study is that they relied on self-reported heart disease. Another study from Lebanon used angiographically defined coronary disease as the outcome. And this study is from Sibai and colleagues, and they enrolled 1,210 patients from four hospitals in Lebanon, and the patients had been admitted consecutively for angiography. Sixteen percent of the patients currently smoked waterpipe, and of those, nearly half or 42% had ever smoked cigarettes.

The patients were interviewed before receiving their coronary artery disease diagnosis to reduce reporting bias. And they conducted two sets of analyses using both dichotomous and continuous CAD outcomes. So in the dichotomous analysis, they assessed the odds of having stenosis of 50% of one coronary artery. Those results were not significant. But when

they defined CAD as having stenosis, 70% in at least one artery, there were significant associations with waterpipe use. And here in this table, they used the waterpipe-years measure of exposure, so compared to people with no waterpipe exposure. You can see the results for people with 1 to 20 waterpipe-years, 21 to 40, and 41 or greater. And again, there's a significant trend here, as we saw in the last study, and you see a significant difference at the high end of exposure.

So for people who have at least 41 waterpipe-years, the adjusted odds ratio is 2.94. And this adjusts for demographics as well as pack-years or cigarette use, alcohol use, physical activity, and several disease outcomes.

Next slide, please.

As I mentioned, this study also looked at CAD as a continuous measure. They used the Duke Coronary Artery Disease progression index. On the left you can see when they stratified waterpipe use simply according to whether the patient was a never user, a past user, or a current user. There's no relationship to severity of atherosclerosis. But on the right you can see when they stratified according to waterpipe-years. You do see a trend for worse stenosis according to waterpipe exposure, and there's a significant

difference between the never users and people who had 41 or more waterpipe-years.

Next slide.

There's one study that examined CHD mortality, and that's a cross-sectional study that comes from Qatar. They enrolled more than 7,900 patients. They had all been hospitalized for acute coronary syndrome, and in the sample, there were 306 patients, about 4% of the sample, that smoked only waterpipe at the time of admission. So no cigarettes, no other tobacco products.

And the in-hospital mortality was higher in the waterpipe smokers than in the cigarette smokers, and the rates were 8.5% versus 3.4%. And the age- and gender-adjusted odds ratio was 1.8. And this study also had similar limitations as some of the other studies that we've already seen. And here particularly, there's no adjustment for other important confounders, including history of tobacco exposure. They're looking simply at current status.

Next slide.

We know very little about how waterpipe is associated with stroke. There are two studies on that topic. One study from Lebanon is cross-sectional and examined stroke symptoms among

people who have never had a stroke, and they found that current waterpipe smokers compared to never smokers were more likely to report stroke symptoms, with an adjusted odds ratio of 3.88. And there's also been one study that examined stroke mortality. This comes from Bangladesh. And the odds of smoking waterpipe were not higher among people with fatal stroke compared to unintentional injury deaths in this case-control study. So again very little data and mixed in that case.

Next slide, please.

So I'll turn my attention now to pulmonary effects of waterpipe use. We know that waterpipe use acutely raises respiratory rate by about 2 to 3.5 breaths per minute after a single waterpipe session. And there have been several experimental lab studies that show decreases in pulmonary function after smoking waterpipe. So, for example, the flow of the air coming from the lung during the middle portion of a forced expiration, as well as peak expiratory flow rate decrease after waterpipe smoking, both of which suggests that there may be some small airway dysfunction.

Next slide.

And there's also evidence of chronic effects of waterpipe smoking on pulmonary function. There was a meta-analysis

published back in 2011 that synthesized the results of six comparisons that came from five different studies of pulmonary function testing in waterpipe smokers versus nonsmokers. So they found that the FEV1, the forced expiratory volume in 1 second, was significantly lower in waterpipe smokers than nonsmokers, and that was a standardized mean difference of 0.43 units, which is equivalent to about a 4% reduction, which would be clinically meaningful.

Other indices in this meta-analysis, including forced vital capacity and the ratio of FEV1 to FVC, were not significant, but they trended in the expected direction. There's actually been several more studies now added to the literature on this topic since that meta-analysis.

And with more studies and larger sample sizes, all of those outcomes have shown significant differences on a long-term basis between waterpipe smokers and nonsmokers. There's also one study in the literature on young adults, which shows that pulmonary changes may occur even with relatively short histories of waterpipe use. On the other hand, though, there have been now four studies that have examined dose effects, and they've had mixed results to finding dose effects and to not finding dose effects.

Next slide.

We've already been hearing about the large amounts of carbon monoxide that waterpipe users take in, and there's quite a bit of evidence in the literature now on carbon monoxide toxicity. There have been several lab and field studies conducted demonstrating that there are large increases in expired CO and carboxyhemoglobin levels of waterpipe smokers relative both to nonsmokers and cigarette smokers.

One of these studies was conducted by Mary Martinasek and myself, and we measured expired CO levels in waterpipe users immediately before they went into a hookah bar and immediately coming out. And we found eightfold increases in expired CO levels, going from an average 6.5 ppm before going in, to 58.2 ppm coming out of waterpipe bars, so quite a large increase.

And now there are also several case reports in the literature of acute CO poisoning after smoking waterpipe, with young adults often showing up in emergency rooms complaining of dizziness and headache and syncope and nausea. Often that's getting called hookah sickness in the popular press.

There are also a couple case reports in the literature now of waterpipe use being associated with secondary polycythemia

or increased red blood cell volume due to chronic hypoxia. And Caroline Cobb's work has shown that the increase in CO is similar in tobacco-containing waterpipe use and the tobacco-free herbal products, indicating that the boost is due largely to the charcoal.

Next slide.

So this is a summary slide showing the studies that have been done on long-term pulmonary outcomes. All of these so far have been cross-sectional. The studies have focused on COPD as well as chronic bronchitis and asthma. And there are some little prospective studies in the literature.

Next slide.

There's a recent updated meta-analysis on health effects that was published in *Tobacco Control* last year by El-Zaatari and colleagues, and they reviewed the literature on the various pulmonary effects. So they identified six studies on COPD outcomes, and four of those six showed positive associations with waterpipe smoking. So just using one as an example, Salameh and colleagues in Lebanon conducted a hospital-based case-control study. They had 211 consecutive newly diagnosed outpatient cases of COPD. The control group was 527 outpatient controls who didn't have respiratory disease, and all patients

were at least 40 years of age. So the adjusted odds of having at least 20 waterpipe-years of exposure was 11.6 in the cases versus the controls.

And that particular analysis included only patients who had never smoked cigarettes and was adjusted for other respiratory disease risk factors, including demographics, home heating source, and having ever lived close to a busy road. And they found similar associations also when waterpipe exposure was categorized in various ways, such as current use and various levels of waterpipe-years as the exposure variable.

Next slide.

So the same meta-analysis identified five cross-sectional and case-control studies that examined chronic bronchitis. All five of those studies showed a positive relationship. And most of the studies used a standard definition of chronic bronchitis, which is chronic cough with sputum production for 3 consecutive months to 2 years. And the odds ratios in these studies ranged from 1.42 to 5.6, and they used a variety of exposure outcomes.

Next slide.

And just as one example, this is another study from Dr. Salameh's group at AUB, and it was a hospital-based

case-control study, and they enrolled 274 newly diagnosed cases of chronic bronchitis. Those were compared to 559 outpatient controls who didn't have chronic bronchitis. And the adjusted odds of having 20 or more waterpipe-years of exposure was 5.65 in cases versus controls.

Next slide.

So those studies represent the bulk of the evidence currently for chronic pulmonary outcomes. There have also been two studies, though, that have examined asthma, and one found borderline significant findings. The other one, unfortunately, wasn't able to control for other forms of tobacco use, so you can't interpret that one. There's also one study in the literature on rhinitis in children, comparing those who were exposed to waterpipe in the home versus those who aren't, and they found an odds ratio of 2.3 for greater odds in children who are exposed.

Next slide.

So overall, waterpipe smoking is associated with cardiovascular and chronic obstructive lung disease outcomes. This is based both on acute biomarker studies as well as epidemiological studies of long-term outcomes. The associations are similar to what we see for cigarette smoking,

reflecting common toxicants between these two methods. But literature is still very scant.

As I've mentioned, the studies have been all cross-sectional, and there have been problems with them, some in terms of sample size, some in terms of not adequately handling confounding, especially for use of other kinds of tobacco use.

The types of tobacco used aren't the same. Some have used raw tobacco, others have used more common maassel, and also there's not been much of an attempt to standardize exposure assessment. But the bulk of the evidence, though, does suggest some important relationships for waterpipe smoking with both cardiovascular and with pulmonary outcomes.

Next slide.

And I will end there. Thank you.

DR. DRESLER: Thank you, Dr. Ward. And we'll come back to you for the panel discussion.

Our next presenter is Dr. Christopher Loffredo from Georgetown University, and he will be speaking on Waterpipe Smoking and Cancer Risk.

DR. LOFFREDO: So Washington is south of the Mason-Dixon line, so I suppose we can group Washington, D.C., with these other great southern cities where so much of this good work is

being done. I don't know why that it is. Maybe, you know, southern hospitality and we care about our people. Who knows?

But nevertheless, thank you to the FDA and the organizers for inviting me. I'm a cancer epidemiologist. I'm at the Lombardi Comprehensive Cancer Center at Georgetown. And so I'm going to be giving you pretty much a cancer-centric perspective of how we would evaluate the evidence that's accumulated on any associations between waterpipe smoking and cancer. It's worth contrasting the areas of the world where the vast majority of the evidence comes from versus the societies now, like the U.S., where we're just starting to see this behavior.

I'll give you a little bit of an overview of the scanty literature that there is. I'll go in depth on the study that we did in Egypt on bladder cancer, which remains the largest case-control study ever conducted on bladder cancer and what that tells us about waterpipe smoking and this tobacco-associated malignancy, and then some conclusions.

So it's worth contrasting a little bit. The situation we're seeing here in the U.S. and in the industrialized or developed countries is an initial appeal of the waterpipe tobacco thing to young adults but maybe spreading into other groups and widening in popularity; as we've heard throughout

this conference, non-daily use; users may be not completely addicted yet but moving in that direction; dual use with cigarettes as being kind of a common thing; and the lack of sort of waterpipe-only heavy addicted waterpipe smokers limiting our ability to look at relationships to chronic disease. And unfortunately, a rather short history of 15-20 years or so.

And, in contrast, in traditional and transitional societies -- and here I'm using the classic epidemiological definition of societies that are moving away from infectious disease causes of mortality and morbidity and moving into chronic disease caused by lifestyle, food, sedentary behavior, all the classic sort of Western "pattern." So in those places, the waterpipe uses were historically older; they were male; they were often in rural areas. But now changing societal norms, as others have said, are attracting women, youth, urban dwellers. There is quite a lot of non-daily use -- I'm sorry. Daily use is common, heavily addicted users by any scale, both solo waterpipe users and dual users, and a history of hundreds of years of this. And so if we're going to look for cancer outcomes, we're going to have to look in these places.

Does it cause cancer? Well, I wish I could say yes. I'm

strongly drawn to that possibility, but it's really difficult to tell given what's in the literature. The recency of its appearance in the developed countries where, after all, we do have the infrastructure to study this thing well, and cancer lag times, requires us to go back to those regions where it has been around sufficiently long that the cancer lag can be overcome and where the appearance of infectious disease and the rise of chronic disease such as cancer is happening.

So the very countries, though, where we would like to study this are, in fact, not able to give us a whole lot of data. They're sparse because cancer registries are uncommon or very recent in their appearance. So why does that matter? It's difficult to know how many cancers do we have. What kind of selection bias are we seeing from single-center studies compared to what's going on in the country or the region as a whole? That's limiting. Transitional pattern of societies means that the sort of recency of cancer and also the aging of the population means only now, at this moment, are we seeing persons who have survived to an old enough age where cancer becomes a prominent cause of disease and mortality. They would have formerly died of competing risk factors.

And then, finally, the infrastructure being very lacking

for cancer epidemiology, it's not even a discipline in many of the medical schools in developing countries. And so there's really a need to collaborate with persons outside of those regions. But the limited evidence that there is -- and this has been reviewed by the same review article that Ken Ward mentioned and others have cited throughout this conference, El-Zaatari in *Tobacco Control*.

Dr. Maziak has another review 2 years older than that that came to many of the same conclusions. That evidence does suggest some possibility of association with lung, esophageal, and oral cancers. But overall, those studies are rather hard to lump together. They suffer from very small sample sizes, in some instances lack of matching of the controls, lack of adjustment for confounding, and very seriously and one of the worst problems, the inclusion of cigarette smokers in the exposed groups. So it's very difficult to tease out the contribution of waterpipe smoking as being independent from cigarette or bidis or other types of tobacco use that are common in many other countries of the world.

Waterpipes and bladder cancer: Why would this be a good thing to do an in-depth study on? Well, because bladder cancer is one of the malignancies. It does come in different

histological types. Urothelial cell cancer is the one we see mainly in the West. But in other parts of the world, there's squamous cell carcinoma and adenocarcinoma.

Most of the burden of bladder cancer in these industrialized countries is due to cigarette smoking and occupational exposures. But there's an interesting phenomenon. In regions where waterpipe smoking is a longstanding practice, it offers the possibility of really looking at that with sufficient statistical power. And there's a competing risk factor here, and that's *Schistosoma haematobium*, which is a parasite that infects the bladder and causes cancer of the bladder, and that's a longstanding problem in parts of the world where these creatures are endemic.

So in areas of the world that are endemic for *Schistosoma haematobium*, which would be like Africa, for example, and there are other regions, too, historically this caused squamous cell carcinoma, a sort of more aggressive type of bladder cancer than we typically see in the industrial societies where cigarettes and occupational chemicals tend to produce urothelial cell carcinoma, which is much better understood.

But these societies that are transitioning from one kind of risk factor pattern to another are really showing us

evolving changes, that their burden is moving toward the Western pattern of urothelial. So this was a study supported by the National Cancer Institute at the NIH, called "Gender Differences in Bladder Cancer Risk Factors."

And the reason why we picked Egypt for the study is it's the most common malignancy in men, so it's a very unusual pattern there, the fifth most common cancer in women. In the United States, it's hard to find these rankings higher than 9 or 10; it's not a common cancer here. Cancer services are concentrated in a very small number of oncology centers, and so a large of number of cases could be efficiently recruited. There are major, major differences in many of these societies, with men being the people who do most of the tobacco smoking and the relative rarity in women. This was really true in Egypt, in terms of self-reported smoking among older women, in particular.

The research objective was to look at the risk factors and try to understand something of the gender difference. In every study ever done on bladder cancer, you see three to four times as many men with bladder cancer than women. That's never really been totally and satisfactorily explained. And so the reason why this study is so large is that it was powered to

look at men and women separately and look at gene environment interactions within genders. So we had to have enough people so that by the time we did all of the stratifications, we have enough people left.

So you see it's a relatively large study. The 2,000 cases had pathology confirmed cancer, and this is very important. We had monthly calls with our pathology team to look at every single case and to verify the classification, to exclude things that weren't true malignancy or were metastatic to bladder, et cetera. Controls here are a true random population sample. And so that got us away from any methodological issues that could have clouded the study results.

Georgetown led the study with some excellent collaborations in Egypt at these particular centers. Also the University of Maryland, at the NCI, the Division of Cancer Epidemiology and Genetics, and MD Anderson Cancer Center, all provided consultation on the study. Where did we do it? Cairo, Minia, Assiut, which gave us a look at cancer patterns up and down the Nile River. And this accounts for, you know, roughly 70% of the entire population of the country. These are the only cancer centers in those cities.

Study procedures: It's a classic case-control study in

which informed consent was obtained. Questionnaires were administered to patients, and blood and urine sampling was done. And importantly, ultrasound exams were done on every control to eliminate the possibility of undiagnosed tumors in the bladder in a country where you have endemic schistosomiasis.

So the results have been published in about eight or nine papers. I've cited a few here that have some of the more important results. And so here's the prevalence of *Schistosoma haematobium*. It's about 55% in the cases and about 50% of controls.

Now, you see some statistics here about tobacco use. So never smokers are uncommon, 7% of all the cases. In the controls, you see that -- I'm sorry, let's go back to the cases, the yellow bars. So 12% of the subjects in the study are exclusive waterpipe users, 60% only using cigarettes, and 14% using both types of tobacco products. How did this play out in terms of the case-control? Well, we have to separate here urothelial carcinoma from squamous cell because it was thought, before we did our study, that these would be incredibly different.

We showed that they're not incredibly different, that in

fact, the two kinds of malignancies shared a very common pattern. The risks from schistosomiasis is modest, about 1.4, but statistically significant. Now, if we look at this pattern of tobacco use, comparing never smokers to the other groups, so waterpipe-only was not associated with an elevated risk of either type of bladder malignancy.

And remember, there are hundreds and hundreds of men in the study who smoked. In this particular table we don't have the females because only about 2% of them were willing to admit to an interviewer that they had any kind of tobacco use. And this is not uncommon in an older group like this, who would be very conservative and very mindful of social norms. Cigarette-only smoking, you see the association with urothelial carcinoma. Dual use, yes, we did see an effect here where waterpipe and tobacco dual users -- it's about 10% of the males in the study -- do have significantly increased risk.

For women, what did we see? A somewhat higher association with schistosomiasis that had been previously reported. Since the women didn't themselves smoke or wouldn't self-report smoking, we did have a chance to look at environmental tobacco smoke from all sources. We didn't parse it out by waterpipe versus cigarette because we didn't ask it that way. But there

is the pattern here of being exposed only at home, which is actually shockingly common there, at work, and in both places. Indoor air smoking regulations have really yet to take hold.

To go deeper into this, in urothelial cell carcinoma in men, here's a more detailed look at their waterpipe smoking habits and behaviors. But any measure we looked at, duration -- we also had things like the number of waterpipe tobacco units. They call them hagars in Egypt. We've talked about muscle. We've talked about tobacco heads. So it's that sort of measure of the amount of material. No association.

When we looked at sort of the pack-years equivalent and waterpipe smokers, no clear association by itself with bladder cancer. So that's what this slide is telling you here. A little bit in the second bullet here, we're sort of seeing that people who did have this dual use, they tended to smoke a little bit fewer cigarettes compared to cigarette-only users, but no significant case-control differences.

We did a lot of work on genetic susceptibility, as has been done in cigarette smoking. I'm only showing you one particular gene here, superoxide dismutase. This gene is very helpful to ourselves because it catalyzes the reaction that detoxifies the superoxide, an ion which is generated by the

smoking of tobacco. And what we see here is that people with -- in yellow, what you're seeing is people who have a variant allele, that's dramatically slower activity, seemed to have higher risks of bladder cancer given different types of smoking. So even for the waterpipe-only, that was significant, so among this subset of the population. It's just an example of sort of the gene environment way of looking at cancer that you could pursue in waterpipe smoking, if one was interested in doing that.

So given all of this, what we saw for men in our study in Egypt, which again, it's the biggest case-control study that's probably ever likely to get funded, waterpipe smoking alone did not appear to raise the risk for bladder cancer independently. But it seems like it might act synergistically, we might say additively, maybe a little bit of super-additively, with cigarette smoking to increase the risk of cancer.

And importantly, this was for all of the flavors of bladder cancer, both urothelial cell and squamous cell carcinoma. And although I didn't show you the data, we have the world's largest series of adenocarcinomas in this study, and they also showed the same kind of pattern with these tobacco products.

There may be some effect modification based on genetic susceptibility to reactive oxygen species. That may put a subgroup of the population at higher risk from that. That's a possibility worth exploring a little bit further. In fact, we are doing that. We're also looking at telomere lengths that seem to be adversely affected by both waterpipe smoking and tobacco smoking and seem to result in higher risk of bladder cancer. Environmental tobacco smoke from all sources, including waterpipes, was also associated with the risk of urothelial carcinoma in men, but not the squamous cell pattern.

So why are women getting bladder cancer? Evidence for women's bladder cancer is a lot less clear because of this fact that fewer women than men would report smoking. And so there may be some weak association for them of all-source ETS with bladder cancer.

Which brings me to the point that the contribution of waterpipe smoking to the overall burden of PM2.5 and other particulates and other undesirable aspects of air quality can be really profound. And in this study, what we did is we went around with a side-pack instrument and simply measured PM2.5 levels in different venues in Cairo back in 2005 and '06.

Restaurants here are smoking venues for cigarettes. They

don't have waterpipes, typically, in these ones that we went to. So you see their overall level was pretty high. Shisha cafés have a little bit of mixed use. There's some cigarette use there. And so you almost can kind of see maybe the waterpipe contribution here is boosting it further.

Now, Ramadan tents. Does anybody know what these are? Not counting those of you who grew up in and visited the Middle East. After Ramadan or -- you know, there's a feast that goes on. A lot of families and a lot neighborhoods may -- members may gather at a large tent and have wonderful feasting and conviviality, and there will be waterpipes there. When Ramadan occurs in the colder times of year, which, you know, happens many, many times, these will have the sides rolled down and even very heavy, beautiful oriental carpets and banners on the sides. In hotter weather, those sides may be rolled up. This was one of the years where Ramadan occurred in the winter, and all the tents were closed up, and the levels were extremely high.

Indoor air in different venues, including offices, out on the sidewalks, because, of course, this thing, PM2.5, will have some contribution from auto exhaust and factory emissions and all that sort of thing.

Mosques, which should be smoke free but aren't always completely, lower levels. And then forget this. This should be 25 or so. It depends on which year you looked. So there is potentially a contribution of waterpipe smoking to indoor air poor quality that we shouldn't forget.

Well, this case-control study was conducted in Egypt, where waterpipe smoking is highly prevalent in men, where such smokers are characterized by very long durations of use. Some of these men had up to 40 years of smoking, very heavy daily consumption. I didn't show you the study, but we did a similar thing to what Dr. Maziak reported and showed various hallmarks of addiction.

Waterpipe smoking alone in this setting wasn't associated with an increased risk for bladder cancer, but a greatly increased risk among the dual users and may contribute to the overall burden of environmental tobacco smoke.

There is some support in the literature for this association, but clearly more studies are needed. Well, more studies are needed for all the cancers. The evidence is quite sparse, very inconsistent, and very inconclusive. It's even a problem to even find these studies. I have to tell, having tried myself to do the literature search and to replicate what

others have done, it's not easy.

There's an unfortunate habit in the literature of some review articles simply quoting other review articles and quoting other review articles. So it leads you on a wild goose chase through the literature. And I think people like Wasim and Dr. El-Zaatari, whom I quoted here, gave us the primary sources, you know, so that one can look at them. But it's not an easy thing to do.

Lung cancer: Why haven't we seen a more consistent finding? Well, it's increasing in many of the developing countries. In many countries it's still not the leading malignancy in men. There are many countries where bladder, for example, liver -- in Thailand, for example, cholangiocarcinoma, which is due to liver fluke infestation in the bile ducts, is the leading cancer.

But as their behavior shifts toward our unfortunate Western pattern of sedentary living, poor diet, use of a lot of tobacco and alcohol, now finally, because of the rise of those factors and the aging of the population, now is maybe the time to start looking. They should be amenable to the kinds of epidemiological studies we would want to do to show really more conclusively whether there is such an association.

But these studies are not going to happen on their own. They're going to require collaboration, and there really is a need to devote funding to this to establish good collaborations between maybe U.S. or Western-based epidemiologists and their colleagues in developing countries, to design really rigorous studies to do this well.

I acknowledge many, many people at Georgetown, Maryland, MD Anderson, our wonderful staff in Cairo, Deb Silverman at the NCI, and many, many outstanding scientists who supported this work.

Since I've got a minute, I'll just tell you a quick story. At the year that I proposed this study to the NCI, all three deans of all three of the medical centers with whom I worked in Egypt were urologists. And if you know anything about doing research in developing countries, it's very hierarchical. If the dean says our institute is going to get behind this and we're going to cooperate, it means every physician down the line will, to a large extent, cooperate. And so that was a fabulous thing. It was almost meant to be. I should be so lucky to do that again.

Thanks very much.

(Applause.)

DR. DRESLER: Thank you. We'll stay in the D.C. area, and we'll go to Dr. Arash Etemadi, who is from the National Cancer Institute and will be speaking on Waterpipe and Mortality.

DR. ETEMADI: Hello, everybody. And I want to thank FDA for organizing this wonderful meeting. I was ready to say good afternoon, but it seems that the times had changed. So today I'm going to talk about mortality, waterpipe use and mortality in the background of the study we did in Iran. And some of the previous speakers briefly talked about this study. So luckily the previous speakers have made life much easier for me because much of what I wanted to say in the background has already been covered.

So as we know, the long-term health effects of waterpipe has been studied in, as some described, smaller and scant studies. But we don't know much about mortality, and usually this is where most epidemiologists are very interested to know what, at the end of the day, happens to people who have this lifestyle or habit. So the only mortality study I was able to find -- and I would appreciate it if anyone has another example, to let me know. There's a cohort study of more than 20,000 people in Bangladesh, which the study was originally to look at arsenic effect on health outcomes, and they observed an

association between waterpipe smoking and both overall and cancer mortality. But unfortunately, the effect was very difficult to separate from tobacco smoking because 99% of the waterpipe users were smoking cigarettes or bidis, and when you adjusted for smoking, almost all the effects were gone. And they also had lower power because the study included people from 18 onward. So lots of people did not -- were not at the age to die of a chronic disease, so the outcomes were not so frequent.

So why do we know so little about mortality and waterpipe use? So again, lots of things that we learned today and yesterday. Waterpipe itself, it is not very easy to measure. It's intermittent. Lots of people use it now and then. So it makes a huge difference how you define the use. And then it's very difficult to assess exposure duration and intensity because people have different habits. It's not like cigarettes. You count how many packs the person bought and used. So it's lots of things coming to effect. And there's lots of diversity in how people use it in different populations and different places, the type of tobacco that's used, the associated risk behaviors, what they do, dual use, and lifestyle and socioeconomic factors.

The other one is study limitations. Lots of studies have been done: case-control, cross-sectional studies. And well, obviously, you cannot do mortality with a cross-sectional study, and you need large sample size over a longitudinal follow-up to be able to really capture mortality effects.

And the population. So it's an emerging risk factor in lots of populations and lots of places in the U.S., and so the only populations that you can go on and find that people have been using it for a long time and you can actually see a long-term effect probably in the Middle East. So from what we heard yesterday and also today, the Middle East is like the epicenter of the, you know, tobacco epidemic.

This is a map I have taken from the Tobacco Atlas, and it shows how almost all the countries, more or less the ones that we have data, have relatively high usage rates of waterpipe. And if you look at male-to-female ratio, unlike what you see for cigarettes -- again, something that Wasim also described yesterday -- you don't see such discrepancy between men and women. And in many of these areas, actually women are the main users of waterpipe because maybe it's flavored, maybe there's less social stigma and that sort of thing.

So now I'm going to talk about the study that I'm

reporting on, and it is based on a collaboration called GEMINI, which stands for Gastro-Esophageal Malignancies in Northern Iran. It is lucky that Gemini is also twins, so we had two studies planned, so just by accident. And this was a collaboration between the Digestive Disease Research Center -- Research Institute recently and Tehran University, NCI, and the WHO IARC.

First, a little historical background is that this is -- Iran is part of -- northeast Iran, actually, is part of what is the so-called Asian esophageal cancer belt. It's a very high-risk region for esophageal cancer. Particularly, squamous cell carcinoma stems from northern China to northeast of Iran. And as you can see, studies in the 1970s also showed even there is a big gradient between the east of the Caspian Sea literal and the west. So as you go along this literal, you can see the differences in rates.

So these were the studies in the 1970s. As you can see, there is a country here which does not exist anymore, but this was -- yeah, back then. So these at first were halted for some time until GEMINI was formed in 2000, almost the beginning of the 21st century. And the core of GEMINI was this Golestan cohort study, which started recruitment in 2004, and more than

50,000 adults above the age of 40 were recruited, mainly female. Most the cohort studies -- as you know, women participate more readily. Eighty percent rural. This is a mainly rural area, so even cities we talk about are really very huge villages, not really cities.

So we had a questionnaire including lifetime tobacco and opium use over the lifespan of people, and biosamples from everybody. And waterpipe use was classified as ever and never in the study, based on regular use. And the regular use was defined as if the person had smoked regularly for at least 1 month during the past 6 months. And we define cumulative use as -- also other speakers mentioned this -- waterpipe-years, the duration of use, and then how often people use daily, so like a pack-year, cumulative measure.

The follow-up is ongoing, so we have had a very good success rate in following people. Up to now, after 8 years, we have only lost 400 people out of 50,000. So this is, really, we have been lucky to be able to follow up people. There's not much emigration here in this region. And we have had 4,500 deaths until March 2015. The most common cause, as you can see, is cardiovascular disease, the number one killer in this region. And I haven't broken up the numbers, but out of these,

about two-thirds are ischemic heart disease, one-third is stroke, cancer is the second. And then you come to external causes, poisoning, accidents, that sort of thing, and then respiratory disease.

So I'm going to show you the main tobacco forms in this study. I checked before to see if it's okay to show this picture, so it's nothing. Just to have, you know, a perspective of what we're talking about.

So these are pictures of two or three cigarette stands in Iran. So as you can see, they're mainly international, a mixture of domestic and international brands, but even the domestic brands mainly use imported tobacco. So it's the same type of cigarettes that everywhere else is used.

The second most common type of tobacco product used in this particular population is Nass, which is a chewed smokeless tobacco. It's a mixture of tobacco and lime, and people usually buy it in these packets, as you can see.

And the third one is waterpipe, which is the main topic of the talk today. And I love those cats, by the way.

(Laughter.)

DR. ETEMADI: So the baseline description and -- yeah, I'm sure I changed these slides a little bit, but probably they

were not updated.

As you can see, by far, cigarette use is more common than waterpipe use in this population, in this particular study that we are doing. And a lot of people are never tobacco users. It means they never used any of those tobacco products we described. Cigarette use is mainly a man's habit, but when it comes to waterpipe use, it's similar to the general population of the cohort. So they are the same proportions.

Waterpipe users are older generally than both the general cohort and the group which are using cigarettes. And the main group, racial group in this area is Turkmens. So interestingly, while about 75% of the population are Turkmen, among waterpipe users, only 10% are Turkmen. So probably it's a special habit among the groups that have migrated to that area.

Opium use is a very important risk factor in this area, and I'm going to talk about it a little bit later. So as you can see, it's associated with the tobacco use as well, and about 50% of cigarette smokers also used opium sometime during their lifetime. But alcohol, on the other hand, is not a big health risk factor in this population, although you can see that the smokers use more alcohol. But if you adjust most of

the outcomes here we've been looking at, alcohol does not play an important role in them. And the smokeless tobacco, again, is more common among people using other types of tobacco. As you can see, the waterpipe users started using waterpipe, on average, 10 years after the cigarette smoker, so it's a later kind of habit. And well, because of that, duration of use is also shorter because when they entered the cohort, they had been using it for less -- a shorter period.

So dual use among waterpipe users: About 73% are exclusive waterpipe users, and 15% were former cigarette users; 6% were current cigarette smokers, so they were using both of them; and about 10% have used smokeless tobacco sometime; and 4% had a history of using all three. So the numbers, I know, don't add up. But at the end of the day, 73% are, you know, exclusive waterpipe users.

Recreational opium use, as I mentioned before, is an important risk factor in this population. About 17% of people reported using opium recreationally, with an average of 12.7 years. So as you can see, people might sit for a meal in their village, and then they use opium aside or as kind of, you know, at the end of the day, that sort of thing. And in parties they might have this beautiful setup of -- you know, sets to serve

the guests or sit down and enjoy it, whatever.

And then this is a paper we published about opium use and mortality in this population. So as you can see, opium use is associated with increased risk of all causes of mortality in this population. And this is not like acute use. These are people that have been using it over a long time, and it's associated with all causes of mortality.

So we did survival analysis in this population using Cox proportional hazards models. Oh, this is going back. I thought I had spoken for 8 minutes. Okay. Cox proportional hazards model with age as the time variable. And we excluded those with a baseline disease because it changes their smoking behavior. And we looked at total and cause-specific mortality.

The reference group for all of these comparisons are never tobacco smokers, so people who didn't use anything like the 30-something-thousand people. And we adjusted for place of residence, education, socioeconomic status, other tobacco use, the dual users. And we stratified by sex, ethnicity, and opium use, as these are the most important confounders.

So waterpipe use and overall mortality. And I know all of you are looking at this picture, so let me explain that first, and then I will go to the table. So this is an ad from an

anti-hookah campaign by Tehran University, and what it says, it says that hookah is more dangerous than -- what do you think? So there's a snake, as you can see.

So these results show that ever waterpipe users had an increased risk of mortality when you adjust in the crude model. But when you adjust it for all those confounders I described, the association becomes weaker, and it becomes borderline, so it's not significant anymore. But keep in mind that we had 570 people among hookah smokers, and we had 8 years of follow-up. So probably this is an issue of power, as well as what we are seeing.

But then when you look at the totals of cumulative use, those who used more than 28 waterpipe-years, they were -- they had 66% more risk of mortality, and this was significant. So if you look at the cause-specific ones, almost whatever you see -- everything you see is for cancer and mortality. So both the ever waterpipe use -- again, borderline is not significant. Again, we were underpowered here. But you can see that, for the cumulative use, more than 28, you have a significant association with cancer and mortality.

So stratifying by opium, as I said, is an important risk factor. When you stratify by opium, everything you see is

among never opium users. So those who used opium at the same time did not have any -- all of these hazard ratios were flat. Probably the opium use wasn't as strong a risk factor, so we kind of masked what we were seeing with the waterpipe.

But among never opium users, you still see this association with overall mortality and cancer, as I mentioned before, just to put things into, you know, perspective and see what cigarette is doing in the same population, because there was a question of how do they compare. So you see pretty much the same hazard ratios for cigarette smoking in this population.

So for overall mortality among all participants, former and current smokers have hazard ratios of about 1.4-1.3. So this is pretty much the same risk that you see with waterpipe. And for cancer, you see higher risk. This is again the same thing that you see with waterpipe. And stratifying by opium use, again, has an effect modification for cigarette smoking, like what we saw for waterpipe. Particularly for cardiovascular disease and cigarette smoking, you can see that among never opium users, you see this association, but among opium users it's pretty much masked or flat. I'm not going into details for the smoking intensity and mortality. Again,

you see a dose-response, particularly among current smokers, with the amount of -- average amount of smoking they do.

And also the starting age, people who started before the age of 20 had a higher risk of dying from cancer particularly, and overall mortality. So what do the trends look like? Again, we didn't have a very high rate of waterpipe use in this population. So if you look by birth cohort, you see that most of the waterpipe users were born before 1940, and the trend seems to be going down as you move to younger cohorts.

But then there seems to be a flattening and then a lifting up in people who were born after the 1960s, and this seems to be the general idea of the popularity among younger cohorts. Of course, the people who were born in 1965 still are not college students in our cohort, but it shows that the habit has been changing. In comparison, if you look at the cigarette smoking trends in the same population, you will see that it generally decreases with the birth cohort, except this hump, which is around the time of people who were born between 1950 to 1960. This is pretty much the peak of probably the tobacco cigarette smoking epidemic in this population.

So the strengths: We had a relatively large sample size, although not many people used hookah. But still, we had enough

to do lots of these analyses. We had minimal loss to follow-up. We were able to capture everybody, almost. Data on lifetime exposures, all the important confounders, we were able to capture these.

Limitations: We were underpowered for some of the waterpipe analyses again. And the other limitation is this is the population we were looking at for waterpipe use, but probably this is the population we should be looking at. So these are the new generation of, you know, hookah culture sitting around, spending time and having fun smoking hookah. So the problem, as lots of speakers also mentioned, is that these people are not yet in that period where you can study their mortality, but a long-term effect should be expected to come in the future decades.

So, in conclusion, we observed a significant association between high cumulative use and overall and cancer mortality. It was independent of cigarette and other tobacco. And also it was modified by opium use. That was the update, which is missing here. So we think that there are lots of other -- as everybody mentioned in this workshop, lots of future studies are needed to better understand the nature of the long-term effect of waterpipe use in other populations.

We can do more studies in the Middle East. For example, we are working on a series of cohort studies across Iran, called the PERSIAN cohort. So it's actually a collection of cohorts in different parts, and some of these are in very high-risk -- high rate of tobacco use in south of Iran, where lots of people from Arab ethnicity live. And so that's probably a better place to look at some of these effects; and also populations with more recent epidemic, like the United States.

And I had a map that also I can show here. But if you look at the world map of use of hookah and waterpipe, there is a very neglected region; that's Russia and also former Soviet republics. There are not very many studies there, but the rate of waterpipe use seems to be very high in those areas, and that's another population that's worth really looking at.

And we're working on having really specific questions to capture waterpipe use because the generic questions we ask about like cigarettes, the similar generic questions seem not to work. And we are also working with FDA and CDC to develop -- to work on biomarkers that can capture waterpipe use and its effect on long-term health.

And well, I couldn't really list all the people who have worked with us. So this from our last slide of visit in 2014,

where we visited the Golestan cohort study site, and you see lots of collaborators from NCI, from the United States, and the Digestive Disease Research Center and also Golestan University, which is the local university which is helping us. And IARC. And I want to thank our participants who were patiently answering all those questions and us going through all the files and stuff.

So thank you all.

(Applause.)

DR. DRESLER: Thank you.

Our next speaker is Dr. Mary Martinasek from the University of Tampa. So again, another Florida person speaking on Infectious Disease Transmission in Waterpipes.

DR. MARTINASEK: Hello. And thank you, everyone. I'm just getting over laryngitis, so hopefully my voice will last through this talk, a short talk. First of all, I'd like to thank the FDA for allowing me to share my research and that of my research team.

So before I start talking about infectious disease, I want to reflect on some of the discussions yesterday because I'd like to add to them. We've done a lot of research. A lot of it has been presented at national conferences, but not all of

it has been presented in peer-reviewed journals as of yet. And in particular, I want to reflect on marketing and messaging.

So clearly messages, in the talk yesterday, do help change behavior. We conducted two social marketing campaigns -- not social media marketing, but social marketing where we actually looked at the four P's: product, price, place, and promotion.

And we conducted these, one at a very large university. It was 52,000 students at a public university and another campaign at a private university with 8,000 students. And what we found is students, college students really lacked education. They didn't know that hookah was bad for them. They perceived it as being less harmful. Many students didn't even realize that it had tobacco in it. So our messages were really geared towards education. We pretested our messages. We developed and pretested them with the college students, and we evaluated them using the stages of change model. And we actually found that students were willing to quit, students were planning to quit, and students had already quit, based on the messages. And that evaluation was of over 800 students at both of those universities.

So even taking the social marketing campaigns, the same town -- it was in Tampa, one at a private and one at a public

university -- the messages were different because the audience was different. When we pretested messages, they had to be different. And it's important, as we go forward, if we develop messages, that we tailor them.

For example, we had a truck in the background and a pipe, a hookah pipe, coming out of the exhaust, for the public university. And when we tested the same messages at the private, it was a Hummer that they wanted to see in the picture. So just even subtleties that they could actually resonate with. So again, we can't necessarily generalize our messages there.

I also want to talk about the carbon monoxide. We've talked about carbon monoxide exposure, and Ken Ward touched on a study that we published in 2014, and that study was a sample size of 166. We measured pre and post carbon monoxide exhaled measurements outside that bar, we measured heart rate, we measured carboxyhemoglobin using the Rad-57 pulse-ox device. And we concluded that study.

So we went from 166 to 200 patrons. And what we found was an even bigger difference. So we reported 6.5 pre to 58.2. Our final study was 5.7 ppm to 66.5 afterwards. We saw statically significant increases in heart rate and the

carboxyhemoglobin using the specific Rad-57 device. And we also saw decreases in oxygen saturation.

And the average stay in those bars was 2 hours. I know there was discussion yesterday. But when we measured them pre and post, letting them come and go as they choose, it was 2 hours on average. And in my observations and experiences doing many observations in the hookah bars for many hours, my own parts per million went from 0 to 13 ppm with only two inhalations of a hookah pipe. So speaking of large inhalations, I think it's important to note that many behaviors go on in the hookah bars that could affect the respiratory system. I'm a respiratory therapist by trade, and one of the behaviors that occurs in our town is bubble blowing in the hookah bars. So not only do these patrons inhale a tidal volume that some noted was 500 mL, but they're holding their breath and then blowing bubbles through these devices that are provided to them.

So down the road, we don't know, but there is potential effects from that. And it extends even beyond the bars, from a public health perspective. I'm a public health practitioner and researcher, and there was a study done in 2012 by Elias, and they talked about the driving behaviors. They did an

experimental study where they looked at the driving behaviors of smokers, hookah smokers versus nonsmokers. And what they found in that study was that those hookah smokers in this driving simulator could not maintain a speed. They crossed the center line and had more accidents. So I think although we have occupational exposure concerns and we have individual concerns, we also have this for the people that live in the neighborhoods.

And we also conducted a carbon monoxide study in 10 bars over 4 hours, and we found similar results to the study that was presented yesterday. And actually eight of the bars that we looked at, the carbon monoxide levels exceeded EPA recommendations. And you heard about the emergency room cases yesterday.

So I appreciate this opportunity to share qualitative research as well, because it's very difficult to get qualitative research published. And Tracey Barnett talked about harm perceptions, and we found the same in our -- I conducted two studies, cross-sectional studies at both of those universities with over 600 participants. We found that they perceived it as being less harmful, the college students, than cigarettes.

Some of the same things -- she mentioned a buzz that they like, this legal high that they say they like. They say they smoke it because -- college students, because they're bored -- so I guess I have to give them more homework -- passing the time and they want to be relaxed. But some of the negative effects that they said were also reflected today. Athletes said they couldn't perform as well the next day. They said they had headaches, lightheadedness, and also shortness of breath. And in particular, with females, we saw nausea come up in our research.

Lastly, I want to reflect on something that hasn't been touched on. And we did 100 interviews in the community, in our community, and this is not published yet. But what we found from these community participants -- similar age as the college students, but they weren't all college students. And they liked the hookah bars because they felt that there was an acceptance, and it's sort of a club environment. Kind of like going to Starbucks and people know what you order and they say hi to you and they know your name. That was one of the attractions that I haven't heard yet that was -- that we heard from our community partners.

So the study that I'm going to share with you now is the

last of 2 years of research. So we should get some writing done now after this. The research is funded by the American Lung Association Social-Behavioral Research Grant. And I have no industry affiliations or relationships here.

So as you heard today and yesterday, we have many hookah bars in Florida, and you know, part of it, I wonder, is because we have really good surveillance. As Tracey Barnett said, we've been including it on our Florida Youth Tobacco Survey since 2007. We have 24, at last count, hookah bars in our county, in Hillsborough County, Tampa Bay area region, and most of those bars are centered around college campuses and high-traffic areas. We have Busch Gardens and other draws such as that.

And so what I noticed in my qualitative research is these hookah bars are very much the social environment. There are couches, there are games, there are the blowing devices, there are low ceilings. Oftentimes they open the door, I think, to sort of vent out some of the smoke.

And what I've noticed is that the devices are consistent in that they're single-hose pipes, they're plastic hose pipes, and there's really no regulation currently on cleaning the devices. When asked about cleaning the devices, the bar

helpers, if you will, I've heard everything from I've taken glass cleaner and we're cleaning the glass out with, like, Windex. They take hot water and they wing it through the hose. Only once have I ever heard of bleach being used, and they say every 2 weeks that they run bleach through the hose.

And so there are reports out there, and these are just a sample of those reports, where they talk about the potential and the risk for communicable diseases or infectious diseases. And so this prompted me to say okay, well, based on what they're saying in the hookah bars and based on what the reports are saying, are patrons, people that are going to the bars -- and let me say that a survey I conducted with 970 smokers, the question on the survey was when you smoke hookah, how often do you share a mouthpiece tip with others? Fifty percent said all of the time, 28% said some of the time, and 22% said none of the time. In addition, with our two surveys with many students, they typically smoke at hookah bars. So it was important to investigate this research.

So the research question was does hookah smoking actually pose a risk of infectious disease transmission? And so this study is a collaboration. It's a collaboration between our department of public health and our microbiology department.

And so Dr. Eric Freundt, Zachary Rivera, and Alexandra Ferrer were involved from the microbiology standpoint. This was a study that was approved by our institutional review board. We trained researchers in data collection, and I'll talk about that.

So, in particular, 10 bars were used to actually culture the pipes. We chose those 10 bars because we had already been in these 10 bars to do the carbon monoxide measurements, to do particulate matter measurements, and so we were staying consistent with the 10 bars that we had gone to. And also they're highly frequented bars around the college campuses and high-traffic areas.

So here's what the typical hookah pipe looks like that's used in the bars. And again, you know, our team was trained on how to actually collect and draw the samples. We had three Petri dishes that were labeled prior to going into each hookah bar, and looking at this pipe up here, we cultured with sterile cotton swab. Inside the mouthpiece was one place. And then we cultured inside the hose, okay? And then we cultured inside what we call the hose connector.

So going into the bars, we ordered a fruit-flavored hookah device. We did not ask the hookah bar owners if we could

culture their pipes. There was a study done in Iran. It's the only study that I know out there where they actually were letting them know they were coming in, and we didn't want to bias, we didn't want them to go and clean the equipment. So we went in covertly and collected our samples systematically as well. And so this is where we cultured. So we had 3 cultures in 10 different bars, so a total of 30 nutrient agar plates were collected. We used nutrient agar because this works well for growing most types of bacteria. And I can say I do have the microbiologist close by. So if you have a microbiology question, he'll be able to answer that for you because I am not a microbiologist; I'm a public health practitioner.

Okay. So this is sort of a schematic of the laboratory methods that were conducted. So the plates were delivered to one microbiologist each evening that they were collected. So it wasn't all in one evening; it was over the course of many evenings, and it wasn't obviously -- it wasn't in one bar; it was 10 different bars.

The morphology and colony counts were conducted and recorded on each plate. And once this initial analysis was completed, the colonies were isolated and then checked for uniformity and morphology type to determine whether or not this

actual isolation was successful. And it was important for us to continue to do the additional tests that we wanted to do. So the plates that showed good growth on them with individual colonies were gram stained, and the gram reactions were noted.

So here you can see is a graph, and on the x-axis is the different hookah bars. So they're numbered, and you see 1 through 9. The reason that we don't have 10 is because one of the bars, the bacteria grew inside the agar as opposed to on top, so we couldn't actually culture it. So what you see on the y-axis is the actual morphology counts here. The red obviously is the mouthpiece for each bar, the hose connector, and the hose. So you can get a sense of how many distinct morphologies were actually counted in these particular bars.

And then we looked at a colony forming units. So all colonies were counted, as seen by the naked eye. And on the y-axis is the bars, and obviously the x-axis is the colony forming units, the CFUs per plate. What you don't see in this graph are those that were greater than 200 CFUs because these were too numerous to count.

And this, in particular, is a plate that had too numerous to count. Visible bacteria that grew on this particular plate was strip negative. So 25 isolates that were either subjected

to growth on selected media or for polymerase chain reaction (PCR) were stained. And here's the percentage, but we had 19 that were gram positive and 6 that were gram negative. And then these colonies were placed on selected media, in particular, MacConkey agar for gram negative and Mannitol salt agar for gram positive, to assess the growth. And on two of the bacteria that showed growth on the MacConkey agar, an enterotube was performed, and this is a rapid method test. And the first enterotube was suggestive of *Enterobacter amnigenus*.

Okay. This causes, typically, clinically lower respiratory tract infections. It's associated with ophthalmic infections, skin infections, and soft tissue infections. The second bacteria was suggestive of *Yersinia pseudotuberculosis*. And I think most people are familiar with that.

So genomic DNA of the selected bacteria were isolated from fresh cultures, and PCR amplification of the 16S ribosomal gene was performed. We did bacterial sequencing to allow for accurate identification of the bacterial isolates, and this is considered to be the gold standard in bacterial identification and classification. So we're able to identify organisms based on sequence alignment with a public database.

And this is just a sample. I only put four bacteria up

here. This data is not published. We've submitted it to *Pediatrics* for consideration and publication. But we were able to identify over 50 bacterial species from 10 bars and 20 plates, which is of a concern. And one thing I haven't heard in terms of we know these are there, but is it a risk? We do have risks. We know there's eosinophilic pneumonia cases out there.

So then the other thing that we did is to check for antibiotic resistance. And I'll go back to this slide because I have antibiotic resistance there. And it has a plus sign, and it means that it was antibiotic resistant to at least one antibiotic that we tested. And the antibiotic resistance was measured using zones of inhibition. So zones of inhibitions are the area around -- we used ampicillin, bacitracin, and oxacillin disk using the disk diffusion method. And what we found were over 12 of the over 50 bacteria were antibiotic resistant.

So my final comments are that, you know, there's no regulation currently for cleaning these devices. There's a high risk, and clearly with these bacteria that is looking for that warm environment in the mouth. Patrons share the pipes. There's tips that are provided in the hookah bars that, through

my observations, they don't use the tips. They simply pass the mouthpiece around for multiple people to use it. Some of the identified strains were pathogenic, and this is a concern, you know, so I think we need to take it a step further. We have ER cases, and I'm sure there's individuals going into the ER with different diseases. But being able to say that it's hookah specific makes it difficult.

Future studies. The microbiologists suggest assessing the pathogenicity of the collected bacteria from an oral ingestion standpoint. So hopefully this information has been helpful as we move forward into considering regulations in the hookah bars.

So I'd like to thank you for your time.

(Applause.)

DR. DRESLER: See, that's the "ew" factor.

(Laughter.)

DR. DRESLER: Thank you.

Our last presenter now -- and thank you for being outside of the Southeast of the U.S. -- Mohammed Jawad from the Imperial College of London, School for Public Health, speaking on Infectious Disease and Waterpipe Use: The Potential for Infectious Transmission Among Users.

DR. JAWAD: Okay, thank you to the FDA for letting me speak twice and also to again have the closing word on this workshop today and yesterday. And I'll be taking Dr. Martinasek's work further and looking at actual transmission between users, between waterpipe users. This work was a systematic review, which I'm going to present, done in collaboration with the American University of Beirut. So I'll be presenting on behalf of both institutions.

Again, I don't have any conflicts of interest with the waterpipe tobacco industry.

And as mentioned, I am from London, so I thought I'd put this picture up, which is -- anyone who's been to London in the last 4 years will see that this is our legacy from the Olympics, and we built this huge monument as a mark of the Olympic games, and it has an uncanny resemblance to waterpipe.

(Laughter.)

DR. JAWAD: It was actually built by an Indian-based steel manufacturer. So there might be some link there.

(Laughter.)

DR. JAWAD: Okay. So back to infectious transmission. So it's an interesting one because many of the health promotion campaigns actually do focus on infection transmission as a

health promotion media, but the evidence on this is actually quite unclear. So what we've done is we've updated a previous systematic review of the health outcomes of waterpipe tobacco smoking, which was conducted in 2008 and only found that one infectious disease was looked at in the literature. That was hepatitis C, and there was no link between the two. So we thought to update this review and to see if there was any additional evidence on waterpipe tobacco smoking and infectious diseases.

And this is just repeating what I've just said. So the aim of the study was to update a systematic review on the literature on the association between waterpipe tobacco smoking and infectious diseases.

Okay. So we conducted what I thought was quite a robust methodology for waterpipe tobacco smoking systematic reviews. We included all observational studies. We had no restrictions on the population of interest. Our main exposure was, of course, waterpipe tobacco smoking, and we looked at any infectious disease. We did exclude case reports, single cases of disease from waterpipe tobacco smoking, and small outbreak investigations. We were more interested in population-wide approaches. And we also excluded waterpipe use for non-tobacco

purposes. And I know there's been a bit of literature out there on pipe use, shared pipe use with cannabis users and outbreaks and clusters of infectious disease. We didn't include this in the purposes of this review. We also excluded studies that looked at surrogate markers of an infection, like blood test results of inflammatory markers.

Okay. So we looked at a number of medical databases. We also used an extensive list of search terms associated with waterpipe smoking. We had no date or language restrictions, and the review was checked by two medical librarians, again just emphasizing that we did take a very sensitive and robust approach to this review. We also hand-searched reference lists of included studies to see if there were any more studies out there that hadn't been picked up by the search.

So two of us worked independently and in duplicate to go through all of the studies that we found and pick out what we thought were the ones relevant to our aim. We resolved disagreements with a third reviewer and abstracted a variety of information relating to the study design, the methodological features and results, and things like the funding of the study just to assess if there's any conflict of interest declared. And we also conducted a risk of bias assessment on the

eligibility criteria of the studies, the measurement of the exposure and the outcome, any control for confounding, and looking at the completeness of data. In terms of the analysis, it was a quite simple analysis.

We just looked at reviewer agreement to see whether we were picking up the same things. And we considered a meta-analysis, which is where we kind of combined studies together and share our common -- and outcome under the assumption that they can be combined as one big study. And for those of you interested in statistics, this is how we conducted our meta-analysis statistical aspect as well. But I won't go through it given the variety of people in the audience.

Okay, so two main results that we found. This is a diagram showing the search -- the study flow of our search. I'm just checking if it's clear on your screen. So actually we found quite a few studies. Four and a half thousand were found from our original search, and as we titered this down to those that met our eligibility criteria, we only found three studies, at the bottom there in the red circle, that had an infectious disease as an outcome and waterpipe tobacco smoking as the exposure. Only three.

DR. DRESLER: Wow.

DR. JAWAD: Yeah. So that was the first study. The first finding is that there are very few studies reporting waterpipe tobacco smoking infectious disease that's given. Okay, all right. And this is the main finding that we found. We found the three studies, and all of them were conducted in Egypt. They were all among males. They were all about hepatitis C again, so no difference to the previous update. And they were all part of a widespread population-level hepatitis C screening program. And the reason for this is hepatitis C is quite a problem in Egypt, and so is waterpipe tobacco smoking. And so when they're looking at hepatitis C screening, they look at risk factors, and one of them is waterpipe tobacco smoking.

So this diagram here on the right, it's always a challenge to explain what this diagram means. This a forest plot which combines all of the studies that we found on hepatitis C and waterpipe tobacco smoking and acts as if they're all one big study. So each of the red squares is a study, and their position on this graph is related to an association between waterpipe tobacco smoking and hep-C. So this vertical line going through the middle is a line of no effect, this one here. And the wings on the red squares are the precision estimates of the studies. And if either the red square or the precision

estimates cross the line of no effect, then there's no statistical association.

The most important part of this diagram is this black diamond at the bottom, which is the summary estimate of all of the studies above it and combines all the ones above it as if they're one big study. And again, because it crosses the line of no effect, there is no statistical association between hepatitis C and waterpipe tobacco smoking.

Some of you may have noticed there's actually four squares here, and I mentioned there were only three studies, and that's because one of the studies used stratification, which we included both aspects of. So it's three studies reporting on four estimates. Okay. So they're finding, too, no statistical association between waterpipe tobacco smoking and hepatitis C.

Now, what sense do we make of this? So there is a surprising lack of studies in this area. However, the hepatitis C findings are relatively unsurprising because hepatitis C is a bloodborne virus; it's transmitted through the blood. And the hypothesis in these studies was that waterpipe tobacco smoking may act as a vehicle of transmission if a user had gingivitis, which is bleeding gums, and then was sharing it around with other people. That's kind of the understanding

behind how this transmission could occur. So we have found no significant finding, and that's perhaps unsurprising.

So what about hypotheses where waterpipe tobacco smoking may induce infection transmission if the infection was transmitted through droplets or through direct contact? And Dr. Martinasek spoke about a few of these infectious diseases, such as hepatitis and herpes simplex virus. The evidence here is still quite weak. We did pick up a few, only a few outbreak investigations in studies in the peer-reviewed literature that looked at other diseases that didn't meet our eligibility criteria. And here the evidence -- there were only literally a handful. You can count on one hand how many studies have looked at this that didn't meet our inclusion criteria. And the evidence was still quite weak and still quite theoretical at this moment.

So certainly there's better quality research needed on this topic area, and part of the problem is that waterpipe tobacco may not be included in surveillance of communicable disease outbreaks. Certainly, in my role as a public health practitioner, I've worked with communicable disease teams, and we don't consider waterpipe tobacco routinely, especially in clusters of disease, and active minorities may be more

susceptible to using waterpipe tobacco in cafés. There might just be a lack of awareness that this is actually a potential vehicle to transmission.

But this is my main point of this slide, and it's about the implications for harm reduction. So my question here that I'm posing is to what extent is a mouthpiece, sharing a mouthpiece, protective against infectious disease transmission?

As you go into a café, some cafés, not all, may give each person in a group their individual mouthpiece to say, oh, this will help reduce any infection transmission, thereby implying a harm reduction.

So there are two main theories that I've -- or hypotheses that I've come up with. And certainly, if we think about a mouthpiece which covers the external end of the hose, I'm not sure that this may act as an effective protecting mechanism if microorganisms are actually already deep inside the hose. Think about it. The inhalation on the hose of waterpipe tobacco would have no bearing to whether or not you're having your own mouthpiece. So that's certainly one hypothesis, that a mouthpiece may not act as an effective protector against infectious disease.

The second aspect is actually the way in which waterpipe

tobacco is smoked. Sitting in close contact with one another for a prolonged period of time may actually be a risk factor in itself for infectious disease transmission, irrespective of whether the pipe actually has an infection inside it. So if you can imagine people sitting closely next to each other, coughing, spluttering, sharing food, drink, sharing even -- even the hose pipe itself, on the outside of the pipe as they pass it around is a risk factor for infectious disease transmission. So whether or not there's a bacteria inside the pipe doesn't really lead to any suggestion that the mouthpiece is protective for that, if that makes sense?

Okay. And the reason I mention this is because certainly I've done some qualitative work with waterpipe café owners and users who think that the mouthpiece given to them is the holy grail for infectious disease prevention in these areas, and I don't think that's the case. Much more thinking and work is needed in this area to see exactly how effective this is.

Okay. So this study also -- the study that we did ourselves has several limitations. We did exclude outbreak investigations, which may have given more insight. But again, I must mention that there were only very few out there that have been published. Additionally, we excluded the gray

literature, the gray literature being studies that aren't peer reviewed and published in journals, certainly government reports, local reports that have been posted on the Internet or elsewhere that may give us more insight. And that was just the design of our study. We decided to exclude the gray literature.

In terms of the studies that were included, granted they were relatively weak methodologies. I didn't present the risk of bias assessments, but certainly those have potential scope for confounding and potential scope of biases creeping into the study designs. And actually because, as mentioned before by a previous presenter, the studies were conducted in Egypt, and waterpipe tobacco smoking, the actual component of the tobacco as well as maybe even the behaviors themselves may be different to Western settings, especially where they're smoking. So it's something to bear in mind as well.

Okay. I'll just end with the acknowledgements, particularly to Dr. Waziry, who is the main author of this review. And thank you for you listening, and I'd welcome any comments or questions. Thank you.

(Applause.)

DR. DRESLER: Could we please have the panelists come on

up to the front? And Dr. Ward will be on the phone.

DR. WARD: Um-hum.

DR. DRESLER: So anyway, thank you for being the last speaker both yesterday and today.

Okay. So a series of questions of, again, a really interesting session. So one question. The adverse health effects associated with inhalation of waterpipe smoke are alarming. What have your data revealed about the infections or other outcomes associated with sharing the mouthpiece? So one of the things that I heard you say, Mohammed, in yours was maybe it's not sliding a protective mouthpiece over. And then I think of Dr. Martinasek's study that, no, you could sample the bacteria throughout. But we don't have any knowledge of any infections that have occurred from that; is that right?

DR. JAWAD: I mean, certainly the work that we did was looking at the peer-reviewed literature. So in terms of the published literature, there's very little out there, and more work needs to be done. That doesn't mean that infections are unlikely to be transmitted through waterpipe use.

There's a very strong hypothetical understanding that this is a risk factor, and I think it's quite clear, particularly sharing of -- I mean, the sharing of waterpipe hoses in terms

of saliva transmission, in terms of -- you know, we've talked a lot about carbon monoxide, and the inhalation of waterpipe tobacco mixed with charcoal certainly induces cough reflexes. And that, itself, is a risk factor for transmission of infectious disease. So despite the lack of available evidence out there, there's certainly a strong theoretical basis on which to assume infectious disease transmission is a risk with waterpipe tobacco smoking.

DR. MARTINASEK: And I'll comment as well. So I mentioned there are three case studies of eosinophilic pneumonia transmission. And I think, you know, the big discussion here is that it's relatively new, the research that we've been doing. And so even to get this research into peer-reviewed journals takes many years. So we don't have that data to look at, at this point.

But, you know, this again is important concepts and things to look at as we move further into the research. Because, you know, simply in 10 bars -- I'm curious. If we expand this study, my study, to multiple bars, to multiple states, will we find -- will we be able to replicate that so that we could say that yes, clinically, this bacteria causes eye infections, skin infections? You know, we know these bacteria are out there and

they can cause clinical -- but to isolate it specifically to hookah, you know, that may be a little bit more difficult.

DR. DRESLER: And maybe think which diseases you would look at. Hepatitis C was probably not such a good one to try and hook to it. TB has been shown -- you know, connected with the cigarette smoking. And so I'm trying to think. Actually, I'm not remembering the etiologic agent for the eosinophilic pneumonia. You know, that bacteria is not popping to mind on which one that is. But what disease would you look for from the bacteria that you're seeing, and what would you be thinking of?

DR. JAWAD: Sure. I mean, in terms of salivary transmission, herpes simplex virus, glandular fever, or infectious mononucleosis can certainly be transmitted through saliva. You'd also be concerned about a droplet form of transmission such as meningitis. And you'd also be concerned about those with fecal or oral transmission such as hep-A, which is probably far more relevant than hep-C, certainly. There are a whole host of different mechanisms in which infectious diseases can be transmitted through waterpipe tobacco use, yeah.

DR. ETEMADI: I just want to add a point here. Well, it's

certainly very useful and important to look at the infectious disease in terms of droplets and how it's transmitted and that sort of thing. Also part of the reason, I think, that the people in Egypt have been looking at hepatitis C in conjunction with this behavior is it's a behavior that is probably associated with lots of other common risk factors. So it's not just that -- well, it seems a bit farfetched that gingivitis should, you know, transmit hepatitis C in this context. But I think, at the same time, something we have to think about is that lots of these people might have other risk factors associated with the risky behavior they're taking. So that might fall into a bigger context of the lifestyle.

DR. DRESLER: Dr. Loffredo, have you examined children in homes of waterpipe-smoking parents or an older sibling? Were there any cancer findings in children?

DR. LOFFREDO: Actually, yes. In a separate study, in 2 years we found 400 kids with leukemia in Cairo, and in the course of investigating what the parental smoking behaviors were like, the information about the father, his brothers, and other adult male relatives living in the same household -- because this contributes to the whole smoking burden in extended families in Egypt. And so a father's smoking was

significantly associated with the risk of childhood leukemia in that study. When the inquiry was widened to those other adults who might be smoking, it was a weaker association. But yes, with paternal smoking that was evident.

DR. DRESLER: Sort of a follow-up question on that. I had a discussion, I think, Ramzi, it was with you yesterday or at SRNT, and you had alluded to it in your presentation, that women might not be telling the truth when they're asked if they're smoking.

DR. LOFFREDO: Well --

DR. DRESLER: And so any biochemical verification?

DR. LOFFREDO: Oh, right. So no, we didn't do cotinine or measures like that. It's a generational thing too. I think it's quite hard for -- in a conservative society, many -- I didn't tell you, but many of the participants in that bladder cancer study, even though they may have come into the city for their cancer care, they resided in rural areas where behavior is even more conservative than in the cities.

And so I think probably their rates are extremely low. And then on top of that is the undesirability to report, to admit to it. So we can't, from that study, really disentangle that, but I believe the rates are really that low. Among

younger people, though, this is changing and has changed already. So a question is what happens to them long term? And we don't know yet.

DR. DRESLER: Okay. All right, what is the evidence that carbon monoxide contributes to the harmful effects of hookah or any other tobacco products?

DR. WARD: Carolyn?

DR. DRESLER: Dr. Ward, go for it.

DR. WARD: Yes. I couldn't hear the whole question. I heard what are the effects of carbon monoxide?

DR. DRESLER: Is there any evidence that carbon monoxide causes disease, whether from waterpipe or from cigarette smoking?

DR. WARD: Well, carbon monoxide has many effects. I had presented a couple of case studies that showed that it looks like there are some chronic adaptations in red blood cell volumes, which is one of the more chronic effects. Certainly, there are a lot of acute effects of it too. And it's especially problematic for people who already have established heart disease, since it has a major effect on being able to transport oxygen throat-to-body. So those are some of the effects. Overall, it's very diffuse. It affects both

cardiovascular and pulmonary outcomes. You know, how much of the effects that we see long term are due to CO versus to all of the other compounds isn't as clear.

DR. DRESLER: Anybody want to address the level of carbon monoxide in the woman who was pregnant and that fetus that is being -- was that what you were going to bring up?

DR. MARTINASEK: I'd like to comment also. I'd like comment also. So, first of all, carbon monoxide, as the pharmacologists have mentioned, has an affinity over 200 times for oxygen. And in addition to that, the half-life is about 5 hours. So even if people are sporadically or intermittently smoking hookah, it takes time for that carbon monoxide to actually leave the bloodstream.

We've had the reported cases of the ER situations. We have hospital data where they actually had to go into the hyperbaric chamber to have the carbon monoxide removed, the levels were so high in individuals. So I think there are concerns with carbon monoxide poisoning with these high levels that we're seeing coming out of the hookah bars.

In addition, we have asthmatics. So our tobacco survey data, asthmatics are more likely to use hookah than are non-asthmatics. So now you've got the underlying condition and

then the carbon monoxide effects on top of that.

DR. DRESLER: So I'd raise the question, too, on top of that, about the pregnant woman who is smoking. Would you like to answer that one?

DR. MAZIAK: Yeah. I think there is ample evidence of the toxic effect of carbon monoxide exposure of pregnant women on their offspring and pregnancy outcomes. And it's basically an asphyxia-like situation.

There is also ample evidence of the carbon monoxide and cardiovascular disease, especially with people with atherosclerosis, when they're actually functioning on a lower kind of residual capacity to carry oxygen. And I think is one of the main mechanisms of how it contributes to cardiovascular disease.

DR. DRESLER: Then just not cardiovascular disease, but the impact of that without having oxygen delivery to the heart, which has one of the highest extraction rates, next to the brain, of oxygen.

MS. BRINKMAN: I just wanted to mention that the woman doesn't have to be smoking. She herself can not be smoking hookah but could live with a hookah smoker, and so those carbon monoxide levels, she's inhaling that, especially indoors where

you're not getting a decent ventilation rate. So she doesn't necessarily have to be smoking to experience carbon monoxide.

DR. DRESLER: So I think the answer to that question is, having high levels of carbon monoxide is disastrous to health, pretty much no matter which disease process we're looking at.

And an important thing to stress is the antibiotic resistance. That was quite striking what you had with the antibiotic resistance, Dr. Martinasek. Even though some of those bacteria were found not to be pathogenic, the resistance itself can propagate and become a risk factor for other infections.

You said you are a respiratory technician, but those -- the ability to acquire resistance can be transmitted from nonpathogenic bacteria to pathogenic ones, and we already have a problem in the United States, and increasingly global, with resistant bacteria. So that was actually quite scary to see also.

Dr. Loffredo, this one is for you. From your studies, did you see any increase in birth defect rates of a waterpipe-smoking household?

DR. LOFFREDO: No, I didn't look for that at all. If cancer is hard to research, birth defects are even more so. In

developing countries, they're often not counted. There are no registries. There's tremendous stigma to even admit that you had a malformed child or a bad birth outcome like this. So it's exceedingly difficult to study. I'm not aware of literature on that question.

DR. DRESLER: All right, we're going to broaden this. This is our last one and we're breaking the rules here. So let's go.

DR. MAZIAK: Well, there are a couple of very well-conducted studies that look at birth outcomes in waterpipe smokers, and one of them, by Nuwayhid, who is now the Dean of Faculty of Health Sciences at AUB -- it's a cohort design, and it was published in one of the best journals in the field, and he showed actually waterpipe smokers exclusively or adjusted for other tobacco use, but they were associated with low birth rate, premature birth, and all of these adverse pregnancy outcomes.

DR. DRESLER: So a bit different than what the question was, was birth defects. So what you're saying is that --

(Off microphone comment.)

DR. DRESLER: Correct. So basically what that study showed was the morbidity from smoking waterpipes is very

similar to what we've seen from other tobacco products, particularly combusted tobacco products. Okay.

DR. LOFFREDO: Well, let me make one more comment, please. We did conduct a case-control study on congenital heart disease in Cairo, not for the purpose specifically of looking at waterpipes. But in the questionnaire, we asked about parental tobacco habits. No tobacco products were associated with the occurrence of those particular defects.

So the study wasn't designed to collect sort of in-depth data on waterpipe smoking, but just sort of ever/never wasn't associated with these. Nor are they in the United States. In other large -- you know, there are very few studies connecting heart defects specifically to any form of tobacco smoking.

DR. DRESLER: To what extent -- so there's a question, and Dr. Ward, you had this one about, in your Aleppo study, that there was increased obesity with waterpipe use. To what extent might the association between waterpipe and obesity be due to the sedentary nature of the activity itself?

DR. WARD: Um-hum. Yeah, we think that's very likely. We actually did a follow-up study to the results that I presented, where we looked as best we could at dietary and physical activity variables. And, you know, we didn't collect the

dataset with that particular question, but waterpipe smokers, though, of course are more likely to socialize over waterpipes. The waterpipe is often done with food and with large amounts of sedentary behavior. And that's what we found in that study as well, but that's the only data we have from that so far.

DR. DRESLER: Yeah, I had found that one interesting, too, because studies that have looked at nicotine increased the basic metabolic rate, which would suggest lower body rate. But you're suggesting --

DR. WARD: Um-hum.

DR. DRESLER: -- it perhaps being with the food too.

DR. WARD: Yeah, maybe. Yeah, we really don't know. But right, it may be the food, and it may be sedentary behavior, but we didn't look at either of those directly. So with cigarette smoking, you know, we know that for established cigarette smoking, there's an inverse relationship with weight. But I also showed data from Pakistan, you know, showing that waterpipe users had more abdominal obesity, and that's the same pattern you see with cigarette smoking. So, you know, there could be metabolic effects, but we need more data.

But my guess is that a lot of this may have to do with the social nature of waterpipes. Remember that that effect only

existed in the daily users. So they're spending quite a bit of time, on average, smoking waterpipe with other people, usually in cafés, over food. So that may drive that association.

DR. DRESLER: Okay. Dr. Etemadi, your slides showed a large variability in the hazard ratio for respiratory disease as compared to cancer or cardiovascular disease. Why is this? Is it a function of the diagnostic tools for respiratory disease?

DR. ETEMADI: Well, thank you for bringing it up. Probably I forgot to explain. As you notice in the first slide, when I was explaining the causes of death in this population, respiratory diseases are not -- I mean, around 5% of the deaths were due to respiratory disease. So we didn't have enough sample size. The reason that some of those hazard ratios have so wide a confidence interval is they were basically underpowered to show anything. And even if you noticed, some of the analyses were not -- the models did not, as statisticians call it, converge. So we were not able to establish it. So the basic reason is that we cannot really judge on respiratory disease, at least from this data, because we were underpowered.

DR. DRESLER: Okay. Dr. Loffredo, it's not uncommon for

Egyptian waterpipe users to mix the tobacco in a solid with hashish and opium. Have you looked at that in your study population?

DR. LOFFREDO: Yeah, we did. We conducted a separate study on youth where we did some of the qualitative assessments that others have spoken about, like focus groups and in-depth interviews with individual youth now who are doing the mixing behavior, and it is pretty common.

One of the patterns we observed is starting around age 13-14, getting access to cigarettes, waterpipe, and alcohol. And then as they get older, 16-17, beginning to mix in hashish, bongo, other things, and also tramadol, which is -- well here, a very regulated drug, but there very common. And the kids get it and get high on that. So glue sniffing. A lot of other kinds of things come in as well.

And yeah, there is a group of young users who go on to worse kinds of substance patterns, but they all seem to start with the most easily available things to get, which are the alcohol and tobacco products, and then they begin mixing. We didn't study adults and that behavior, so I can't really say anything about that.

DR. DRESLER: And this goes -- brings in something that

Dr. Bhatnagar said earlier today. And yesterday's presentation, looking at the respiratory disease that -- in the slide that Dr. Bhatnagar had, that acrolein is 88% of the pulmonary changes. So how do we, in waterpipe, if we're looking at respiratory effects, how do we effect change in that acrolein level?

DR. ETEMADI: Could you repeat the question?

DR. DRESLER: So the question -- we had some information yesterday, and then also from Dr. Bhatnagar this morning, that acrolein has 88% of the pulmonary changes, that is, responsible for it. What is that from, and how would we change that?

DR. ETEMADI: Well, I don't know whether any other people have comments, but I'm not sure --

DR. DRESLER: Dr. Ward?

DR. WARD: Yeah, I don't know the answer to that. I'm sorry.

DR. DRESLER: Okay. Dr. Jawad or Dr. Martinasek, did you study the transmission possibility from the removable mouthpiece? Did you study the transmission possibility from the removable mouthpiece? Many are made from soft porous material and often are not disposable but rather reusable. So I think this is implying, then, that the disease or the

infections could come from the disposable mouthpiece also.

DR. MARTINASEK: So our particular study, we did not culture the disposable mouthpieces. We actually went inside the permanent mouthpiece because what we found in our observations is that's primarily what's passed from smoker to smoker.

DR. JAWAD: And in our review, there was no indication of that at all due to the nature of our inclusion criteria. However, it's probably a good point, a good time to mention that Turkey is the only country I'm aware of worldwide that actually has legislation on cleaning protocols for waterpipe apparatuses. And I know Dr. Martinasek was talking about the variety of -- the heterogeneity of cleaning products, or lack of, used in waterpipe cafés.

And bearing in mind kind of our understanding of infectious disease transmission leads us to conclude that the route of transmission may be through several mechanisms, not just the mouthpiece, but perhaps deeper inside the hose. You didn't sample the water, did you, Dr. Martinasek? But also perhaps the reservoir for things like --

DR. MARTINASEK: We sampled inside the mouthpiece, and then we disconnected the hose and sampled inside the hose, and

then we went inside the connector.

DR. JAWAD: So there are probably a variety of routes of infectious transmission, not just the mouthpiece. But certainly, more work -- more work is certainly needed in this area. Yeah.

DR. MARTINASEK: And clearly some of the bacteria that we weren't -- I did not present today, you know, causes dermal infections, causes external infections. So it doesn't even have to be from the smoker. It could be from those passing the smoker on to someone who's going to smoke, from those cleaning the devices. So I think it's a concern all the way around from the smoker to the friends that go with them and also the people working in the bars.

DR. DRESLER: One of the questions that I had, when you had mentioned the cleaning protocol of putting bleach through the tubing, made me wonder what bleach did to Tygon or to leather. I just was picturing that.

DR. MARTINASEK: And I don't know the answer to that, but I would think an environmental specialist would know, even just the leaching out here of plastic, you know, what it leaches into -- when it's mixed with other products such as -- you know, we talk about thirdhand smoke now. So what does that

plastic do? And that's a whole other variable that needs to be taken into consideration.

DR. DRESLER: It makes me think of the presentation we had yesterday on NEPA, so what they are doing for that environmental analysis. Okay.

Dr. Ward, when you were doing your presentation, you hadn't mentioned diabetes. Has diabetes been looked at in any of the waterpipe studies?

DR. WARD: I'm not aware of any studies that directly looked at diabetes. The most relevant one we have is the Shafique study that I mentioned, and that saw a strong association with metabolic syndrome, which of course would raise the risk quite a bit of diabetes. And when they broke it up by subcomponents, too, they found that waterpipe smokers had higher blood glucose levels as well.

DR. DRESLER: How do the anesthetic, bronchodilating, and anti-inflammatory properties of flavorants influence the clinical response of waterpipe users? So what are those flavors doing for anesthetic, bronchodilating, and anti-inflammatory? A hard question, huh?

(Off microphone comment.)

DR. DRESLER: I'm sorry?

(Off microphone comment.)

DR. DRESLER: Very hypothetical, okay. So a question to be asked and addressed in research.

(Off microphone comment.)

DR. MAZIAK: I mean, why one would think it has anti-inflammatory properties, the flavor? To begin with, I mean -- I know, I know. I'm just going to -- what's underlying that question? It has to have some kind of foundation, rational or scientific or something, why we need to know -- whoever asked the question? What are the bases of that assumption?

DR. MARTINASEK: And let me just comment on that. When you talk about bronchodilation, we're actually seeing the opposite effect. When you have an FEV1/FVC decrease, you're actually seeing restrictive lung disease. So it's just the opposite of even, you know, considering bronchodilation.

DR. DRESLER: Okay. And maybe that leads to one of the other questions. So what are clinically meaningful biomarkers of inflammatory response that leads to the impairment of respiratory function? Do we have any clinically meaningful biomarkers for inflammatory changes?

DR. MAZIAK: We know from the cigarette smoking and COPD, for example, research, there are a lot of cytokines that are

associated with the ongoing inflammation and subsequent fibrosis and kind of thickening of the bronchial tree and the lack of its responsiveness, as well as destruction of the dural process and spaces and gas exchange tissue. And they're numerous, from chemotactins, IL-6, to the anti-inflammatory also that usually comes in association with inflammatory as IL-12, IL-10; there's ample evidence about that. IL-8, we've seen yesterday, was associated. Tumor necrosis gamma was associated. These are primary cytokines that are involved in a lot of inflammatory processes but most importantly in the cigarette and COPD kind of relationship.

DR. DRESLER: Okay. Dr. Loffredo, did you consider other methods of tobacco use history in your study other than self-report, hair, or saliva?

DR. LOFFREDO: A good idea, but no, we couldn't do that on the scale of this study. We were barely able to do the study with the funds we had. This was in the era where NCI was cutting awards by 27%, so we had to curtail. We were going to do a lot more biochemical stuff and -- ultimately what we could do.

DR. DRESLER: All right. This next question we've sort of asked and addressed before. So since how people use waterpipe

in the Middle East and tobacco use is different, how does this impact the ability to draw disease and mortality conclusions in the U.S.? Are they relevant to the U.S. prevalence?

DR. ETEMADI: So this is actually a very good question, because whenever you talk about epi data and epi studies, this comes up because you have to focus, you have to restrict yourself to a specific population at the specific time. You can ask whether -- if I repeat this study for years later, will I see the same results or not.

So the answer is a mixture of yes and no. What we do, we try to increase the -- usually, in epi data and big data, we try to decrease the level of confounding and the level of bias by trying to design your pools correctly, seeing all the factors that may contribute, adjusting for all of the confounders, potential confounders. But at the end of the day, well, yes, there will be differences left there which mandates some more studies and, you know, repeating of the same results in other populations.

But I should just remind you that a lot of what we know, a lot of what we knew initially about cigarette smoking came from British doctors. So studies and British doctors, which should be completely different people from the general population and

their smoking habits, et cetera, gave us really valuable hints into the effect of smoking and, you know, health hazards. So it's an open question, but I think that we cannot completely ignore the evidence there.

DR. LOFFREDO: Well, in public health there's a long history of studying phenomena in high-exposure/high-prevalence settings, understanding better what's happening, and then using that information to improve the general health. So it's a very well, you know, established, time-tested way of doing research.

DR. JAWAD: Can I also add something? We're in a very interesting time research-wise and with emerging tobacco products, because we have this long history of doing research with cigarettes, 70-80 years, and we're still finding things out today and reinforcing with better study designs as to the health effects of cigarette smoking.

So I really want to ask a question. Given what we know from the cigarette literature, and given what we know from all of Dr. Maziak's and Dr. Cobb's work on toxicant exposure from waterpipe, do we really need to wait another 20, 30, 50 years until the really high-quality health effect studies of waterpipe tobacco smoking in Western settings get published and are made available to us?

I really want to, you know, pin people down on this question because many of us won't be alive when the good research comes out on the effects of Western patterns of waterpipe tobacco smoking and health effects come out. So, you know, this is a perfect window of opportunity for policy because we know so much from cigarettes. And combustible tobacco is combustible tobacco. There's no safe way to consume it.

DR. DRESLER: I'm going to leave that question as you phrased it, okay? Well heard.

So one more question, as we're getting near time. Today we were talking -- we heard waterpipe-years. So we're familiar with pack-year history, right? We heard waterpipe-years. And the other one I heard was the number of heads that are used today. Do you want to discuss what would be your recommendations for a good way to track exposure to waterpipe?

DR. JAWAD: It's extremely difficult to do because --

(Off microphone comment.)

DR. DRESLER: You know, as you've been looking at the literature and you were going to design a study, what would you think about using?

DR. JAWAD: From my perspective, the wisest thing to do is

defer to Dr. Maziak, who's currently leading on measuring exposure.

DR. DRESLER: I'll get to him.

(Laughter.)

DR. JAWAD: So in my opinion, if you're conducting a study looking at waterpipe exposure, you need to know the number of heads that you're consuming per session, the number of sessions per day, and work out a pack-year history based on that because, of course, even in a given session, you may replenish the head of tobacco. And it's not that common, but it does happen. And the session length. Are you smoking for 20 minutes, 30 minutes, 2 hours? That's going to affect how much exposure you -- how much you're exposed to tobacco-related toxicants and the number of people you're sharing with and what that does to your toxicant exposure. It's extremely complex to capture exactly what the exposure is.

I think I'll probably stop there, but if anyone else wants to answer that?

DR. MARTINASEK: You know, I just want to also talk about the difficulty just because the devices are coming out now, there are new devices, and the college kids are using these sling-pack devices. There are fanny pack devices. So they're

not all the traditional hookah that we see in the hookah bars.

They're adding substitutes, obviously, to the water. It's not clearly water. It's usually alcohol or it's Red Bull or it's Kool-Aid or it's milk. It varies. So there's so much variability. The size of the hookah affects, you know, the constituents as well. So there are just so many variables.

You know, with cigarettes it's different. Waterpipe is very, very difficult.

DR. ETEMADI: So this is actually a very good question, and what I would do in addition to everything that was mentioned, well, I would first do a biomarker study and try to really validate the question, a different question there, to see which one captures actually the level of PAHs and other toxic material that is absorbed. So all of these that were mentioned probably and definitely play an important role.

The type of tobacco. Even I would ask the people whether they smoked -- they use it alone, or do they generally go to a hookah bar, or whether the place they smoke is closed, or is it in the open or that sort of thing. So there are lots of these factors.

And I think a very important thing that we should do is to develop a really valid tool for an epidemiology study. What we

have done so far is basically the same question that we ask for other tobacco type. When did you start? How long have you been using? Have you been using it for at least 1 week during the past 6 months? That sort of thing.

But when a person says regularly every day for a week during the past 6 months, maybe it didn't happen, but he went to some place every other day for part of that period, and that might have the same health effect. So I would begin by actually going and doing a study and validating the question or a proper question there for capturing waterpipe use.

DR. DRESLER: Okay. Dr. Loffredo.

DR. LOFFREDO: No, I don't have any other comments. These are all perfectly valid. Yeah, I agree. More work.

DR. DRESLER: Dr. Ward.

DR. WARD: I agree.

(Laughter.)

DR. DRESLER: Oh, come on. Okay.

Okay, Dr. Maziak.

DR. MAZIAK: This is very, very important, but we have to differentiate long-term exposure from short-term exposure. I think all of these nuances will be very important in assessing short-term exposure health effects. For long-term exposure

health effects, knowing the context, of course, is important, what people are using most commonly and so forth.

But these variations in use that we see even with cigarettes seems to become important when you're assessing 20 years of smoking one pack a day or 20 years of smoking one waterpipe a day. Of course, there will be months that people can be sick and be smoking less or smoking with friends or not friends. But long-term exposure -- and actually, we don't have even biomarkers for long-term exposure for cigarettes. The furthest we can go back is 1 week with cotinine and so forth, and probably longer with hair, but it's not that much validated.

So we have to rely on a specific waterpipe-sensitive instrument that measures long-term exposure. And I think the waterpipe-years is very good and makes it very simple. If somebody smokes an average of 15 waterpipes per month for 2 years, that's one waterpipe-year. And again, there is nothing that can be very sensitive.

And kind of the problem is, within each individual, their smoking pattern changes, it goes up and down, and it's never captured even with cigarette long-term exposure. So the variability seems to be very important for long term.

DR. ETEMADI: Can I add something? This is really an important discussion, and yeah, I agree, there are lots of things that we don't have biomarkers. And probably this is a situation that we also see for nutritional epidemiology, for example. Their FFQs are capturing, you know, the sense of nutrition that the person has been taking all through their life or not, or the 24 dietary recalls are good devices or not. These are still ongoing, you know, the rates and compensation. So I assume that there are different ways of tackling this question, and we'll continue to, you know, develop the methods and improve them over time.

DR. DRESLER: Okay. Any of the other speakers want to address that question?

DR. SALLOUM: I agree with the other positions. And I just wanted to also mention that in terms of -- the lack of product standardization is also contributing to this problem with respect to the charcoal and with respect to tobacco packaging, weight and then volume. And there are also additional products that weren't discussed yesterday, where you have ready-to-consume tobacco heads now for waterpipe that are on the market. Those are not well studied either, and those sort of are prepackaged and they have -- they're labeled as

standard weight, and they're not well understood.

DR. DRESLER: So what I've heard is it's very complex and we need more work. Last comment -- I don't think they turned you off.

(Off microphone comment.)

DR. DRESLER: Oh, okay. Okay, all right.

Well, with that, I would like to thank both this panel, the speakers answering the hard questions, our previous speakers, the audience. I know there are many people online. I thought this was a fantastic 2 days very much needed on a topic that's quite complex. I think we've got that message across. This is a complex topic, but an important one to address.

So thank you all very much for your participation. Thank you.

(Applause.)

(Whereupon, at 12:58 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

WATERPIPES: A PUBLIC WORKSHOP

March 18, 2016

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

_____

ED SCHWEITZER

Official Reporter